Carotenoids and Cardiometaboblic Risk in Youth with Obesity

Recent Advances

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Director of Pediatric Endocrinology and Diabetes, Department of Medicine

October 17th, 2019

JOHNS HOPKINS
All Children's Hospital

1

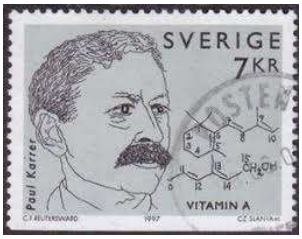
Disclosures

My wife is a distributor for NSA and promotes their products in her Pediatric Private Practice

2

Commemorative Stamps of Novel Laureates

Richard Willstatter



Paul Karrer

Richard Kuhn

Objectives

- Review the metabolism of carotenoids and their retinoid conversion products
- Do levels matter?
- Define the cardiometabolic risk factors in youth
- Present results from recent clinical trials
- Propose collaborative clinical and basic science research opportunities

Current State of Affairs

- Overweight and obesity during childhood and adolescence presents the greatest challenge for healthcare systems worldwide.
- The global rate of overweight and obesity in children has increased from 4.2% in 1990 to 6.7% in 2010 and is expected to reach 9.1% in 2020, which accounts for approximately 60 million children in the USA alone.
- Hence, the mechanisms underlying excessive fat storage and its clinical implications remain a challenge to understand and treat.

Graf, C., 2016, *Visc Med;*32(5):357–362

What are Carotenoids?

- Carotenoids (aka) tetraterpanoids are a class of more than 750 naturally occurring red/orange pigments synthesized by plants, algae, and photosynthetic bacteria which are used mainly for photosynthesis
- Fruits and vegetables provide most of the 40 to 50 carotenoids found in the human diet
- The provitamin A carotenoids are α-Carotene, β-carotene and β-cryptoxanthin which are amenable to central enzymatic cleavage and can convert to retinol (Vitamin A).
- The non-provitamin A carotenoids are lutein, zeaxanthin, lycopene, astaxanthin, fucoxanthine, violaxanthin etc. which upon side cleavage give rise to apocarotenals.

Wang XD. Carotenoids. In: Ross CA, Caballero B, Cousins RJ, Tucker KL, Ziegler TR, eds. Modern Nutrition in Health and Disease. 11th ed: Lippincott Williams & Wilkins; 2014:427-439.

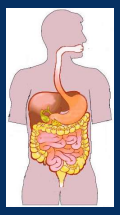
Carotenoid Metabolism

Target tissue

SR-B1 CD36 STRA-6

Carotenoids RBP4:retinol

Lipoproteins (VLDL, LDL, HDL) Apo RBP4 :TTR (circulation)



micelle

diet

Passive Absorption?/SR-B1 ; CD-36

carotenoids

Intracellular conversion

liver

lymphatic system carotenoids/retinyl esters

chylomicrons

Retinol; Retinaldehyde; RA

Courtesy J. von Lintig PhD

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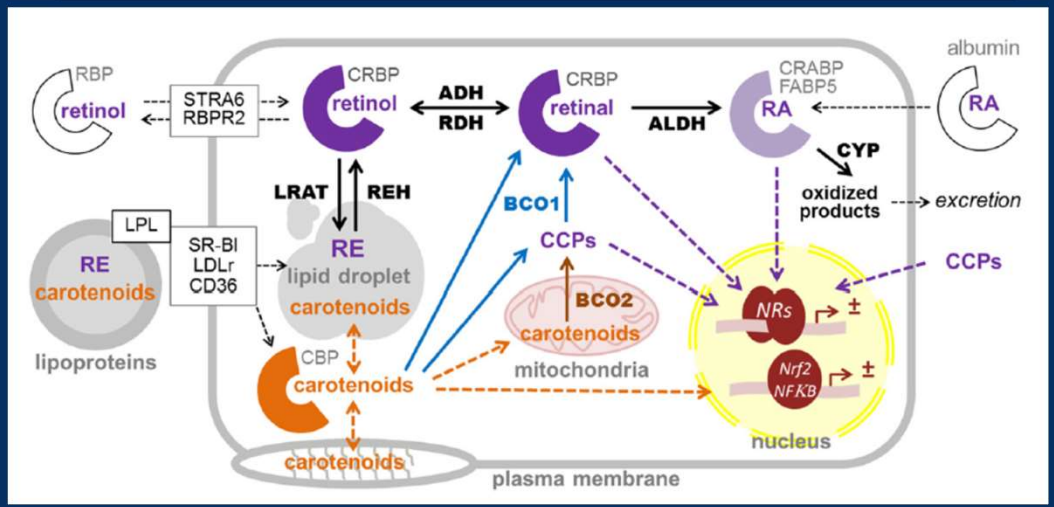
Carotenoid Metabolism



Rodriguez-Concepcion, M et al. *Prog in Lipid Res* 2018 70(4):62-93

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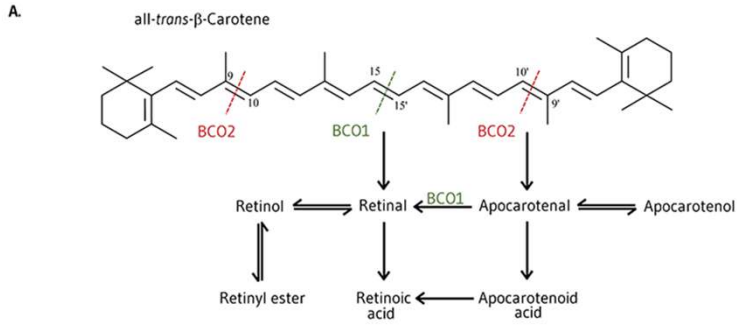
Figure 3. Metabolic Pathways of Carotenoids



A. BCO1 catalyzes the symmetrical cleavage of provitamin A carotenoids like β-carotene at the 15, 15' double bond to produce one or two molecules of retinal. Retinal can be oxidized to retinoic acid or reduced to retinol, and further converted to retinyl ester for storage or transport. Provitamin A carotenoids may also be cleaved by BCO2 at either the 9,10 or 9',10' double bond, giving rise to apocarotenals. The latter can be converted to apocarotenols or apocarotenoid acids. Apocarotenals and apocarotenoid acids can be converted to retinals and retinoic acids.

Jane Higdon, Ph.D. Linus Pauling Institute, Oregon State University
https://lpi.oregonstate.edu/

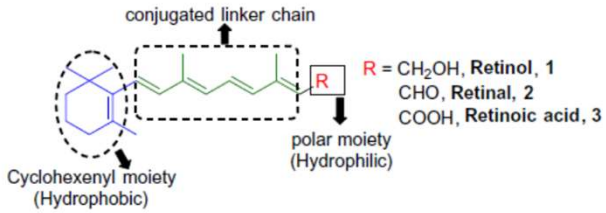


Figure 1. Basic structure of retinoids.

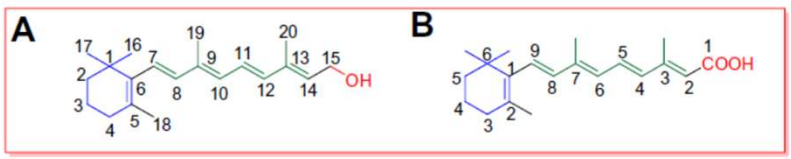
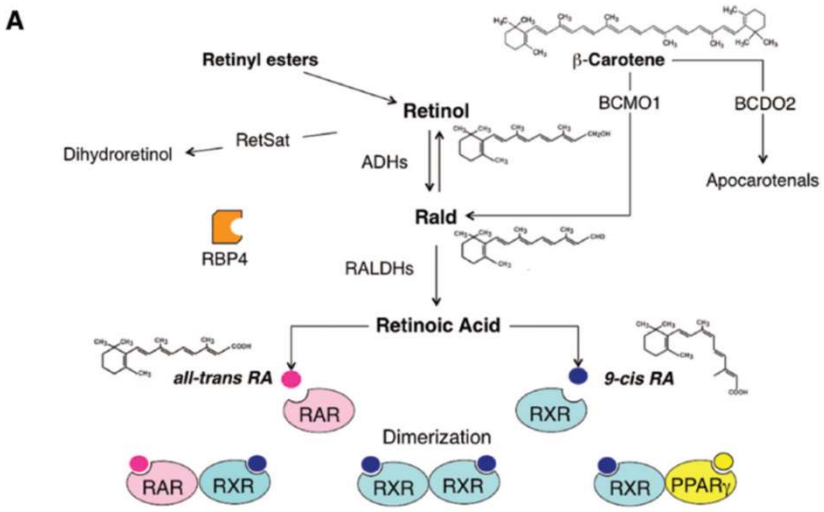


Figure 2. Numbering of retinoids.

Das, B et al. 2014 *Bioorganic and Medicinal Chemistry*, 22(2):673-683

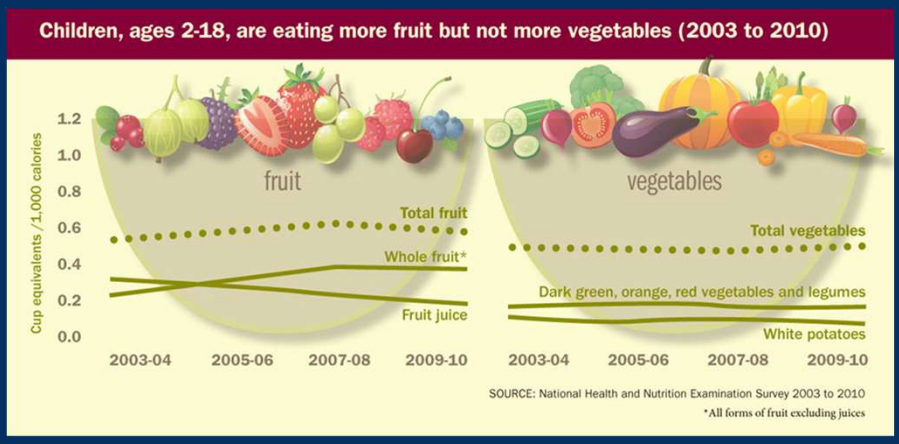


Plutzky, J et al.. Clin Res 2011; 108:1002-1016

How much should we consume?

- As of 2000, the Food and Nutrition Board of the Institute of Medicine has found insufficient evidence to establish a recommended dietary allowance (RDA) or adequate intake (AI) for carotenoids
- It is suggested that a level of 0.4 µmol/L (21.4 µg/dL) β-carotene should be aimed in order to have any "preventive" health potential.
- This concentration can be achieved with consumption of 2–4 mg/d β-carotene or 2-5 servings of fruits and vegetables

Biesalski H., 1997 *J. Clin Nutr*, 16(3):151-155.



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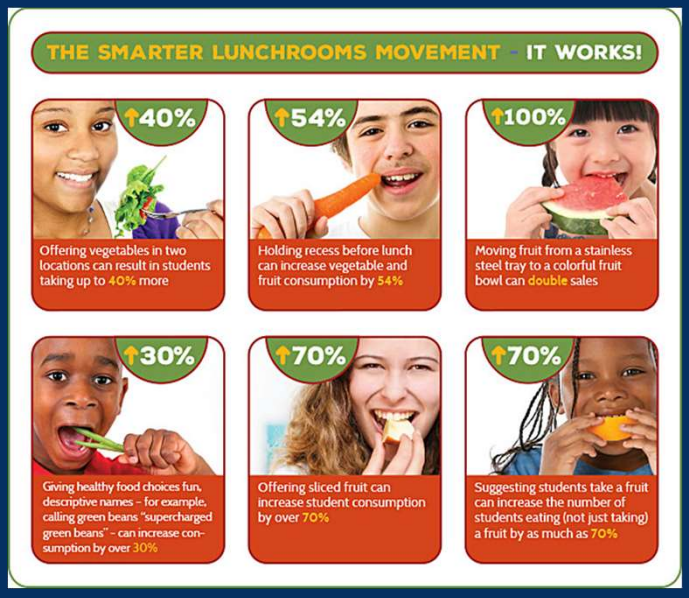

http://www.smarterlunchrooms.org/

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The Journal of Nutrition
Nutritional Epidemiology

Serum Antioxidant Concentrations and Metabolic Syndrome Are Associated among U.S. Adolescents in Recent National Surveys[1–3]

May A. Beydoun,[4]* J. Atilio Canas,[5] Hind A. Beydoun,[6] Xiaoli Chen,[7] Monal R. Shroff,[8] and Alan B. Zonderman[4]

[4]National Institute on Aging, National Institute on Aging, National Institutes of Health, and Intramural Research Program, Baltimore, MD; [5]Pediatric Endocrinology, Diabetes and Metabolism Nemours Children's Clinic, Jacksonville, FL; [6]Graduate Program in Public Health, Eastern Virginia Medical School, Norfolk, VA; [7]Center for Human Nutrition, Department of International Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD; and [8]Michigan Public Health Institute, Okemos, MI

Beydoun, M., 2012 *The Journal of Nutrition* 142(9):1693-1704

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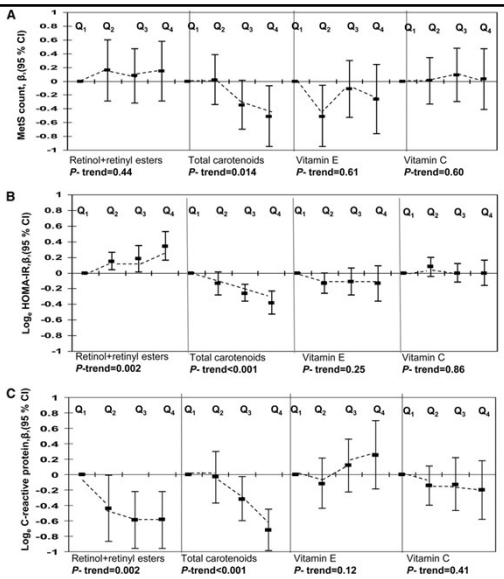

From: Serum Antioxidant Concentrations and Metabolic Syndrome Are Associated among U.S. Adolescents in Recent National Surveys
J Nutr. 2012;142(9):1693-1704. doi:10.3945/jn.112.160416

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Special Article

Carotenoids, vitamin A, and their association with the metabolic syndrome: a systematic review and meta-analysis

May A. Beydoun, Xiaoli Chen, Kanishk Jha, Hind A. Beydoun, Alan B. Zonderman, and Jose A. Canas

Affiliation: *M.A. Beydoun* and *A.B. Zonderman* are with the Laboratory of Epidemiology and Population Sciences, National Institute on Aging, National Institutes of Health, Intramural Research Program, Baltimore, Maryland, USA. *X. Chen* is with the Bureau of Family Health and Nutrition, Massachusetts Department of Public Health, Boston, Massachusetts, USA. *K. Jha* is with the Nemours Children's Clinic, Jacksonville, Florida, USA. *H.A. Beydoun* is with the Department of Medicine, Johns Hopkins Medical Institutions, Baltimore, Maryland, USA. *J. A. Canas* is with Johns Hopkins All Children's Hospital, St. Petersburg, Florida, USA.

Systematic review and meta-analysis following PRISMA guidelines
Primary outcome MetS defined using NCEP-ATP III criteria
Assessed the strength of the association between MetS and Carotenoids/Retinoids

Beydoun, M., 2018 Nutrition Reviews doi: 10.1093/nutrit/nuy044

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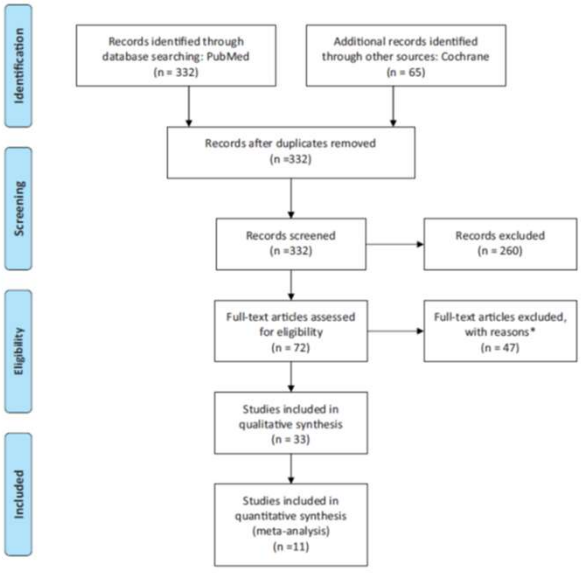

Figure 1 **Flow diagram of the literature search process.** *Main reasons for exclusion were as follows: non-English language (n = 15), animal or basic study (n = 4), reviews (n = 10).

Beydoun, M., 2018 *Nutrition Reviews* doi: 10.1093/nutrit/nuy044.

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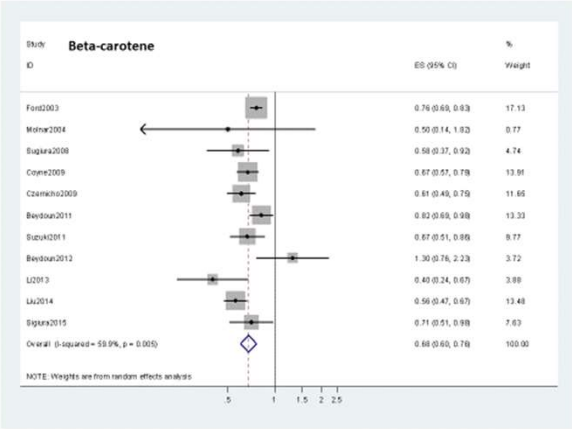
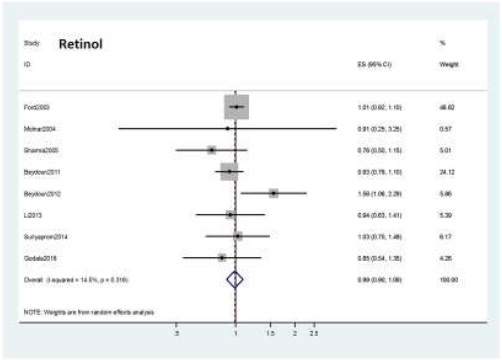
Beta-carotene vs. Retinol levels and Met-S
A Meta-analysis





SD 0.38 ± 0.07 µmol/L

Beydoun, M., 2018 *Nutrition Reviews* doi: 10.1093/nutrit/nuy044.

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Metabolic Syndrome in Childhood

- Definition ?: Cluster of CVD risk including:
  central obesity; dyslipidemia (↑Tg and ↓HDL); hyperglycemia
  FBG >100 mg/dl or HbA1c >5.7% and hypertension (>90th%)
- Prevalence varies by age, adiposity, gender, pubertal status and criteria used to define it
- 15 X more common in adults when diagnosed in childhood
- Pediatric MetS persists 66% into adulthood
- Increased the risk of developing diabetes by 5 fold
- Increases the risk of developing CVD by 1.7 fold

Galassi, A., et al 2006 *Am J Med;* 119(10):812-819
Roberts, C., et al 2013 *Comp Physiol*; 3(1):1–58

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Meta-analysis of Prevalence of Metabolic Syndrome in Children

- For all 87 studies, the median (range) prevalence of metabolic syndrome in the whole population was 3.3% (range 0%–19.2%)
  - Non-overweight 0-1%
  - Overweight 11.9% (2.8%–29.3%)
  - Obese 29.2% (10.0%–66.0%)

Friend, A., 2013 *Metab Syndr Relat Disord*, 11(2), 71-80.

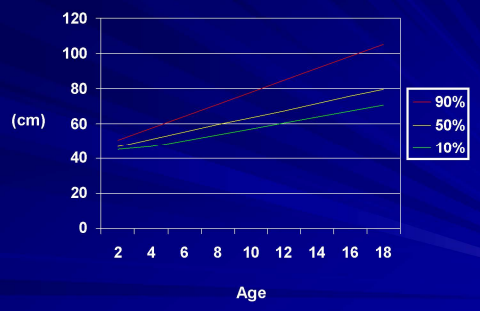
TABLE 2. Definition of Metabolic Syndrome in Children and Adolescents by the International Diabetes Federation

6-<10 YEARS	10-<16 YEARS	>16 YEARS
• Cannot diagnose in this age group	• Obesity ≥90th percentile by waist circumference • 2 or more of the following: - Fasting glucose >100 mg/dL (5.6 mmol/L) or known type 2 diabetes -SBP ≥130 mm Hg or DBP ≥85 mm Hg -Fasting TG ≥150 mg/dL (1.7 mmol/L) -HDL <40 mg/dL (1.0 mmol/L)	• Central obesity: waist circumference >94 cm (men) or >80 cm (women) • 2 of the following: -Fasting glucose >100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes -SBP ≥130 mm Hg or DBP ≥85 mm Hg or treatment for hypertension - Fasting TG ≥150 mg/dL (1.7 mmol/L) or treatment for hyperlipidemia -HDL <40 mg/dL (1.0 mmol/L) (men) or <50 mg/dL (1.3 mmol/L) (women) or treatment for hyperlipidemia

DBP=diastolic blood pressure, HDL=high-density lipoprotein cholesterol, SBP=systolic blood pressure, TG=triglycerides
The IDF Consensus Definition of the Metabolic Syndrome in Children and Adolescents. International Diabetes Foundation. *Accessed 4/1/2016 at http://www.idf.org/webdata/docs/Mets_definition_children.pdf. (c) 2007, International Diabetes Foundation*

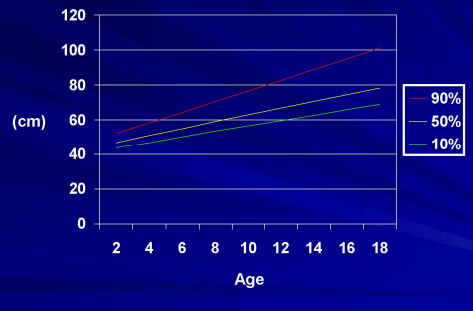
Withcopp, C., et al. 2016, *Pediatrics in Review* 37(5):193-202

WC Boys



Fernandez et. al. J. Pediatrics 2004:145; 439-444.

WC GIRLS



Fernandez et. al. J. Pediatrics 2004:145; 439-444.

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The Adipocentric View of The Metabolic Syndrome

- Android obesity over-represented among CVD populations
- Increased abdominal circumference is the most sensitive marker
- Best cut point in childhood beyond age 5 years Waist to Height ratio > 0.5
- Rate of Accrual and Storage Capacity of SAT vs VAT may differ?

Maffeis, C. et al. *J Pediatr*. 2008;152(2):207-13.

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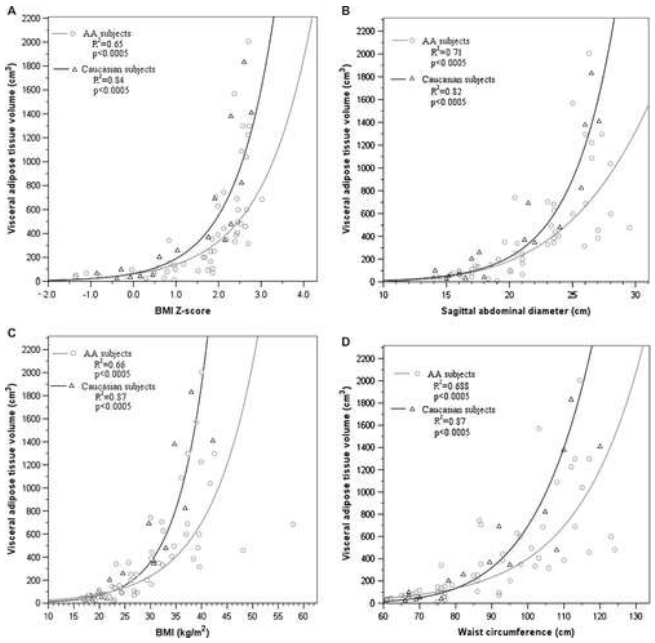

Koren, D., 2013, *Pediatric Diabetes.* 14(8):575-584

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Simple Obesity vs. Lipotoxic Insulin Resistance (MetS)

Metabolically Stable Obesity

- High capacity for adipose tissue expandability in SQ depot (SAT)
- Slow expandability of visceral adipose tissue (VAT)
- Low adipocyte IR associated with beneficial adipocytokine output
- Low lipotoxic output of ceramides, diacylglycerol (DAG) and ROS

Dysmetabolic Obesity IR

- Low capacity for adipose tissue expandability in SQ depot (SAT)
- Rapid expandability of visceral adipose tissue (VAT)
- High IR associated with dysmetabolic adipocytokine output
- High lipotoxic output of ceramides, diacylglycerol (DAG) and ROS

Medina-Gomez, G., 2005, *Diabetes* 54(6):1706-16
Rosen, E., 2000 *Ann Rev of Cell Dev Bio* 16(1):145-71

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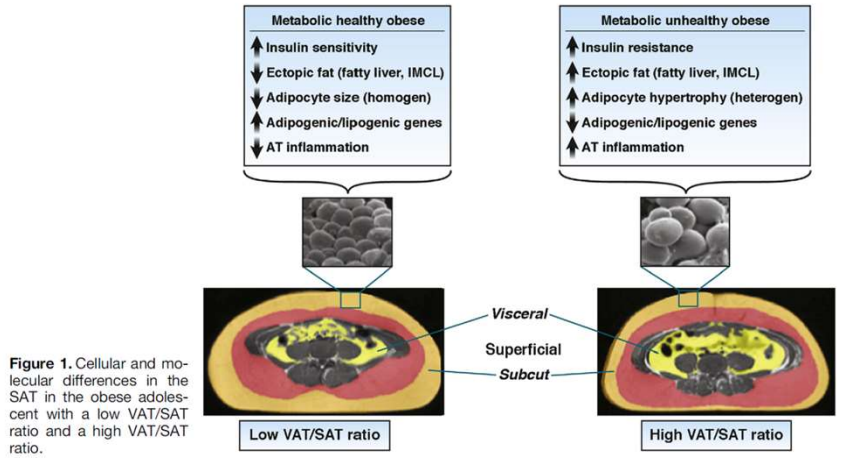

Figure 1. Cellular and molecular differences in the SAT in the obese adolescent with a low VAT/SAT ratio and a high VAT/SAT ratio.

Caprio, S., 2017 *Gastroenterology*, 152(7):1638-1646

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Visceral Adipose Tissue by DEXA

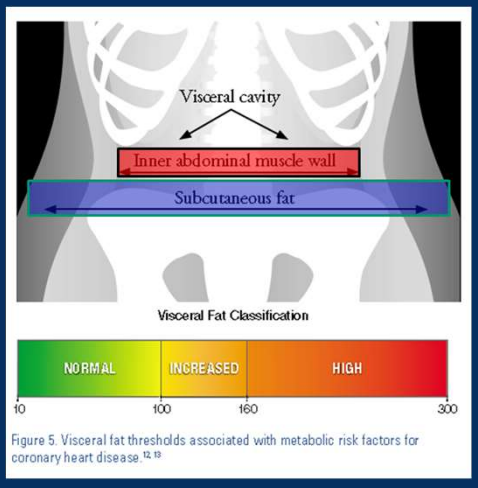

Figure 5. Visceral fat thresholds associated with metabolic risk factors for coronary heart disease.[12,13]

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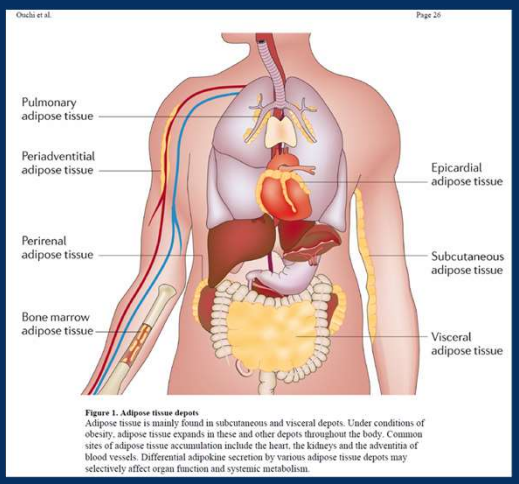

Ouchi, N. 2011 Nat Rev Immunol 11: 8-97

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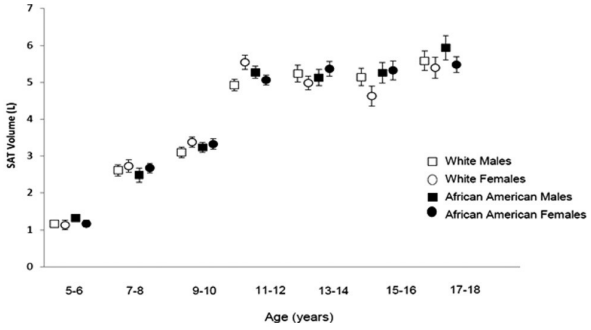
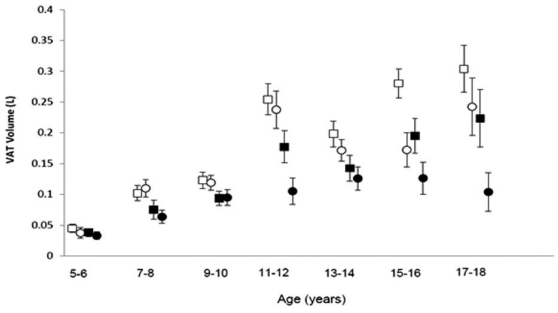
DEXA SAT and VAT in Children and Adolescents





Staiano, A., et al. 2013 *Obesity* 21(6):1251-5

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Strategies to prevent lipotoxicity

- Regulate the mechanism of adipogenesis vs. lipohypertrophy of adipose tissue via regulation of PPARγ activators such as thiazolidinediones (TZD's) which improve IR but increase adipogenesis, hypertrophy and redistribute TG's from skeletal muscle and liver to adipose tissue.

  Hauner H. el at. 2002 *Diabetes Metab Res Rev* 2002; 18 [Suppl.2]

- "Adaptive Thermogenenesis and Mitochondrial Biogenesis": Increase the capacity of adipose tissue to oxidize fatty acids as heat via PPARγ coactivator-1α (PGC-1) which induces the expression of beiging genes.

  Rodgers, J. et al., 2008 *FEBS Letters* 582(1):46-53

Is PPARγ2 the gate keeper of VAT expandability?

PPARγ1

- Many tissues
- Sufficient to support development of adipose tissue and fat deposition requirements

PPARγ2

- Restricted to white and brown adipose tissue
- Key regulator of adipogenesis (increased lipid buffering) in the face of HFD 2.
- Nutritionally regulated via ligand regulation RAR-RXR and VDR, THR, LXR and others.
- HFD induced ectopic expression in liver, muscle and β-cells

Medina-Gomez et al 2007 *PLOS Genetics* 3:e64
Grey, S. et al 2006; *Diabetes* 55:2669-2677

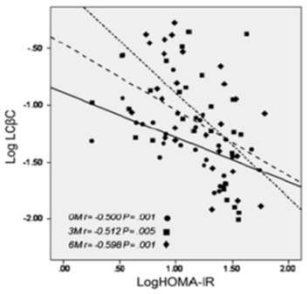
ORIGINAL ARTICLES

www.jpeds.com • THE JOURNAL OF PEDIATRICS

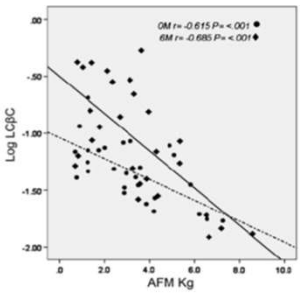
Insulin Resistance and Adiposity in Relation to Serum β-Carotene Levels

Jose A. Canas, MD[1], Ligeia Damaso, ARNP[1], Astrid Altomare, BS[2], Kelleigh Killen, RD[1], Jobayer Hossain, PhD[3], and Prabhakaran (Babu) Balagopal, PhD[2]

A) Correlation between Log Lipid Corrected β-carotene and LogHOMA-IR



E) Correlation between Log Lipid Corrected β-carotene and Abdominal Fat Mass (Kg)



Canas, J. et al., 2012, J. Pediatr. 161(1):58-61

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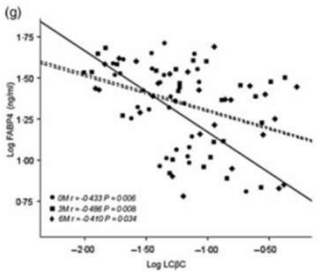
JNS
JOURNAL OF NUTRITIONAL SCIENCE

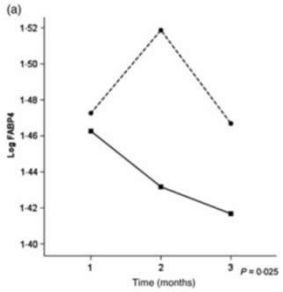
RESEARCH ARTICLE

Fatty acid binding proteins 4 and 5 in overweight prepubertal boys: effect of nutritional counselling and supplementation with an encapsulated fruit and vegetable juice concentrate

Jose A. Canas[1]*, L. Damaso[1], J. Hossain[2] and P. Babu Balagopal[3]
[1]Pediatric Endocrinology and Metabolism, Nemours Children's Specialty Care, Jacksonville, FL 32207, USA
[2]Bioinformatics Core Facility, Nemours Children's Specialty Care, Jacksonville, FL 32207, USA
[3]Biomedical Research, Nemours Children's Specialty Care, Jacksonville, FL 32207, USA

(Received 22 August 2015 – Final revision received 25 September 2015 – Accepted 5 October 2015)
Journal of Nutritional Science
doi:10.1017/jns.2015.29





Canas, J., 2015, *J Nutri Sci*. 4(12):e39-e47.

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Effects of Mixed Carotenoids on Adipokines and Abdominal Adiposity in Children: A Pilot Study

J. Atilio Canas,[1] Amanda Lochrie,[2] Amy Galena McGowan,[3] Jobayer Hossain,[4] Christopher Schettino,[5] and P. Babu Balagopal[6]

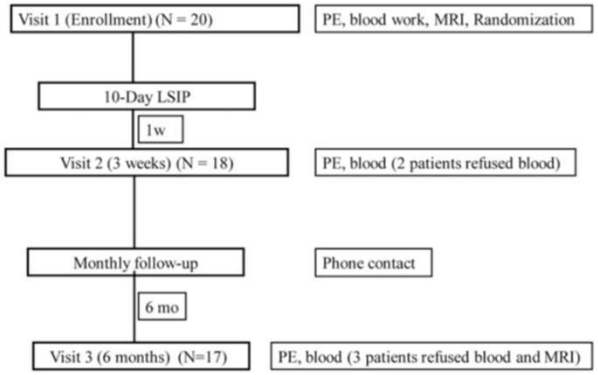

Figure 1. Protocol study flow. PE, physical examination; LSIP, lifestyle intervention program.

Canas, J., 2017 J Clin Endocrinol Metab 102(6):1983-1990.

Table 2. Pairwise comparisons for mean treatment effects of carotenoid concentrations over time between MCS and placebo groups

Carotenoid (μg/mL)	MCS (n=8)			Placebo (n=9)			Mean Trt Difference	*P* value*
	0 mo	3 wk	6 mo	0 mo	3 wk	6 mo		
α-Carotene	.041 ± .013	.137 ± .019	.111 ± .015	.030 ± .012	.037 ± .018	.020 ± .014	1.018 ± .144	**<.001**†
β-Carotene	.127 ± .024	.221 ± .025	.224 ± .024	.116 ± .019	.127 ± .024	.107 ± .023	.288 ± .049	**<.001**†
β-Cryptoxanthine	.070 ± .015	.062 ± .011	.093 ± .029	.057 ± .014	.048 ± .010	.061 ± .027	.129 ± .118	.297†
Lycopene	.185 ± .049	.262 ± .025	.239 ± .045	.194 ± .046	.186 ± .024	.227 ± .035	.101 ± .072	.185
Lutein	.094 ± .012	.423 ± .052	.280 ± .055	.083 ± .011	.078 ± .049	.089 ± .051	.242 ± .052	**.001**
Zeaxanthine	.040 ± .005	.122 ± .009	.099 ± .016	.032 ± .005	.030 ± .008	.034 ± .015	.070 ± .010	**<.001**
Retinol	.351 ± .039	.274 ± .016	.281 ± .023	.365 ± .036	.346 ± .015	.373 ± .022	-.076 ± .015	**<.001**

All values presented as estimated marginal means ± SEM adjusted for baseline levels, Tanner stage and BMI *Z*-score. *Bonferroni adjusted *P* value for treatment effects between MCS vs. placebo. †log transformed values.

Canas, J., 2017 *J Clin Endocrinol Metab* 102(6):1983-1990.

Composition of Mixed Carotenoid Supplement

		RDI
Per day :	2400 µg β-carotene	80%
	non-GMO palm fruit (EVTeneTM)	
	1000 µg α-carotene	N/A
	1000 µg astaxanthine	N/A
	20 mg lutein	N/A
	4 mg zeaxanthin	N/A
	10 mg lycopene (Lyc-O-Mato®)	N/A
	10 mg γ tocopherol	N/A

(CarotenALL®; Jarrow Formulas, Los Angeles, CA)

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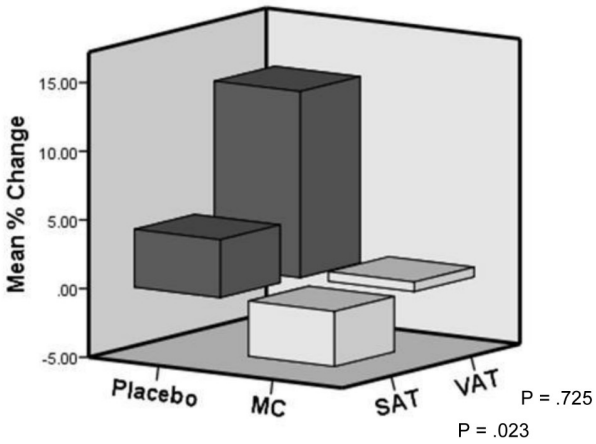
Percent change in SAT vs VAT by MRI after 6 months of MCS vs Placebo



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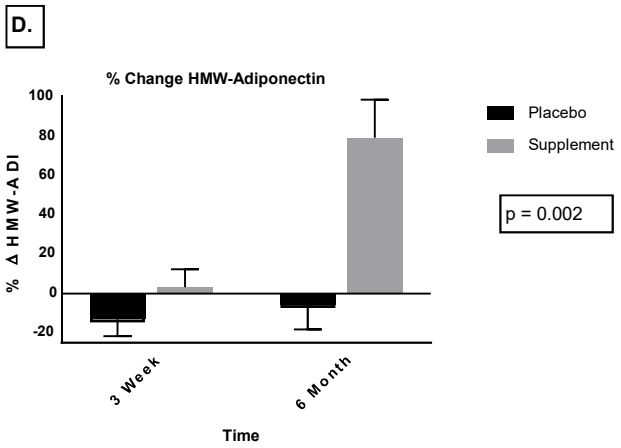
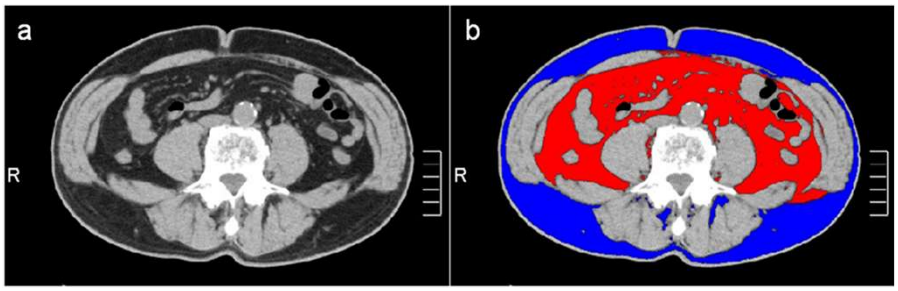
Change in HMW Adiponectin



Canas, J., 2017 *J Clin Endocrinol Metab* 102(6):1983-1990.

Visceral Adipose Index



Visceral Fat Index= VAT (red)/VAT (red) + SAT (Blue) (1).
Visceral Adipose Index = VFI + WC-z * (Tg/adj) * (adj/HDL) (2).

1) Taksali, S., 2008, *Diabetes* 57(2):367-371.
2) Amato, M., 2010, *Diabetes Care* 35(4):920-922

TABLE 2. Demographic, Anthropometric, and Clinical Characteristics of the Study Cohort Across Visceral Adipose Index (VAI) Tertiles

	Tertile 1:	Tertile 2:	Tertile 3:	*P* for trend	
VAI	< 0.91	0.91-3.2	> 3.21	Unadjusted	Adjusted*
n	19	19	19		
Sex (M:F)	19:0	14:5	9:10	**<0.001ϕ**	
Tanner stage (I-II:III-V)	19:0	17:2	16:3	0.216ϕ	
Race/ethnicity					
White (n=36)	14 (74%)	10 (53%)	12 (66%)	0.299ϕ	
African American (n=14)	3 (16%)	8 (42%)	3 (16%)		
Hispanic (n=7)	2 (11%)	1 (6%)	3 (16%)		
Age (month)	111 ± 3.8	114 ± 3.8	125 ± 3.8	**0.020**	
BMI (kg/m²)	18.7 ± 1.0†	26.6 ± 1.0	30.1 ± 1.0	**<0.001**	**<0.001**
BMI z-score	0.68 ± 0.18†	2.14 ± 0.18	2.23 ± 0.16	**<0.001**	**<0.001**
Waist circumference (cm)	63.4 ± 2.7†	85.8 ± 2.7	97.4 ± 2.7	**<0.001**	**<0.001**
Waist circumference z-score	-0.032 ± 0.2†	1.86 ± 0.2	2.14 ± 0.2	**<0.001**	**<0.001**
Waist/height ratio	0.47 ± 0.02	0.60 ± 0.02	0.65 ± 0.02	**<0.001**	**<0.001**
SBP-z	0.921 ± 0.19	1.11 ± 0.25	1.15 ± 0.32	0.898	0.276
DBP-z	0.250 ± 0.13	0.400 ± 0.17	0.486 ± 0.22	0.593	0.695
VAT (g) DEXA	207 ± 23	362 ± 22	478 ± 22	**<0.001**	**<0.001**
SAT (g) DEXA	418 ± 139	1335 ± 143	1885 ± 139	**<0.001**	**<0.001**
VAR (VAT/SAT)	0.40 ± 0.12†	0.23 ± 0.06	0.21 ± 0.04	**<0.001**	**<0.001**

Data are *n* (%) and means (± standard error of mean). *Adjusted for age, sex, and race/ethnicity. †$p<0.01$ for difference between tertile 1 and tertile 3. ϕChi-square test. Data in bold indicate significance. BMI=body mass index, DBP-z=diastolic blood pressure z-score, DEXA=dual energy absorptiometry, SBP-z=systolic blood pressure z-score, SAT=subcutaneous adipose tissue, VAR=visceral adipose ratio, VAT=visceral fat

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TABLE 2. Metabolic Characteristics of the Study Cohort Across Visceral Tertiles, Adjusted for Age, Sex, and Race/Ethnicity

	Tertile 1:	Tertile 2:	Tertile 3:	*P* for trend	
VAI	<0.91	0.91-3.2	>3.2	Unadjusted	Adjusted
n	19	19	19		
Glucose (mg/dL)	81.1 ± 5.7	83.3 ± 8.1	82.5 ± 6.8	0.577	0.220
Insulin (mIU/mL)	8.9 ± 1.8	20.0 ± 2.9	21.5 ± 2.7	**<0.001**	**0.009**
iHOMA-2	1.1 ± 0.21	2.5 ± 0.35	2.6 ± 0.31	**<0.001**	**0.007**
RBP4 (µg/mL)	22.0 ± 2.0	23.9 ± 2.6	33.3 ± 3.3	**0.023**	0.211
Total adiponectin µg/dL	12.2 ± 1.4	9.5 ± 1.3	9.1 ± 1.3	0.245	0.158
Adiponectin/FABP4 ratio	1.04 ± 0.13	0.38 ± 0.12	0.28 ± 0.12	**<0.001**	**0.003**
Leptin (µg /L)	7.8 ± 3.2	28.2 ± 3.1	30.8 ± 3.3	**<0.001**	**<0.001**
hs-CRP	0.86 ± 0.6	2.3 ± 0.6	2.2 ± 0.6	**0.028***	0.066
Metabolic syndrome score					
Cook +/-	1/18	3/16	13/6	<0.001**	
IDF +/-	0/19	1/18	5/14	0.020**	
ATP III +/-	0/19	2/17	2/17	0.341**	

All values estimated marginal mean ± standard error of mean. *p*-value analysis of covariance, *Kruskal-Wallis test, **Chi-square test. ATP III=Adult Treatment Panel III, FABP4=fatty acid binding protein 4, hs-CRP=high-sensitivity C-reactive protein, IDF=International Diabetes Federation, iHOMA-2=homeostatic model assessment of insulin resistance, RBP4=retinol binding protein 4, VAI=visceral adipose index

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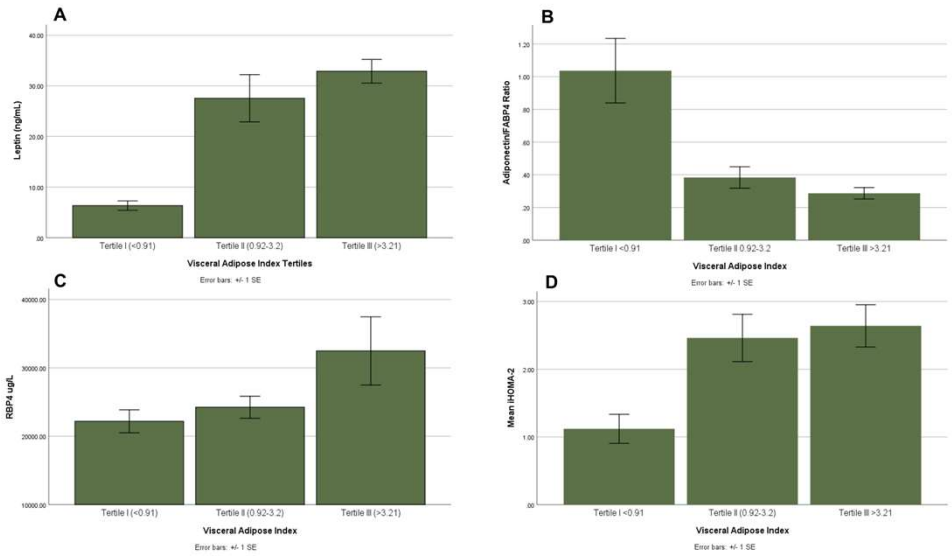
Figure 2: **Mean +/- SEM Concentrations of A: Leptin (µg/L), B: Adiponectin/FABP4 Ratio, C: RBP4 µg/mL, and D: iHOMA-2 Across Tertiles of Visceral Adipose Index (VAI)**



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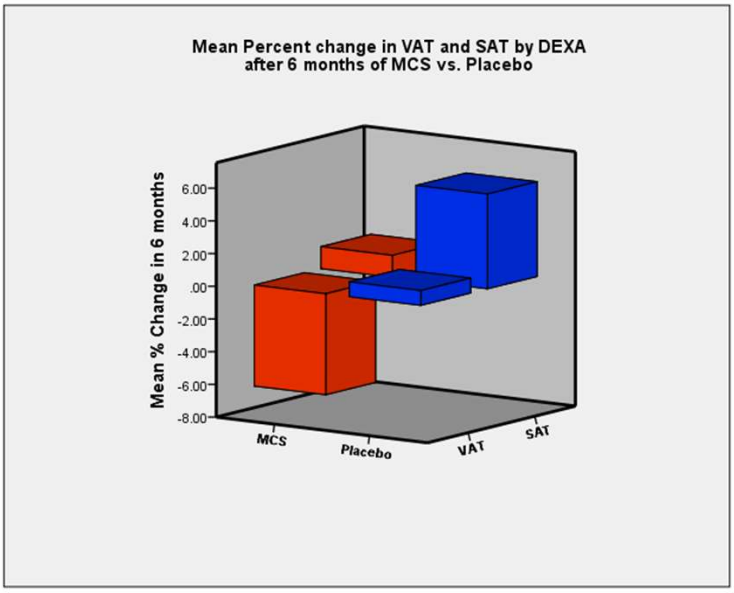

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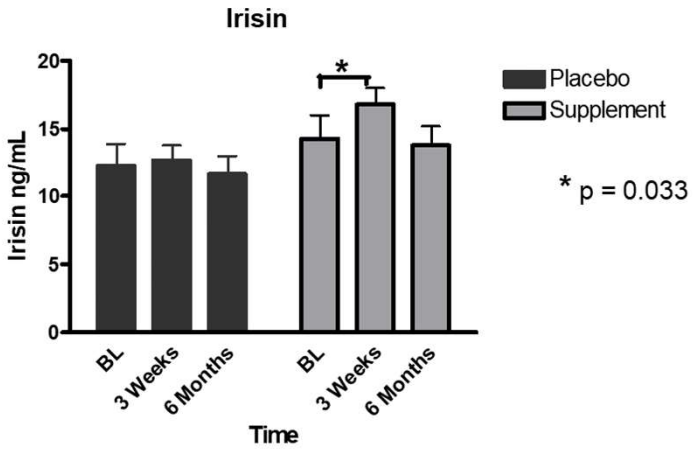
Met S scores based on VAI tertiles at baseline and after 6 months of MCS

MetS Criteria		VAI Tertile I (N=19)		VAI Tertile II (N=19)		VAI Tertile III (N=19)	
Treatment Group		Placebo	MCS	Placebo	MCS	Placebo	MCS
NCEP ATP III	BL / 6M	0 / 0	0 / 0	0 / 1	1 / 0	0 / 0	2 / 1
NHANES	BL / 6M	0 / 1	0 / 0	2 / 3	2 / 1	6 / 3	7 / 1
IDF	BL / 6M	0 / 0	0 / 0	1 / 1	0 / 0	1 / 1	4/ 0

Canas, J., 2019 Unpublished.

Change in Irisin



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Exercise induced fat beiging and thermogenesis

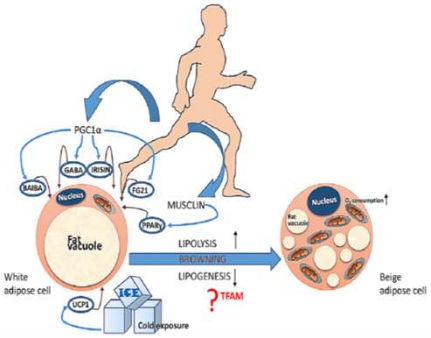


Fig. 2. A comprehensive view of the factors involved in the process of browning. Exercise has beneficial effects on browning but many other factors are also promoted according to physical activity such as (1) beta aminoisobutyric acid (BAIBA); (2) gamma aminobutyric acid (GABA); (3) IRISIN; (4) fibroblast growth factor 21 (FGF21); and (5) musclin (PPARγ agonist). Beside all these factors cold exposure can lead to browning through UCP1. The possible mechanisms involve lipogenic pathways.

Jeremic, N., 2017, *J. Cell. Physiol.* 232(1):61-68.

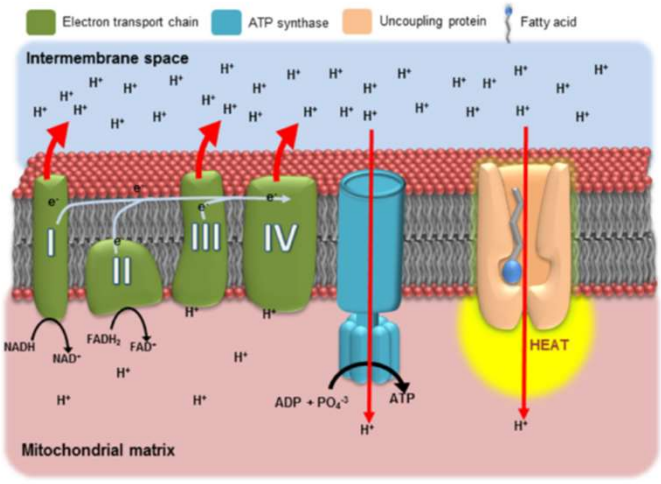
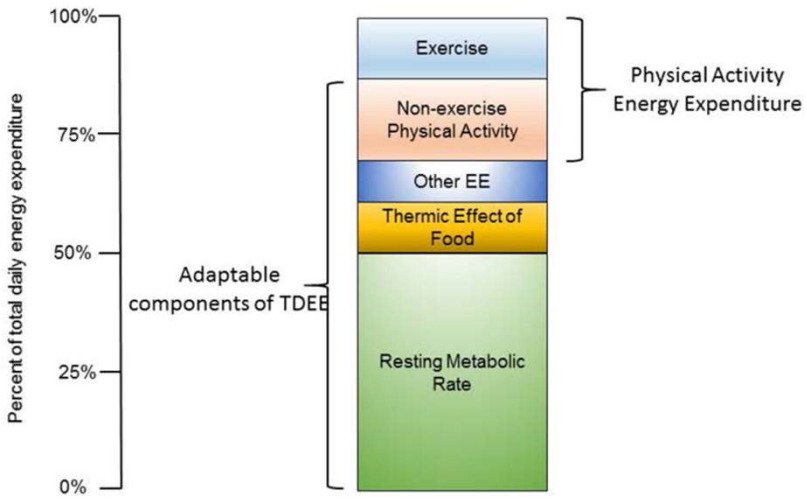


Figure 1
Schematic of mitochondrial uncoupling and the cellular process of thermogenesis. Metabolic processes such as glycolysis, β-oxidation and the citric acid cycle contribute electrons through the nicotinamide adenine dinucleotide (NAD+) and flavin adenine dinucleotide (FAD+) carriers to the electron transport chain. The action of the electron transport chain (complexes I–IV) results in the pumping of protons across the inner mitochondrial membrane from the matrix into the intermembrane space and the establishment of the electrochemical gradient. Normally, this proton motive force is harnessed by ATP synthase to produce ATP from ADP. UCPs provide an alternative means through which protons can cross the inner membrane. Fatty acids activate UCPs by binding to a hydrophobic pocket within the protein that increases proton conductance. The leak of protons across the inner mitochondrial membrane results in the dissipation of energy through heat production.

Fuller-Jackson, J., et al. , *J Endocrinol*. 2018 Jun;237(3):R99-R115.

Total Daily Energy Expenditure (TDEE)



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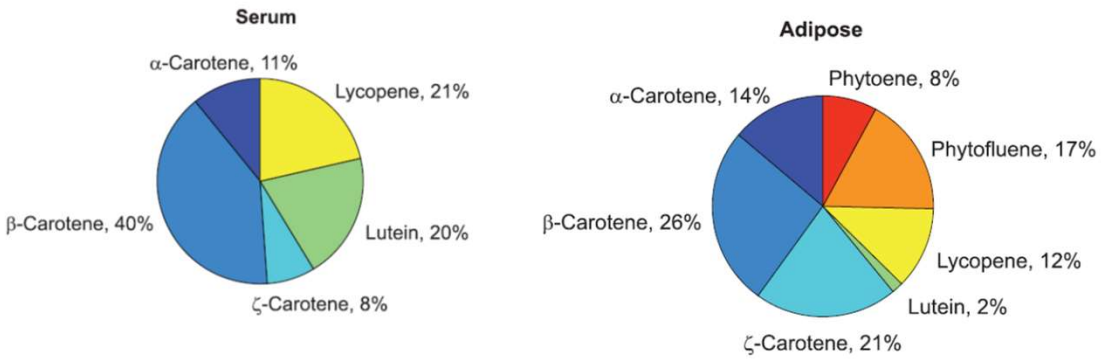
Distribution of carotenoids in serum and adipose tissue in 16 adults.



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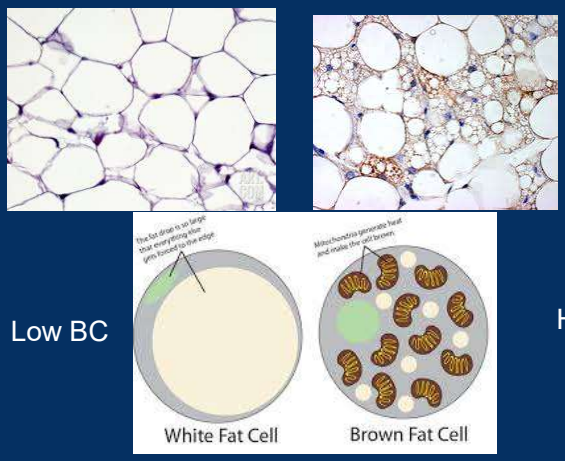

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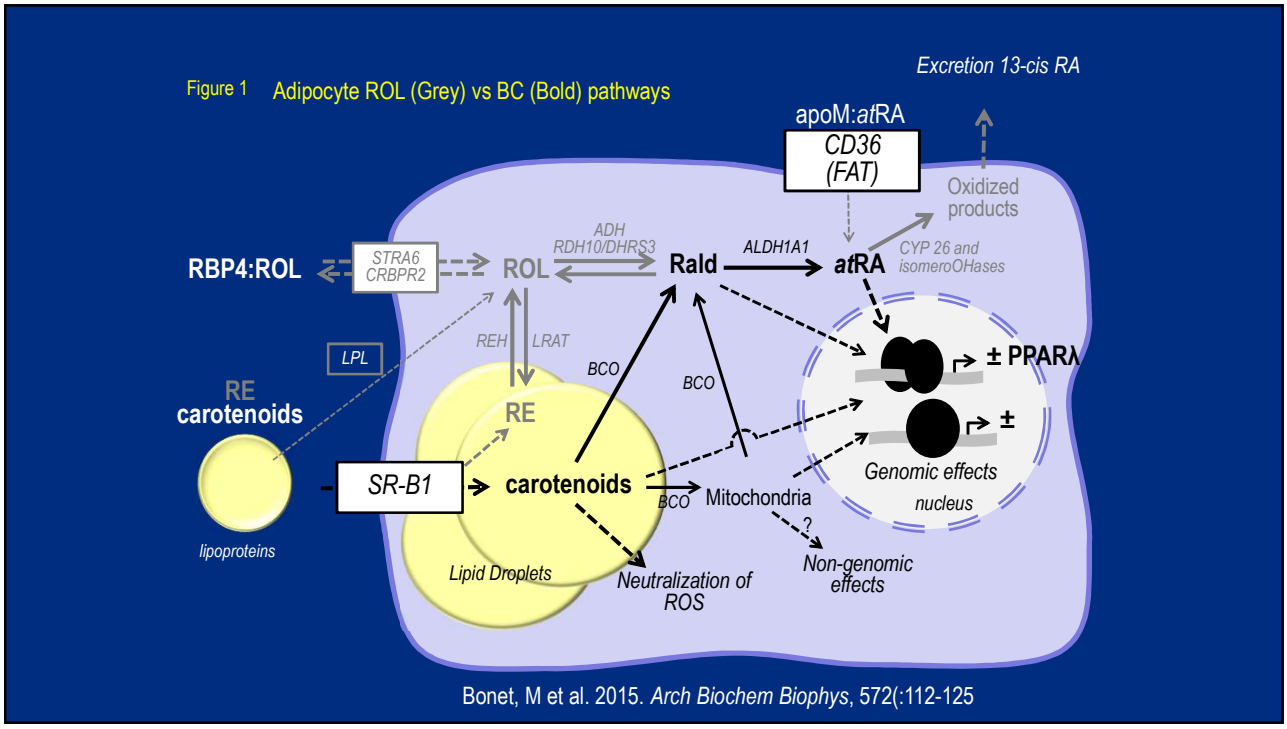

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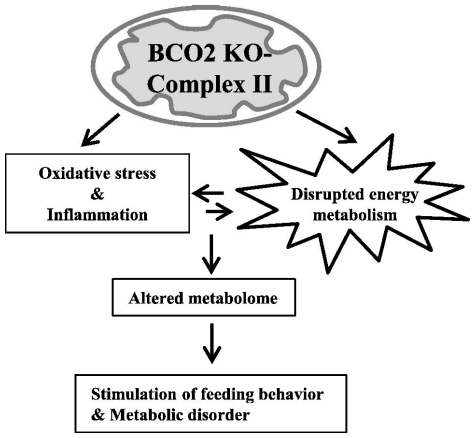
Journal of Nutritional Biochemistry

Ablation of β,β-carotene-9′,10′-oxygenase 2 remodels the hypothalamic metabolome leading to metabolic disorders in mice☆

Xin Guo[a,1], Lei Wu[a,1], Yi Lyu[a,b], Winyoo Chowanadisai[a], Stephen L. Clarke[a], Edralin A. Lucas[a], Brenda J. Smith[a], Hui He[a], Weiqun Wang[c], Denis M. Medeiros[d], Dingbo Lin[a,*]



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Associations for *BCO2*, *PCSK9*, and *TR1B1* Polymorphism and Lifestyle Factors with Ischemic Stroke: A Nested Case-Control Study

Tian-Yu Zhao[1,2], Zheng Li[2], Song Lei[1,2], Liu Huang[2], and Lei Yang[2]
[1]Medical School, Shihezi University, Shihezi, Xinjiang;
[2]Medical School, Hangzhou Normal University, Hangzhou, Zhejiang, China.

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In summary

- Serum β-Carotene is lower in obese vs. lean children and correlates inversely with BMI-z, VAT and SAT
- Dietary advice was not sufficient to increase β- Carotene level at 6 months as opposed to MCS in obese children
- MCS supplementation produced a 2-3 fold increase in β-carotene and 20% reduction in ROL vs. placebo
- MCS supplementation reduces the MetS scores over 6 months of supplementation.
- β-carotene vs. placebo leads to reduced SAT accrual over 6 months of supplementation possibly by inducing mitochondrial uncoupling.

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CONCLUSIONS

- Taken together the data suggest:
  - A potential therapeutic window to use MCS in the regulation of adipose tissue accrual during childhood
  - The data suggests beneficial effects of low dose supplementation of mixed carotenoids on insulin sensitivity and fat beiging in overweight children
  - Population wide studies are needed to better define these associations.

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Thank you

Asclepius (medicine)
Epione (soothing pain)
Hygeia (health)

The Vigil of Dr. Kauffman (Benjamin Cañas 1933-1987)

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