Adult Diseases Now Seen in Childhood

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5-1-2010

Conflicts of Interest / Disclosures – None

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Atherosclerosis

- Degenerative disease of the vasculature.
- Multiple etiologies.
- Slowly progressive.
- Silent until effects of vascular occlusion or embolization manifests –
- *myocardial infarction,*
- *stroke,*
- *sudden death,*
- *peripheral arterial disease.*

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Burden of Atherosclerosis

- Mortality from coronary artery disease due to atherosclerosis has decreased in recent decades.
  - Better treatments –
  - Better control of risk factors –

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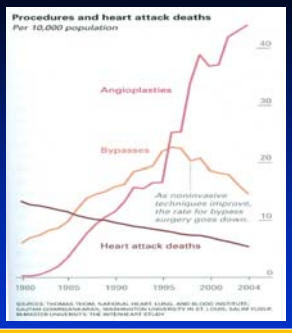
Better Treatments



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Better control of risk factors

- Dyslipidemia – statins.
- Tobacco smoke – Legislation, education.
- Diabetes treatments.
- Hypertension treatments.

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Burden of Atherosclerosis

- But coronary artery disease is still a leading cause of death and disability in the US.
- Economic costs.
- May further increase due to the childhood obesity epidemic.

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Childhood Origins – Autopsy Studies

- Coronary artery stenoses common in United States Korean and Vietnam war victims – healthy youth in their 20s.

Enos et al; JAMA, 1953.
McNamara JJ. et al; JAMA, 1971.

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Childhood Origins – Autopsy Studies

- United States teenagers killed in motor vehicle accidents had evidence of atherosclerosis in the coronary arteries on autopsy.

Stary HC. Arteriosclerosis 1989: 9(1 suppl):119-132.

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Pathobiological Determinants of Atherosclerosis in Youth study – Autopsy Studies

- 15-34 year accidental death victims.
- 3000 cases – 14 centers –
- Prevalence of gross and microscopic lesions in the coronary arteries.

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Relationship of atherosclerosis in young men to serum lipoprotein cholesterol concentrations and smoking. A preliminary report from the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. JAMA. 1990;264:3018-3024.

Table 1. Risk Factor Criteria and Prevalence in PDAY Study Subjects

Risk Factor	Criterion	Prevalence (%)
Non-HDL cholesterol	≥ 160 mg/dL	28.0
HDL Cholesterol	<35 mg/dL	18.7
Smoking	Thiocyanate ≥ 90µmol/L	44.0
Hypertension	MAP≥ 110 mm Hg	15.5
Obesity	BMI ≥ 30 kg/m^2	14.3
Hyperglycemia	Glycohemoglobin ≥ 8%	4.3

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Atherosclerosis in Children

- Although the atherogenic process begins in the first decade of life there is a long preclinical phase.
- Intervention beginning in childhood is expected to have the maximum potential for preventing and reversing atherosclerosis.

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Pathogenesis and Pathology of Atherosclerosis

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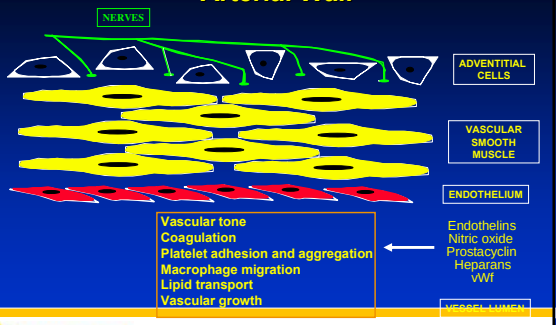
Arterial Wall



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Arterial Endothelium

- Vasoconstrictor-Proliferative.
- Vasodilator-Antiproliferative.

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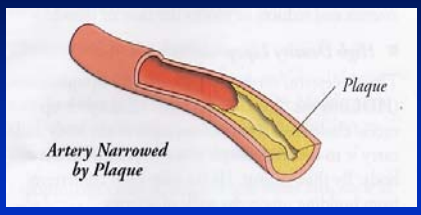
Pathology



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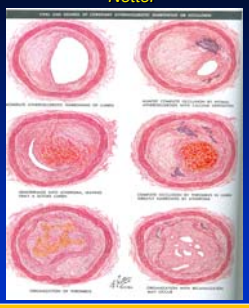
Pathology

Netter



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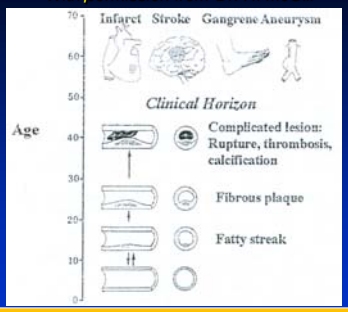
Atherosclerosis Natural History

With permission from Dr. H. McGill



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Reduction of Coronary Artery Disease

- **Cannot be achieved if adults only are targeted for prevention as the disease is end stage by then.**

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Atherosclerosis

DEADLY QUARTET is likely to expedite the disease process.

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Lifetime Risk of Childhood Obesity
Evidence

- **In a large cohort of children born in Denmark and followed for over 5 million person-years, *a higher BMI during childhood* was associated with increased risk of coronary artery disease in adulthood.**

Baker JL, Olsen LW, Serenson TIA. Childhood Body-Mass Index and the Risk of Coronary Heart Disease in Adulthood. N Engl J Med. 2007;357:2329-2337.

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Lifetime Risk of Childhood Obesity
Evidence

- A follow up of the Harvard Growth Study of 1922 to 1935 showed that being *overweight in adolescence* resulted in a relative risk of coronary artery disease mortality of 2.3, independent of adult weight after 55 years of follow-up.

Must A. Jacques PF. Dallal GE. Bajema CJ. Dietz WH. Long-term morbidity and mortality of overweight adolescents. A follow-up of the Harvard Growth Study of 1922 to 1935. N Engl J Med. 1992;327:1350-1355.

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Lifetime Risk of Childhood Obesity
Evidence

- A British study involving a 57 year follow up of a cohort also confirmed that all-cause and cardiovascular mortality were associated with *childhood BMI when even >75th percentile.*

Gunnell DJ, Frankel SJ, Nanchahal K, Peters TJ, Davey Smith G. Childhood obesity and adult cardiovascular mortality: a 57-y follow-up study based on the Boyd Orr cohort. Am J Clin Nutr. 1998;67:1111-1118.

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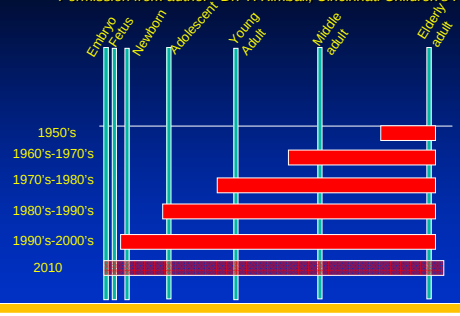
Need for Medical Involvement In Coronary Heart Disease As a Function of Era and Patient Life Stage

Permission from author - Dr. T. Kimball, Cincinnati Children's Hospital



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Immutable Risk Factors for Atherosclerosis

- **Age.**
- **Male sex.**
- **Family History.**

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Mutable Risk Factors for Atherosclerosis Modifiable Risk Factors

Source – National Geographic, February 2007

HEART ATTACK RISK FACTORS

- **Unhealthy combination of "good" and "bad" cholesterols** quadruples the risk.
- **Diabetes** quadruples the risk for women and doubles it for men.
- **Hypertension** nearly triples the risk for men and doubles it for women.
- **Stress and depression** almost triple the risk.
- **Healthy diet** decreases the risk by close to 30 percent.
- **Abdominal obesity** more than doubles the risk.
- **Lack of exercise** increases the risk by about 20 percent.
- **Smoking** can double, even triple, the risk.

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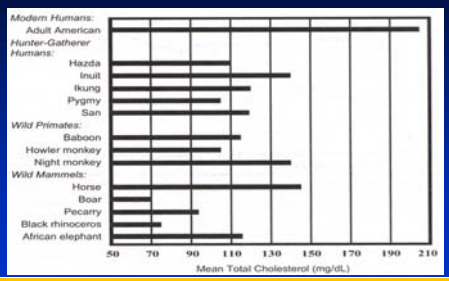
Cholesterol Levels in Various Species

Eur J Clin Nutr 2002;56:S42-52



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Dyslipidemia

- High Total or LDL Cholesterol.
- Low HDL Cholesterol.
- High Triglycerides.
- High VLDL Cholesterol.

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Optimal Cholesterol Levels

- Total Cholesterol – < 170 mg/dl.
- LDL - atherogenic. Makes up majority of TC – < 110 mg/dl.
- HDL - non atherogenic. Made in liver and small intestine. Makes up 25% of TC. Transports surplus cholesterol back to liver and out of body – ≥ 45 mg/dl.
- VLDL - formed in liver, helps transport triglyceride from liver to fat cells.
- Triglycerides are the main storage form of fatty acids - < 100 mg/dl.

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Dyslipidemia Causes

Inherited Disorders of Lipid Metabolism

- Familial Dyslipidemia – 1 in 400.
  - TC > 300 mg%, LDL >240 mg%.
  - Premature onset of coronary artery disease.

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Dyslipidemia - Diet and Lifestyle *AKA* Obesity

- Childhood obesity and overweight – 1 in 3.
- Premature onset of coronary artery disease likely - ? more likely.

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Dyslipidemia - Diet and Lifestyle *AKA* Obesity

- High fat, low fiber foods.
- Fast foods.
- Sugar consumption – pop, orange juice.
- Portion sizes.
- Sedentary life style.
- Behavioral, psychological, cultural aspects of eating.
- Hunger and eating.

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Dyslipidemia Causes – Diseases

- Diabetes.
- Hypothyroidism.
- Nephrotic syndrome.
- Renal failure.
- Storage diseases.
- Liver disease – cirrhosis, biliary atresia.

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Dyslipidemia Causes – Drugs

- Steroids.
- Retinoic acid.
- Thiazides.
- Anticonvulsants.
- Beta blockers.
- Contraceptives.
- Alcohol.
- Psychotropics.

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Risk Stratification beyond risk factors?

- Conventional cardiovascular risk factors explain only up to 50% incidence of heart disease and strokes.
- Unknown risks ??

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Risk Stratification beyond risk factors?

- Risk factor assessment alone may not be entirely sound in predicting atherosclerosis as at every risk factor level there is variation in amount of atherosclerosis due to -
  - Genetic factors.
  - Risk factor interaction.
  - Duration of exposure.

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A tool that assesses "end organ damage" may be useful.

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Risk Stratification beyond risk factors?

- Children do not have symptoms of coronary artery disease.
- Sub clinical Markers of Atherosclerosis – (surrogate markers).
- Increased carotid artery intima-media thickness.

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Atherosclerosis in Children Summary

1. Atherosclerosis is a progressive, degenerative disease beginning in childhood BUT SILENT UNTIL ADVANCED.
2. Assessing sub clinical markers should aid in evaluating "end organ damage" as these markers represent the end result of all risk factor exposures.
3. Atherosclerosis may be more prevalent and clinical effects may be manifesting earlier due to the prevailing obesity epidemic.

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"A man is as old as his arteries."

Dr. Thomas Sydenham

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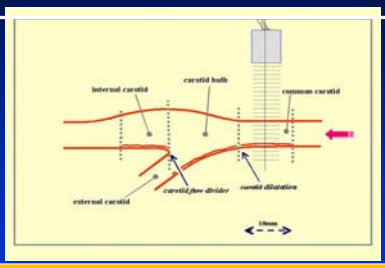
Carotid Artery Intima Media Thickness



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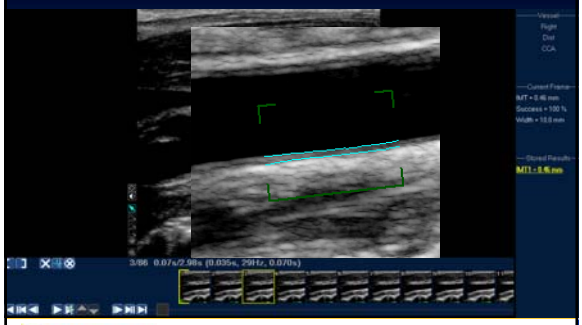

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Carotid Artery Intima Media Thickness

- Non invasive.
- Easy to perform.
- No radiation.
- Can be repeated.
- Inexpensive.

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Carotid Artery Intima-Media Thickness

- Carotid artery intima-media thickness is an independent predictor of future cardiovascular events, heart attacks, strokes and death.
- Progression in carotid artery intima-media thickness predicted events better than risk factor measurements.
- "Window to the coronary arteries".

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Population based prospective studies affirming prognostic value of carotid artery intima media thickness assessment

- ARIC Atherosclerosis Risk in Communities - 12,841 subjects.
- CHS Cardiovascular Health Study - 4476 subjects.
- Increased carotid artery intima media thickness was associated with increased risk of myocardial infarction, stroke or death even after adjusting for other risk factors.

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Carotid Artery Intima-Media Thickness in Childhood

Epidemiological Studies

- Bogalusa study and Muscatine study – High childhood body mass index and high childhood cholesterol levels resulted in increased carotid artery intima media thickness in young adulthood.

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Carotid artery intima-media thickness in Childhood

Clinical Observational and Case Control Studies

- Hypercholesterolemia.
- Hypertension.
- Diabetes.
- Obesity.
- Tobacco smoke exposure.

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High Risk Child Population

- Familial Dyslipidemia.
- Obese children with atherosclerosis promoting risk factors.
- Obese and Familial Dyslipidemia – Increasing.

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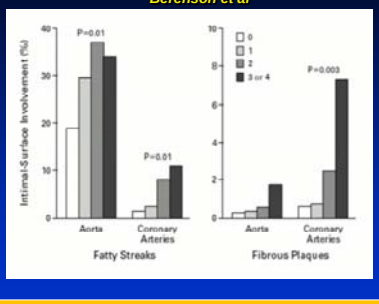
Multiple risk factors – Deadly Quartet Effect

Berenson et al



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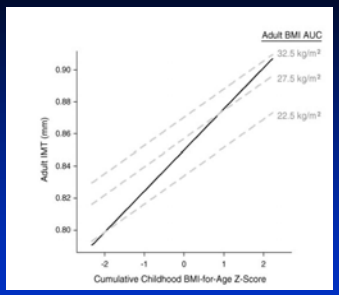
Cumulative burden of childhood obesity

Berenson et al



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"Vascular age" vs. "Chronological age"

- *Le J, Zhang D, Menees S, Chen J, Raghuveer G. "Vascular Age" is advanced in children with atherosclerosis promoting risk factors. Circ Cardiovasc Imaging. 2010;3:8-14.*

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Aim

- **To delineate if children with obesity and atherosclerosis promoting risk factors and children with familial dyslipidemia had premature aging of their arteries.**

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Methods

- **"Vascular age" was evaluated by comparing the child's CIMT against percentile data for a race and sex matched 45 year old.**

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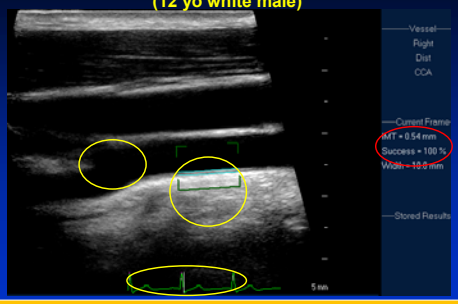
Carotid Artery Ultrasound

(12 yo white male)



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CIMT 0.54 mm in a12 year old white male

Howard G, Sharrett AR, Heiss G, et al. Carotid artery intimal-media thickness distribution in general populations as evaluated by B-mode ultrasound. Stroke. 1993; 24: 1297–1304.

White Men			
Percentile	45 yo	55 yo	65 yo
P05	0.40	0.45	0.50
P10	0.44	0.49	0.56
P25	0.50	0.57	0.65
P50	0.57	0.66	0.76
P75	0.66	0.77	0.90
P90	0.75	0.88	1.07
P95	0.83	0.96	1.25

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Results

	Obese n=40	Familial dyslipidemic n=30
▪ Age (years)	13.2 ± 2.9	12.7 ± 3.8
▪ White n (%)	35 (88)	27 (90)
▪ Male n (%)	23 (58)	11 (37)

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Results

	Obese n=40	Familial dyslipidemic n=30
Family History n (%)	29 (73%)	29 (97%)
Tobacco smoke n (%)	18 (45%)	7 (23%)
BMI (kg/m2)	30 ± 4	20 ± 3*
Systolic BP (mmHg)	124 ± 14	114 ± 13*
Diastolic BP (mmHg)	66 ± 7	64 ± 8

*p<0.05

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Lipid Profile and Insulin

	Obese n=40	Familial dyslipidemic n=30
TC (mg/dL)	204 ± 42	249 ± 65*
LDL (mg/dL)	130 ± 66	175 ± 66*
HDL (mg/dL)	42 ± 11	52 ± 14*
TG (mg/dL)	187 ± 121	104 ± 53*
Insulin (uIU/ml)	16 ± 8	9 ± 4*

*p<0.05

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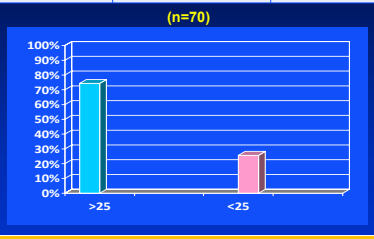
Vascular Age	Number	Percentage
>25	52	74.3%
<25	18	25.7%



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Vascular Age

	Obese	Familial dyslipidemic
▪ ≥25th percentile n (%)	30 (75)	22 (73)

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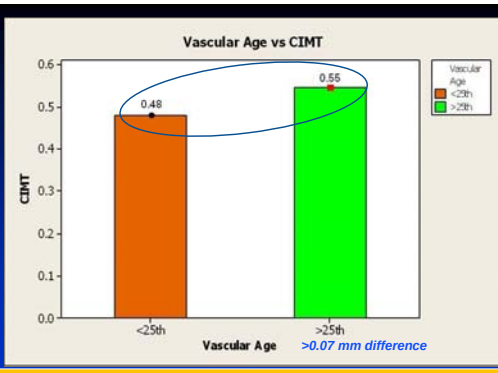

>0.07 mm difference

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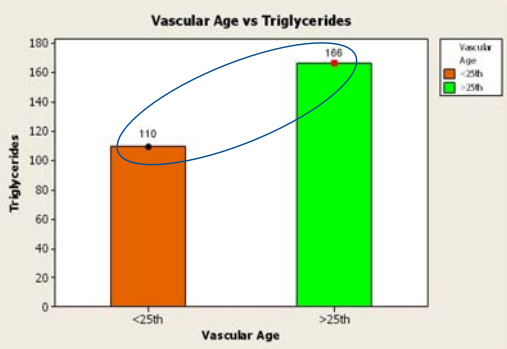

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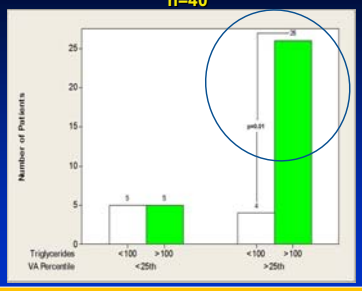
Vascular Age and Triglycerides

BMI ≥ 95th percentile
n=40



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Mutable Atherosclerosis Promoting Risk Factors in Obese Children

- Obesity.
- Systolic Blood Pressure.
- Total Cholesterol.
- Triglyceride.
- HDL Cholesterol.
- Insulin.
- Exposure to tobacco smoke.

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Mutable Atherosclerosis Promoting Risk Factors in Obese Children

- 75% had > 3 Risk Factors.

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CIMT vs. # of Atherosclerosis Promoting Risk Factors

Risk Factor #	# of patients	CIMT(mm)	SD (mm)
▪ >3	30	0.54	0.06
▪ ≤3	10	0.53	0.03

P 0.07

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Conclusions

- "Vascular age" is similarly advanced in children with obesity and atherosclerosis promoting risk factors and in children with familial dyslipidemia.
- Estimation of "vascular age" may help further stratify children who are at high risk for developing premature atherosclerosis.
- These children may need intensive management including pharmacotherapy for risk factor modification.

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Do Clinic Based Interventions Help?

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Ashley Sherman MS†
Hongying Dai PhD†
Dr. Geetha Raghuveer, MD MPH†*

†Children's Mercy Hospital – Dept of Cardiology
*University of Missouri-Kansas City School of Medicine

- BMI and BMI Z Scores.
- Risk Factor Measures.
- Vascular Measures.

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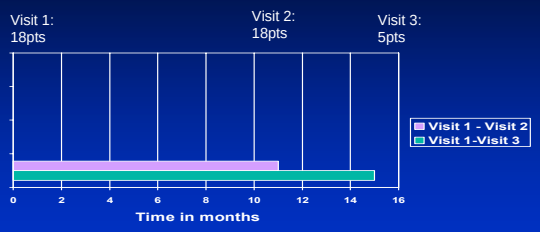
Non Obese Dyslipidemic Children



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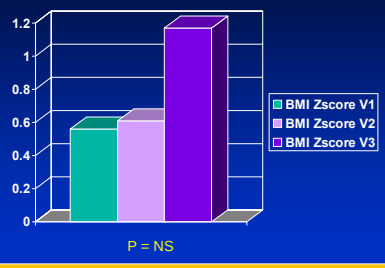
BMI Z Score



P = NS

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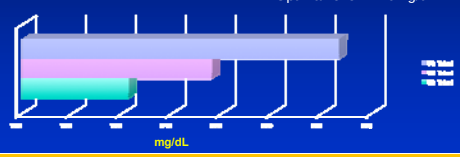
Total Cholesterol (mg/dL)

Visit 1	273
Visit 2	248
Visit 3	231

Optimal level <170mg/dL



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P = 0.08

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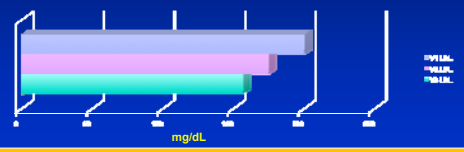
LDL (mg/dL)

Visit 1	200
Visit 2	175
Visit 3	157

Optimal level <110mg/dL



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P = 0.10

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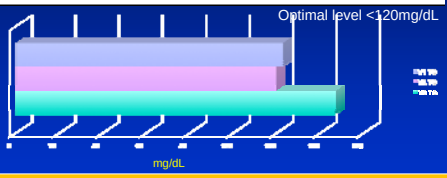
Triglycerides (mg/dL)

Visit 1	123
Visit 2	119
Visit 3	146

Optimal level <120mg/dL



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P = NS

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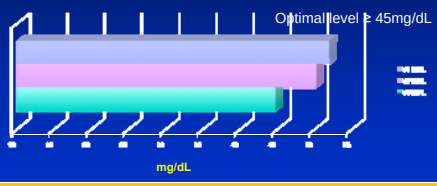
HDL (mg/dL)

Visit 1	52
Visit 2	50
Visit 3	45

Optimal level ≥ 45mg/dL



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P = NS

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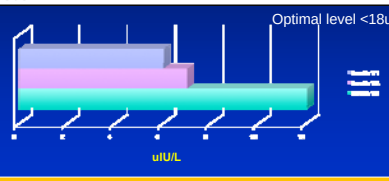
Insulin (uIU/mL)

Visit 1	6
Visit 2	7
Visit 3	12

Optimal level <18uIU/mL



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P = 0.09

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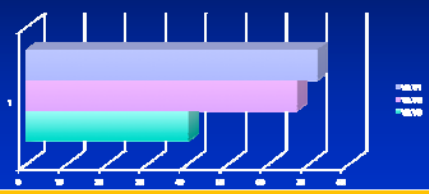
Advanced Vascular Age

Visit 1	72%
Visit 2	67%
Visit 3	40%



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P = NS

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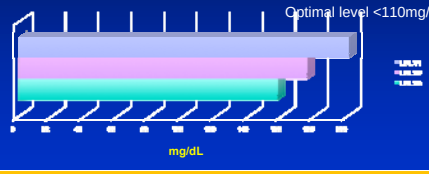
LDL of Children Treated with Statins (mg/dL)

Visit 1	200
Visit 2	175
Visit 3	157

Optimal level <110mg/dL



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P = 0.01

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Non-Obese Statin Children vs. Non-Obese Non-Statin Children

Risk Factor	P Value Stain	P Value Non-Statin
Total Cholesterol	0.01	0.86
LDL	0.01	0.88

	Statin	Non-Statin
Vascular Age Visit 1	6 (67%) n=9	7 (78%) n=9
Vascular Age Visit 2	5 (56%) n=9	7 (78%) n=9
Vascular Age Visit 3	0 (0%) n=2	2 (67%) n=3

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P=NS

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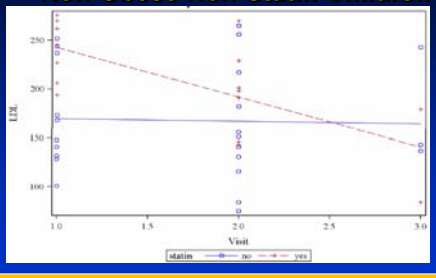
Non-Obese Statin Children vs. Non-Obese Non-Statin Children



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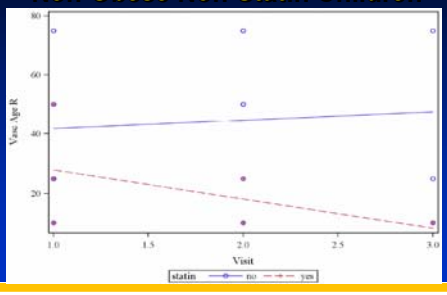
Non-Obese Statin Children vs. Non-Obese Non-Statin Children



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Conclusions

- Overtime, there was an emergence of a second disease i.e. obesity and obesity associated risk factors in the group of non obese dyslipidemic children.
- Although there was no improvement in CIMT, the proportion whose vascular age was similar to that of a race and sex matched 45 year old decreased over time.

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Conclusions

- We speculate that clinic based interventions, including the use of statins and its effect on the vasculature might have dampened the ill affects of the superimposed obesity associated vascular damage.
- The emergence of obesity in this population is a concern.

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Obese Children with Dyslipidemia

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Obese Children with Dyslipidemia

- Each child seen twice and 11 of 23 seen three times.

Total Number of Children	23	23	11
Time Interval	10.1 ± 5.5 months		
	18.6 ± 3.1 months		

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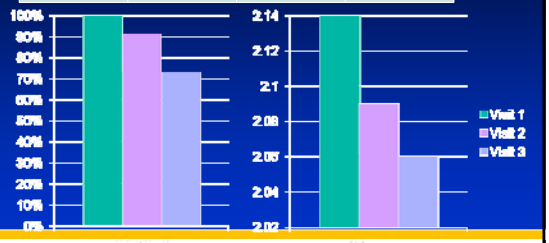
BMI

	Visit 1	Visit 2	Visit 3	
BMI	28.78 ± 4.42	29.28 ± 4.82	30.28 ± 5.25	P=NS
BMI ≥95	23 (100%)	21 (91%)	8 (73%)	P=0.03
BMI z-score	2.14 ± 0.44	2.09 ± 0.41	2.06 ± 0.47	P=NS



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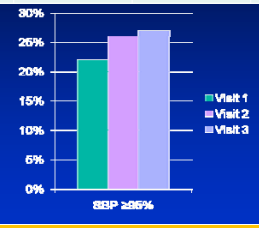
Systolic Blood Pressure (SBP mmHg)

	Visit 1	Visit 2	Visit 3	
SBP	118 ± 11	117 ± 9	122 ± 7	P=NS
SBP ≥95%	22%	26%	27%	P=NS



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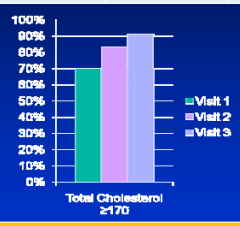
Total Cholesterol (mg/dl)

	Visit 1	Visit 2	Visit 3	
Total Chol	210 ± 55	212 ± 56	210 ± 39	P=NS
Total Chol ≥170	70%	83%	91%	P=NS



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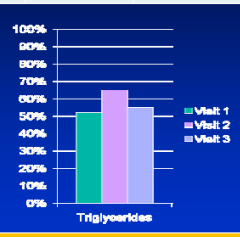
Triglycerides (mg/dl)

	Visit 1	Visit 2	Visit 3
Trigs	146 ± 86	154 ± 84	158 ± 118
Trigs ≥120	52%	65%	55%



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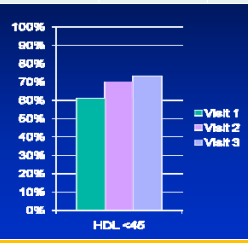
HDL (mg/dl)

	Visit 1	Visit 2	Visit 3	
HDL	42 ± 15	42 ± 12	43 ± 13	P=NS
HDL <45	61%	70%	73%	P=NS



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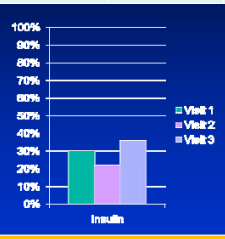
Insulin (uIU/ml)

	Visit 1	Visit 2	Visit 3	
Insulin	17 ± 5	16 ± 9	19 ± 16	P=NS
Insulin ≥18	30%	22%	36%	P=NS



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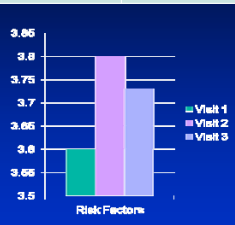
Risk Factors Score out of 7

	Visit 1	Visit 2	Visit 3
Risk Factor Score out of 7	3.6 ± 1.1	3.8 ± 1.2	3.7 ± 1.8



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Advanced Vascular Age

	Visit 1	Visit 2	Visit 3
Vascular Age ≥25*	18 (78%)	17 (74%)	10 (91%)

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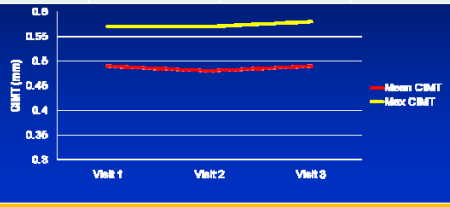
CIMT

	Visit 1	Visit 2	Visit 3
Mean CIMT (mm)	0.49 ± 0.04	0.48 ± 0.03	0.49 ± 0.04
Max CIMT (mm)	0.57 ± 0.06	0.57 ± 0.05	0.58 ± 0.08



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OBESE VS NON-OBESE

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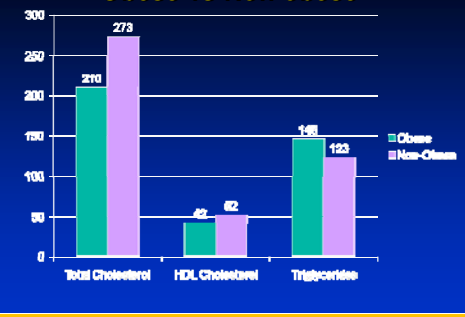
Obese vs Non-obese



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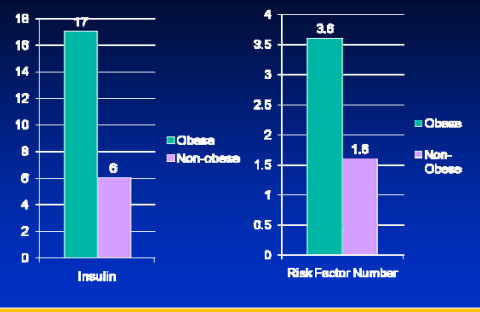
Obese vs Non-obese



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Conclusion

- Decrease in percentage of children who were obese over time.
- No significant change in number or intensity of risk factors over time.
- No worsening of CIMT or vascular age over time.

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How can we Improve?

- Resources.
- Compliance.
- Phone calls/closer follow up.
- Schools.

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Therapeutic Life Style Changes

- Liquid calories vs. water.
- Breakfast (protein, good fat and fiber).
- Colorful foods (fruits and vegetables).
- Source of calcium (skim milk, low fat cheese).
- Screen time.
- Sleep time – 8 hours/day.

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Therapeutic Life Style Changes
Exercise and Activity

- Family deal.
- Exercise 30 minutes at least every day.
- Positive emphasis on cardiovascular health. Avoid negative approach and labeling.
- Schools – Major influence in Diet and Activity.

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Drug Therapy

- 8 - 10 years.
- LDL > 190 mg/dl or,
- LDL > 160 mg/dl associated with family history of premature coronary artery disease (<55 years of age) or child with 2 other risk factors (diabetes, hypertension, obesity, low HDL, smoking).
  - *Statins – studies short-term, approved by FDA for children.*

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Statins

- 35 to 40% reduction in LDL.
- Generally well tolerated.
- Need to monitor liver enzymes and muscle enzymes.
- Effect on growth and puberty – so far safe.
- Teratogenic effects – contraception for girls.

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Usefulness of Intervention in Children?

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Intervention in Children Reduces Risk Factors.

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Intervention in Children Improves Their Vascular Health

- Few pediatric reports have described short-term, favorable changes in vascular function *(de Jongh et al, Woo et al, Meyer et al)* and structure *(Wiegman et al, Meyer et al)* after life style alterations or statin therapy in children with atherosclerosis promoting risk factors.

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Intervention in Children Changes Long Term Outcome

There will likely be no controlled trial comparing the effect of risk reduction beginning in childhood on the subsequent development of atherosclerotic heart disease.

But our data and other epidemiologic, observational, circumstantial data indicate that prevention of atherosclerotic disease should begin in the first decade of life.

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Integrated CV Health Schedule

- Family History.
- Smoking.
- Diet.
- Growth.
- Lipids – Universal screen at 9-11 years.
- BP – Annual BP from 3 years.
- Activity – 1 hour Screen time ≤ 2 hours per day.
- Diabetes – Insulin at 9 -11 years.

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Children are our future

- Potential.
- Purpose.
- Passion.
- Perseverance.
- Patience.
- Protein, Color, Complex Carbs and Good Fats – Paleolithic Genome – Hunter Gatherer Diet.

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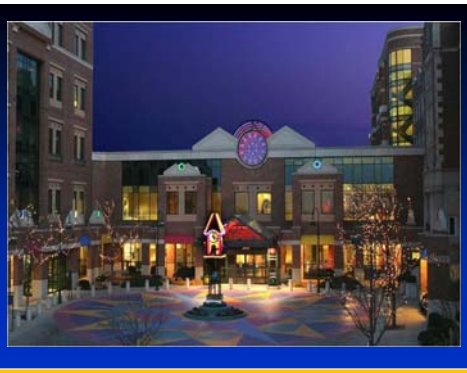

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