Metabolic Alterations in Children with Obstructive Sleep Apnea

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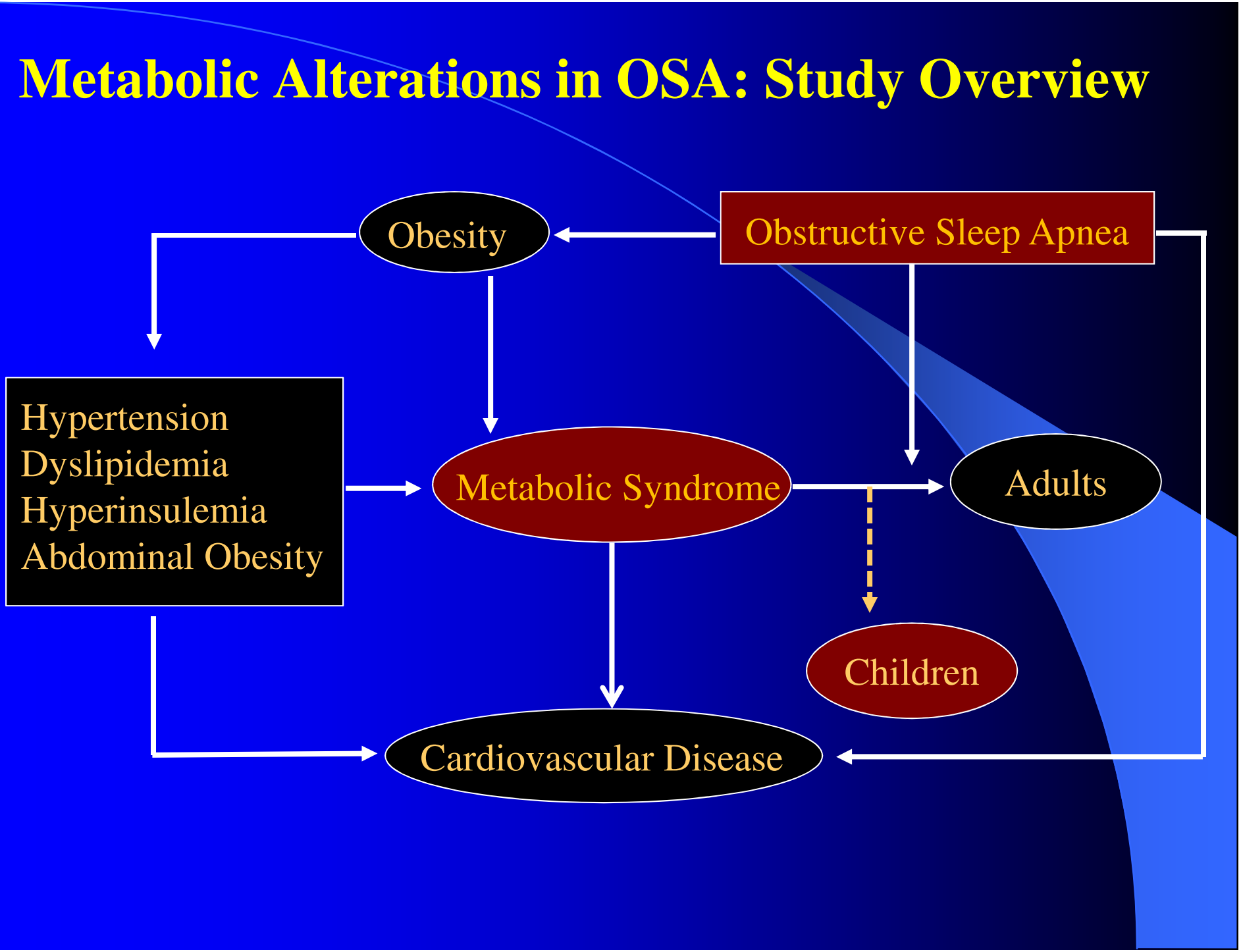
Disclosures: None

Metabolic Alterations in OSA: Study Overview



Introduction

- Childhood Obesity

6-11 years	1980	7%
	2012	18%
12–19 years	1980	5%
	2012	21%

CDC, Atlanta

Introduction

- Annual medical cost of obesity in the U.S.
  - 2008 - $147 Billion
  - 2012 - $190.2 Billion
  - 21% Annual medical spending
  - Childhood obesity medical cost: $14 billion

Cawley et al, 2012
Marder et al, 2009

Introduction

- OSA – Disorder of breathing during sleep

  Characterized by upper airway collapse that disrupts normal respiratory gas exchange or causes sleep fragmentation.

  (Tripuraneni *et al*, 2013)

- Prevalence of OSA in prepubertal children – 12-14%

  (Bhushan *et al*, 2011; Gozal *et al*, 2008)

- Prevalence of OSA in obese children – 34-36%

  (Canapari *et al*, 2011)

Introduction

- Risk of developing OSA is 4-5 times higher in obese compared to non-obese children
  (Tripuraneni *et al*, 2013; Canapari *et al*, 2011)

- Prevalence of Metabolic syndrome
  - Adults 20%
  - Children 8-10%

(Ferranti *et al*, 2004)

Literature:

Severity of OSA is linked with Metabolic Alterations

- De La Eva RC, 2002 (Children + adolescents)
- Redline S, 2007 (Adolescents)
- Verhulst SL, 2007 (Children)
- Hannon TS, 2011 (Adolescents)

Obesity is linked with Metabolic Alterations

- Arens R, 2011 (Children)
- Kaditis AG, 2005 (Children + adolescents)
- Tauman R, 2005 (Children)
- Nakra N, 2008 (Children + adolescents)

Literature:

- Direct comparisons of these studies are difficult because of
  - Different Inclusion/Exclusion Criteria
  - Differences in overall duration and severity of OSA
  - Different cut-off values for the AHI used to define OSA

Metabolic Alterations in OSA

Hypothesis:

Variations in the components of Metabolic Syndrome (dyslipidemia and insulin resistance) are associated with OSA in young children independent of their BMI z Score.

Objectives:

- Compare differences in metabolic variables and insulin resistance among patients with or without OSA

- To determine if alterations in metabolic variables and insulin resistance in patients with OSA occur independent of their BMI z Score

Metabolic Variables in OSA: Methods

Setting/IRB: Ann & Robert H Lurie Children's Hospital
Pediatric Specialty
Tertiary Care Medical Center

Time line: January, 2010 - December, 2013

Metabolic Variables in OSA: Methods

Total identified: 144

Inclusion Criteria: (n=76)

- Age 2-12 years
- Overnight polysomonography
- Height and Weight (BMI)
- Metabolic Lab Data
  - Lipid panel
  - Glucose
  - Insulin
  - Blood Pressure

Metabolic Variables in OSA: Methods

Exclusion Criteria (n=68)

- Receiving CPAP (n=4)
- Genetic Abnormalities (n=11)
- Craniofacial Anomalies (n=2)
- Organ Transplant Recipients (n=8)
- Diabetics (n=11)
- Multiple Medical Problems (n=6)
- Patients with incomplete or no information on glucose and insulin (n=21)
- Lipid Lowering Meds (n=5)

Metabolic Variables in OSA: Methods

- Polysomnography: Standard overnight hospital based

- Routine lab tests: Lipid Profile
  Blood Glucose level
  Insulin level

- BMI z score Calculation:
  Growth standards
  Online software (Epiinfo)
  www.cdc.gov

Metabolic Variables in OSA: Methods

- Homeostasis Model Assessment (HOMA) calculation:

[Fasting Insulin (μIU/mL) x Fasting blood glucose (mmol/L)/ 22.5]

(Matthews *et al*, 1985)

- Insulin resistance (HOMA-IR):

Gender Specific pre-pubertal cut-offs (Kurtoglu *et al*, 2010)

Boys >2.67

Girls >2.22

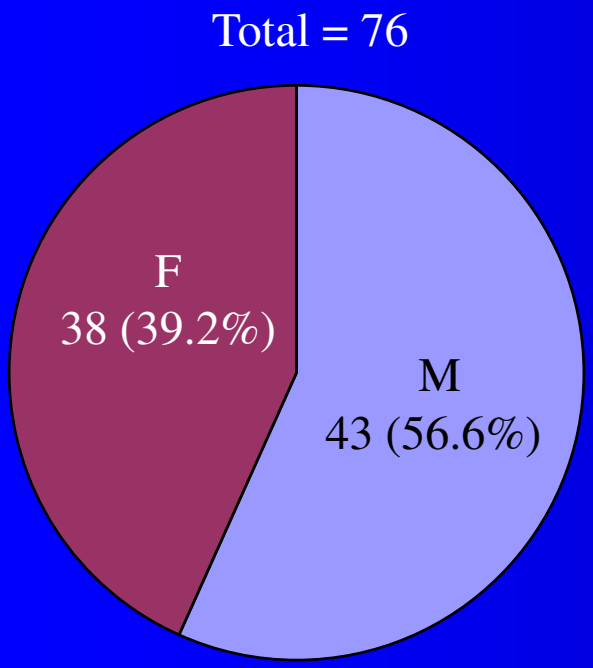
Metabolic Variables in OSA: Definitions

Obesity : BMI z score > 95th percentile

OSA: Mild : AHI between 1 and 4.99/hour
Moderate : AHI between 5 and 9.99/hour
Severe OSA : AHI ≥ 10/hour

No OSA : AHI < 1/hour

Results: Description of Patient Population



- Age 8.1 ± 2.5 (range, 2.4-11.9 years)
- BMI z score 2.8±0.75 (range, 1.7-6.3)
- Obese (100%)

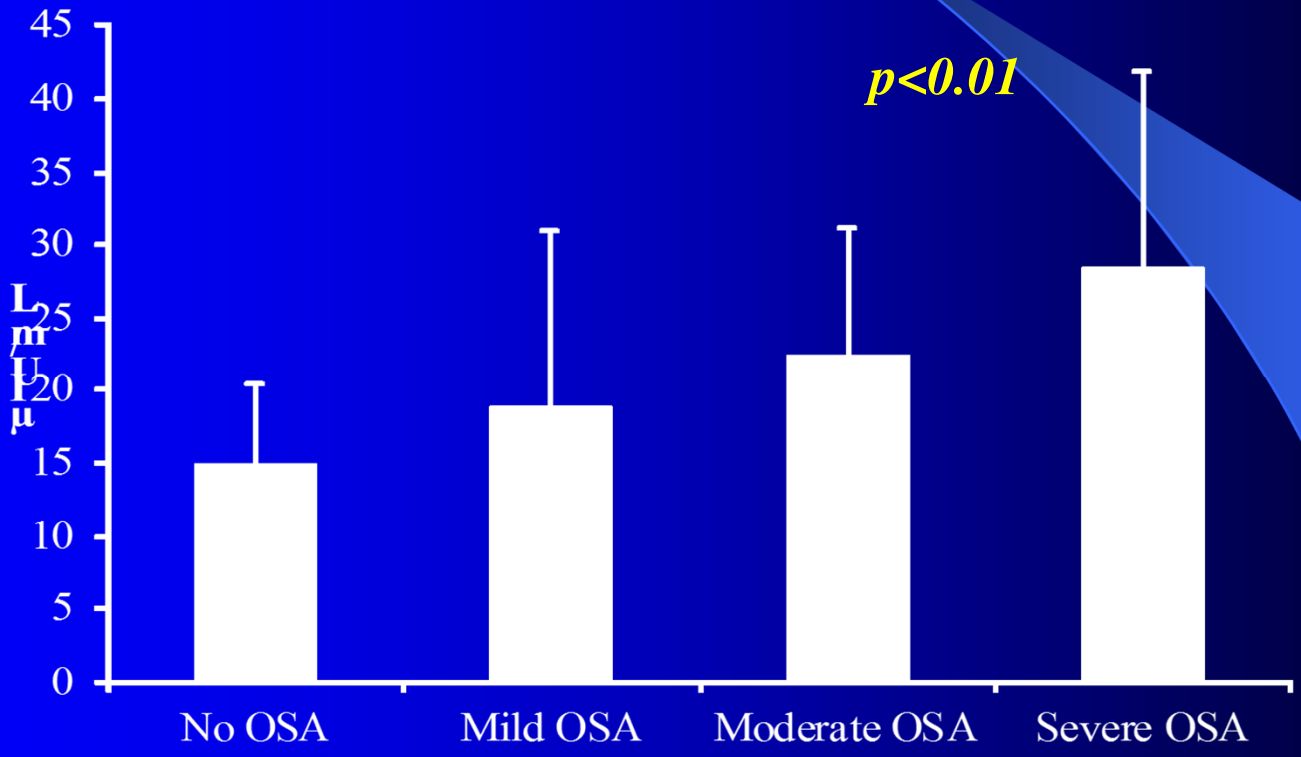
Results: Profile of Age and BMI z Score of Patients Included in the Study

Variables	No OSA (n=22)	Mild OSA (n=27)	Moderate OSA (n=12)	Sever OSA (n=15)	Overall p value (ANOVA)
Age (years)	8.0 ± 2.1	8.6 ± 2.6	8.6 ± 3.1	7.7 ± 2.6	*0.68*
BMI z Score	2.7 ± 0.8	2.7 ± 0.5	2.8 ± 1.2	2.8 ± 0.6	*0.96*

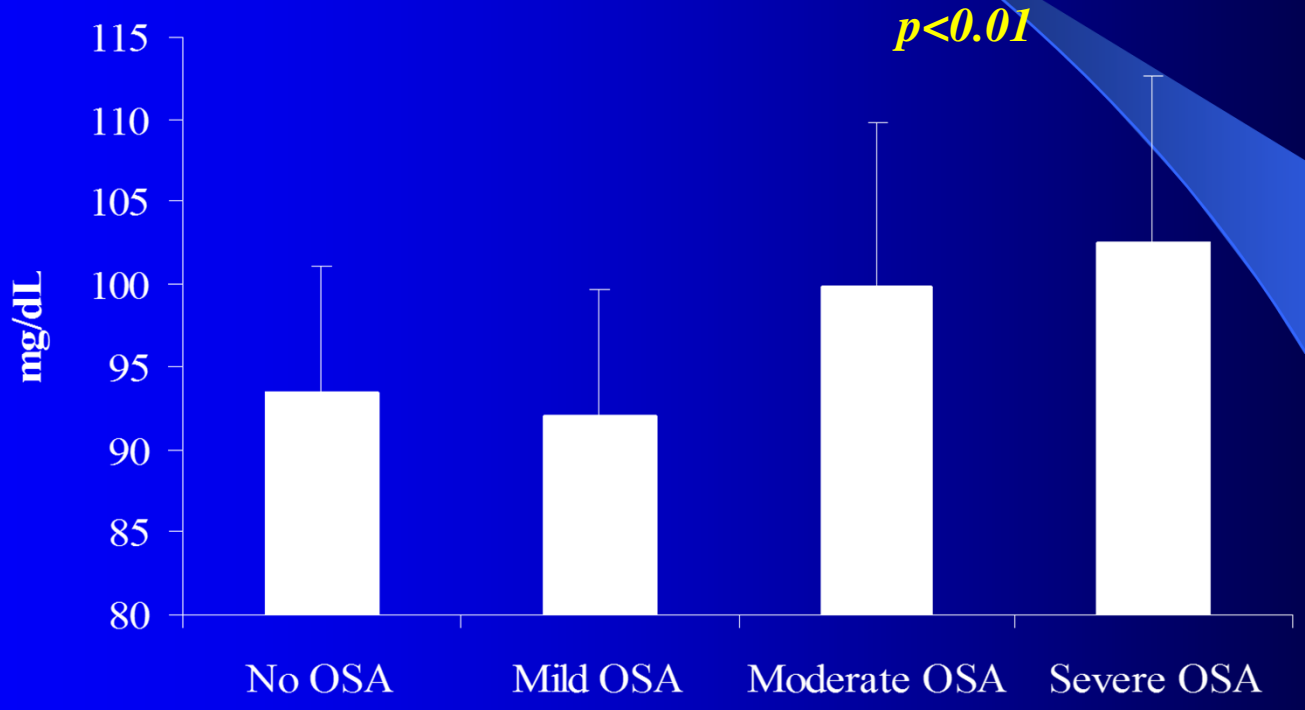
Results: The Relationship between Metabolic Variables and Worsening OSA

- *No Significance (ANOVA)*
  - Total cholesterol (p=0.14)
  - Triglycerides (p=0.86)
  - HDL-C (p=0.99)
  - LDL-C (p=0.13)
  - Diastolic Blood Pressure (p=0.33)
  - Systolic Blood Pressure (p=0.12)

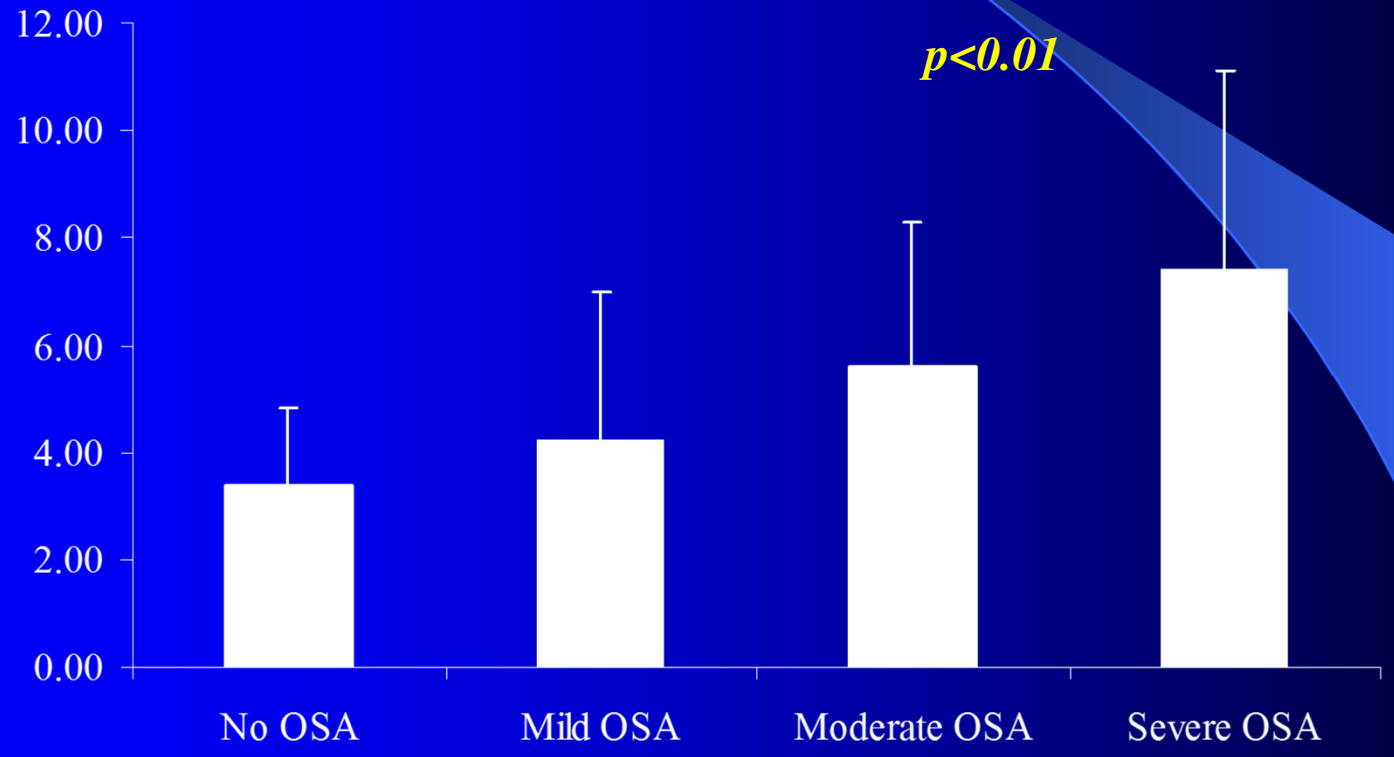
Results: The Relationship between Fasting Insulin, and worsening OSA



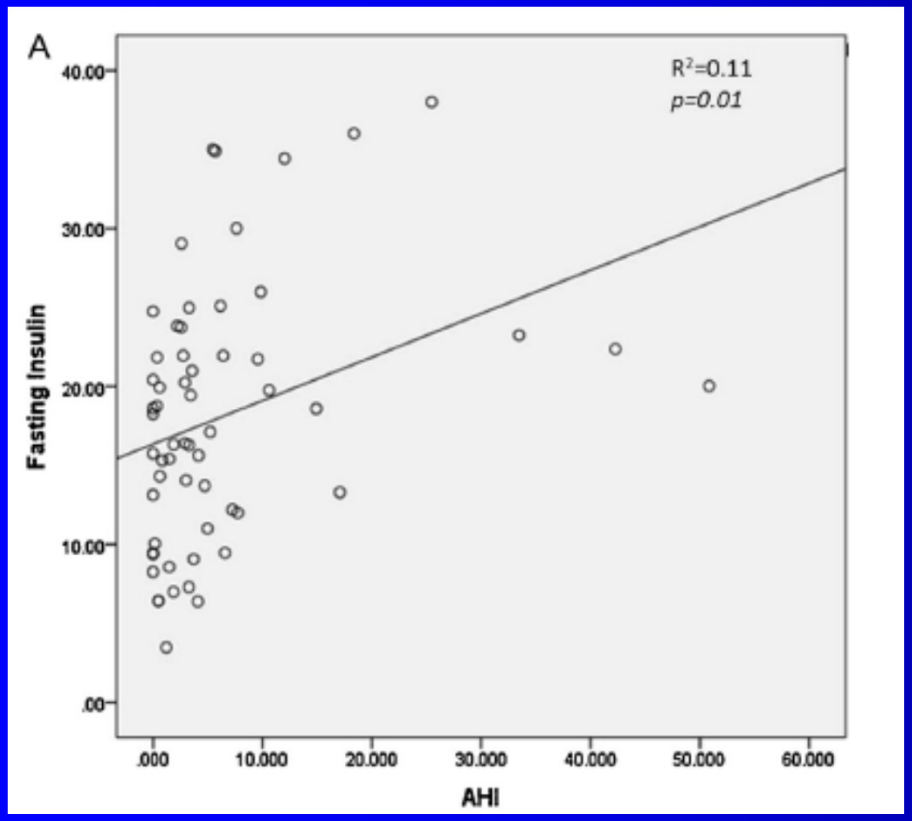
Results: The Relationship between Blood Glucose and worsening OSA

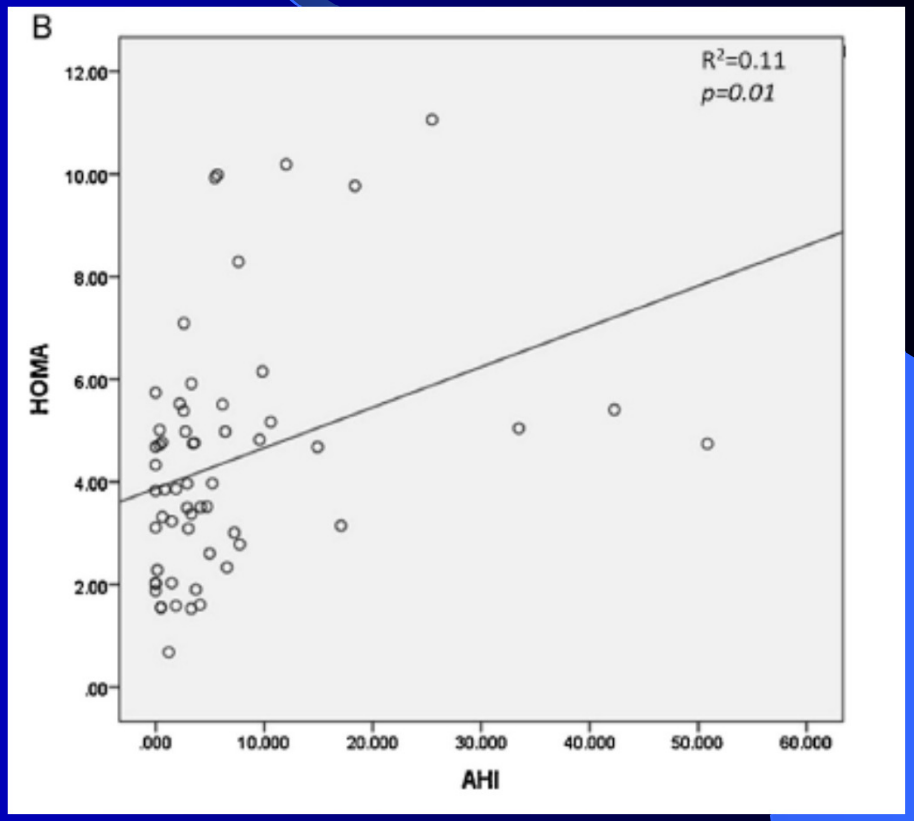


Results: The Relationship between HOMA-IR and worsening OSA



Results: Correlation Analysis Demonstrating the Relationship of AHI to Fasting insulin and HOMA





Results: Linear Regression Analysis Showing Relationship of a Number of Variables to Fasting Insulin and HOMA-IR

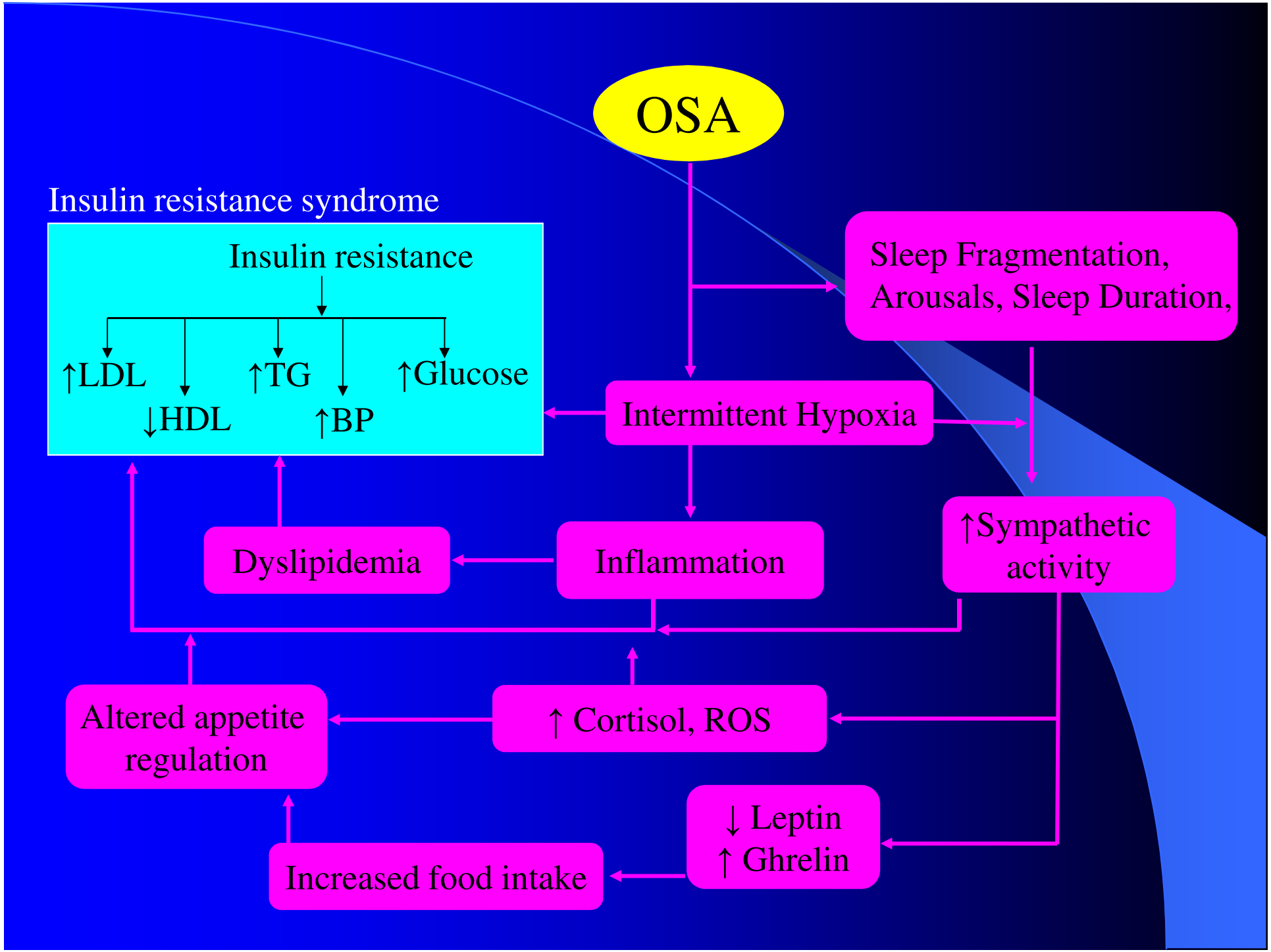
Independent variables	β (Standardized coefficient)	*p value*	β (Standardized coefficient)	*p value*
	Dependent variable: **Fasting Insulin**. Adjusted r^2 =0.07, *p=0.10*		Dependent variable: **HOMA-IR**. Adjusted r^2 =0.08, *p=0.08*	
Age (years)	0.05	0.10	0.05	0.15
Gender	-0.11	0.45	-0.13	0.43
TST (hours)	-0.03	0.65	-0.06	0.43
BMI z Score	0.13	0.17	0.14	0.19
AHI (/hour)	0.02	**0.04**	0.02	**0.03**

Results: Multinomial Logistic Regression Analysis of the Effect Of Moderate and Severe OSA on Elevations in Fasting Insulin and HOMA-IR Independent of BMI z Score

Independent variables		β Coefficient	*p* Value	O.R.
Pseudo R^2 (Snell & Cox) = .318, *p<0.01*				
Moderate OSA	Age (years)	0.06	0.73	1.10
	Gender (male)	-0.90	0.31	0.41
	BMI z Score	**0.02**	0.97	1.01
	Fasting Insulin	**0.10**	**0.05**	**1.10**
Pseudo R^2 (Snell & Cox) = .337, *p<0.001*				
Moderate OSA	Age (years)	0.04	0.81	1.04
	Gender (male)	-1.15	0.21	0.32
	BMI z Score	0.07	0.90	1.07
	HOMA-IR	**0.44**	**0.04**	**1.55**

Results: Multinomial Logistic Regression Analysis of the Effect Of Moderate-Severe OSA on Elevations in Fasting Insulin and HOMA-IR Independent of BMI z Score

Independent variables		β Coefficient	***p* Value**	O.R.
Pseudo R^2 (Snell & Cox) = .318, *p<0.01*				
Severe OSA	Age (years)	-0.11	0.57	0.90
	Gender (male)	-1.92	0.11	0.14
	BMI z Score	0.32	0.57	1.34
	Fasting Insulin	**0.16**	***<0.01***	**1.20**
Pseudo R^2 (Snell & Cox) = .337, *p<0.001*				
Severe OSA	Age (years)	-0.13	0.52	0.88
	Gender (male)	-2.20	0.08	0.11
	BMI z Score	0.40	0.48	1.49
	HOMA-IR	**0.67**	***<0.01***	**1.96**


OSA
Insulin resistance syndrome
Insulin resistance
↑LDL
↓HDL
↑TG
↑BP
↑Glucose
Sleep Fragmentation, Arousals, Sleep Duration,
Intermittent Hypoxia
Dyslipidemia
Inflammation
↑Sympathetic activity
Altered appetite regulation
↑ Cortisol, ROS
↓ Leptin
↑ Ghrelin
Increased food intake

Metabolic Alterations in OSA: Conclusions

- OSA severity is associated with HOMA-IR even after controlling for the Age, BMI and TST in young children

- Components of the Metabolic Syndrome known to be associated with an increased risk for cardiovascular disease, including insulin resistance start developing in childhood, and appear to be related to the severity of OSA.

Metabolic Alterations in OSA: Conclusions

- Further studies are required to determine the effect of interventions (like T&A/CPAP/weight reduction/exercise training/dietary changes) on glucose levels and insulin resistance.

Challenge

- Lack of standard definition of OSA and Metabolic syndrome *per se* in pediatric population

Suggested Solution

- We need to conduct an extensive literature survey and propose consensus for OSA

Metabolic Alterations in OSA: References

- Redline S, Storfer-Isser A, Rosen CL, et al. Association between metabolic syndrome and sleep-disordered breathing in adolescents. *Am J Respir Crit Care Med* Aug 15 2007;176(4):401-408.

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- Tauman R, O'Brien LM, Ivanenko A, Gozal D. Obesity rather than severity of sleep-disordered breathing as the major determinant of insulin resistance and altered lipidemia in snoring children. *Pediatrics* Jul 2005;116(1):e66-73.

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