Sant Joan de Déu

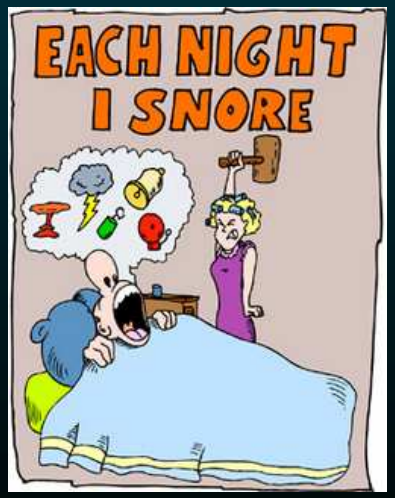
HOSPITAL MATERNOINFANTIL - UNIVERSITAT DE BARCELONA

MARCADORES BIOLÓGICOS Y GENÉTICOS DEL SAHS INFANTIL

Dr. Oscar Sans Capdevila
UNITAT TRASTORNS DEL SON
HOSPITAL SANT JOAN DE DÉU
BARCELONA

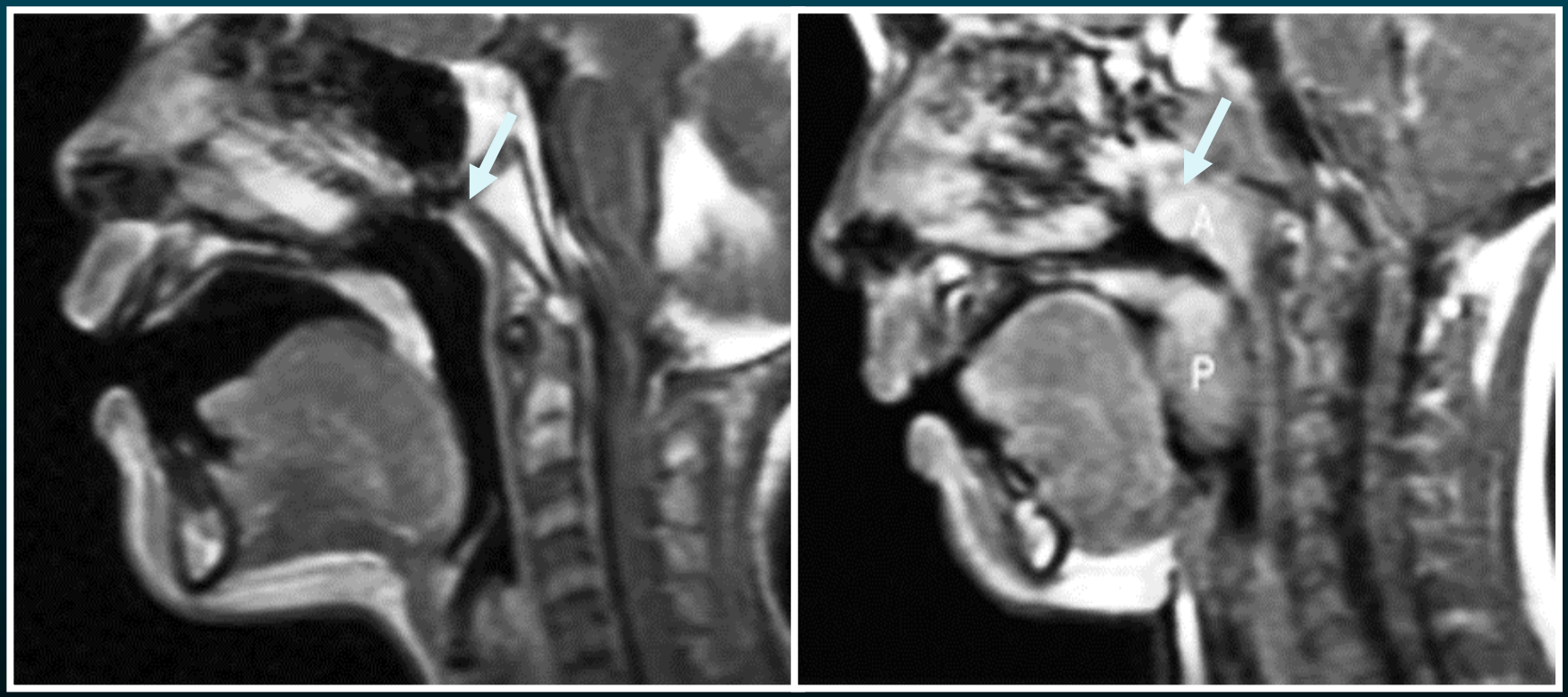
Definición del Sleep Disordered Breathing (SDB)

SDB : hipoxia Intermitente (IH), hipercapnia episódica, y fragmentación de sueño.



Normal

Enlarged



CONTINUUM DEL SDB EN NIÑOS

RONCADOR I

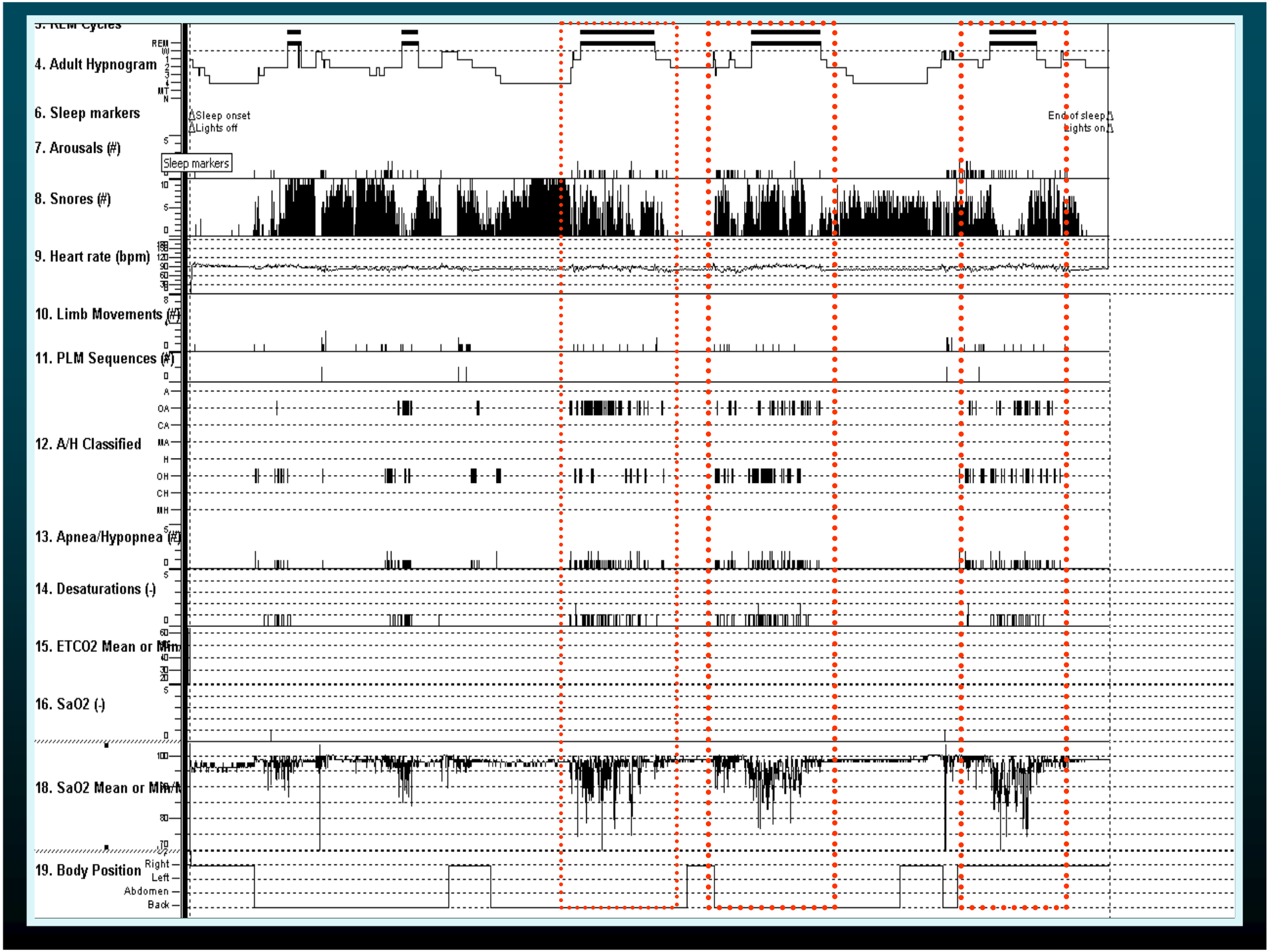
~10%

AHOS 2-3%

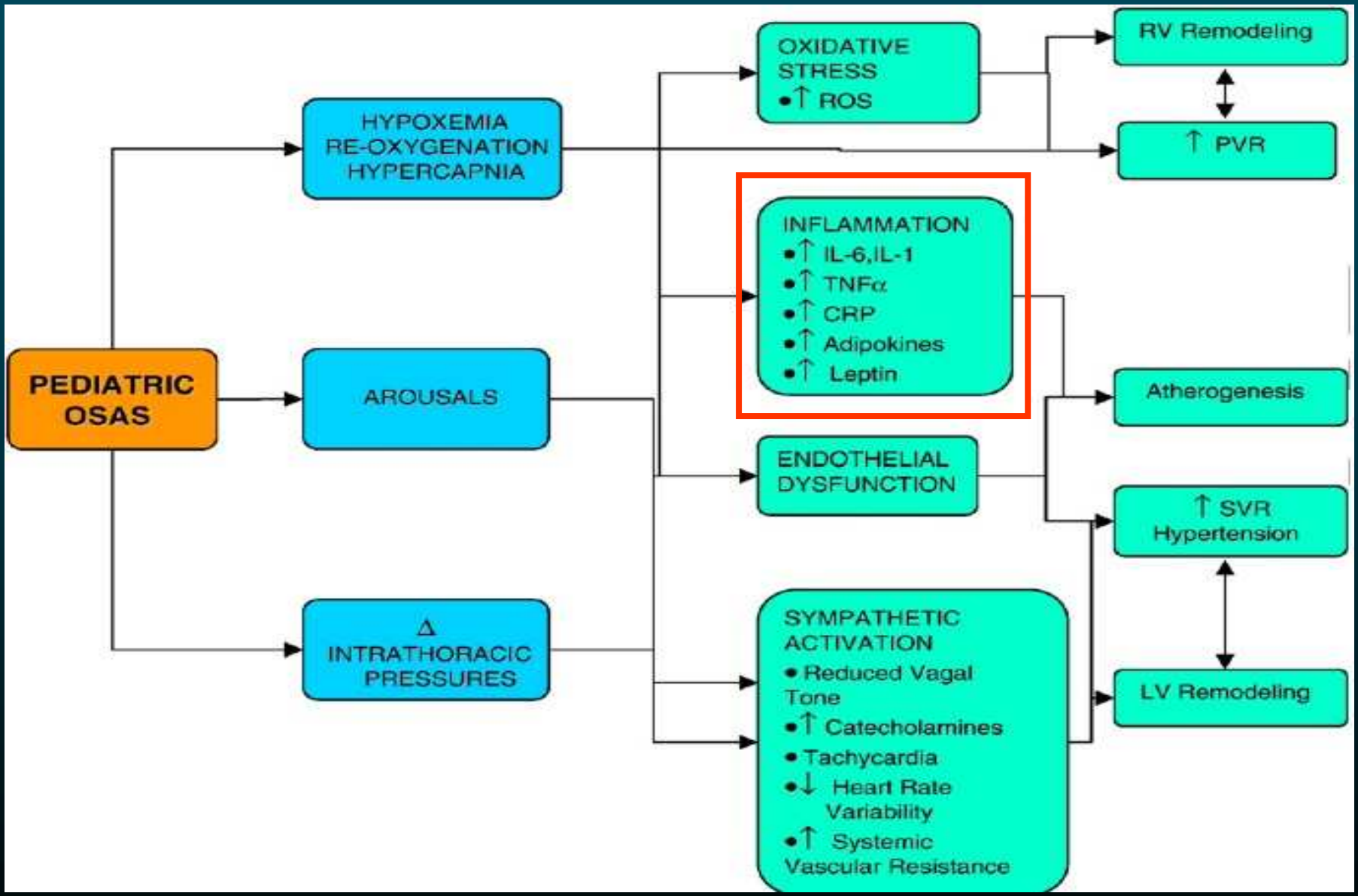
GRA

Minima / Parcial

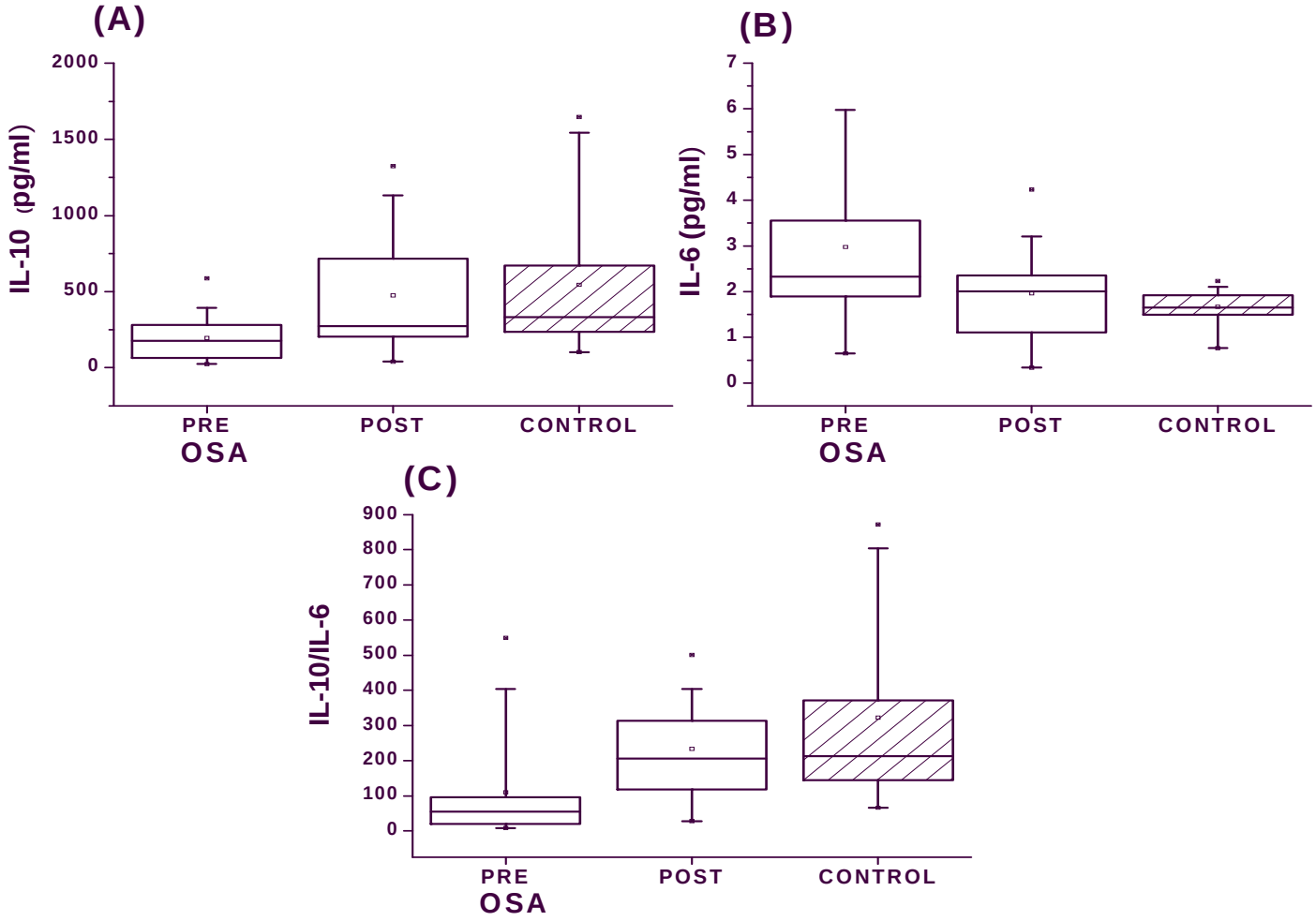
Máxima /Completa


5. REM Cycles
4. Adult Hypnogram
REM
W
1
2
3
4
MT
N
6. Sleep markers
Sleep onset
Lights off
End of sleep
Lights on
7. Arousals (#)
Sleep markers
8. Snores (#)
9. Heart rate (bpm)
10. Limb Movements (#)
11. PLM Sequences (#)
12. A/H Classified
A
OA
CA
MA
H
OH
CH
MH
13. Apnea/Hypopnea (#)
14. Desaturations (-)
15. ETCO2 Mean or Min
16. SaO2 (-)
18. SaO2 Mean or Min
19. Body Position
Right
Left
Abdomen
Back

Cardiovascular Morbidities of OSA



IL-6 and IL-10

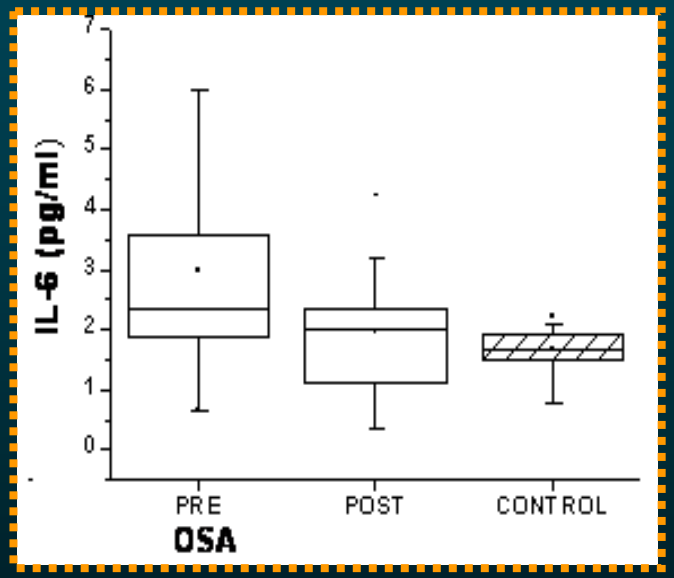


Gozal et al., 2007

Evidence for systemic inflammation ,IL6 and IL10 in non-obese children with OSA before and after T & A

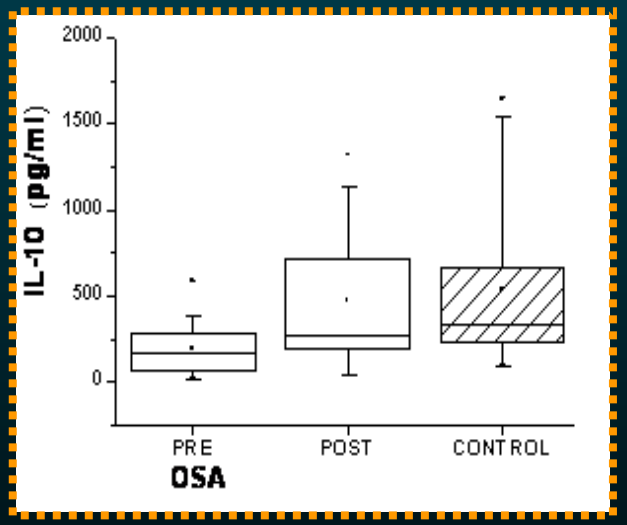
n=20
Non-ob, OSA

⬆ IL-6
Pro-Inflammatory



A

⬇ IL-10
Anti-Inflammatory



B

Gozal et al, Sleep Med 2008

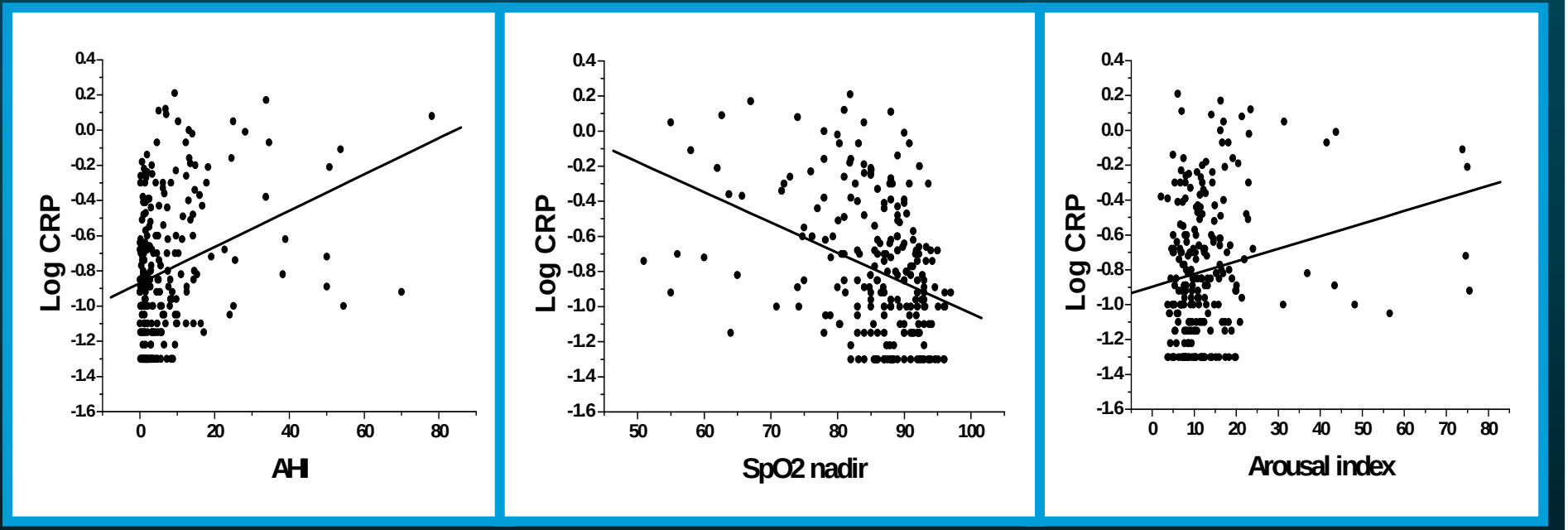
C-Reactive Protein

- Produced by the liver in response to upstream IL-6 activity.
- Is an independent marker of future cardiovascular events.
- Actively participates in atheromatous lesion formation through induction and enhanced expression of adhesion molecules.
- Is strongly associated with the presence of obesity.

hs C-Reactive Protein and OSA

n=110

◎CRP levels are reduced after adenotonsillectomy



r= 0.30, p<0.0001

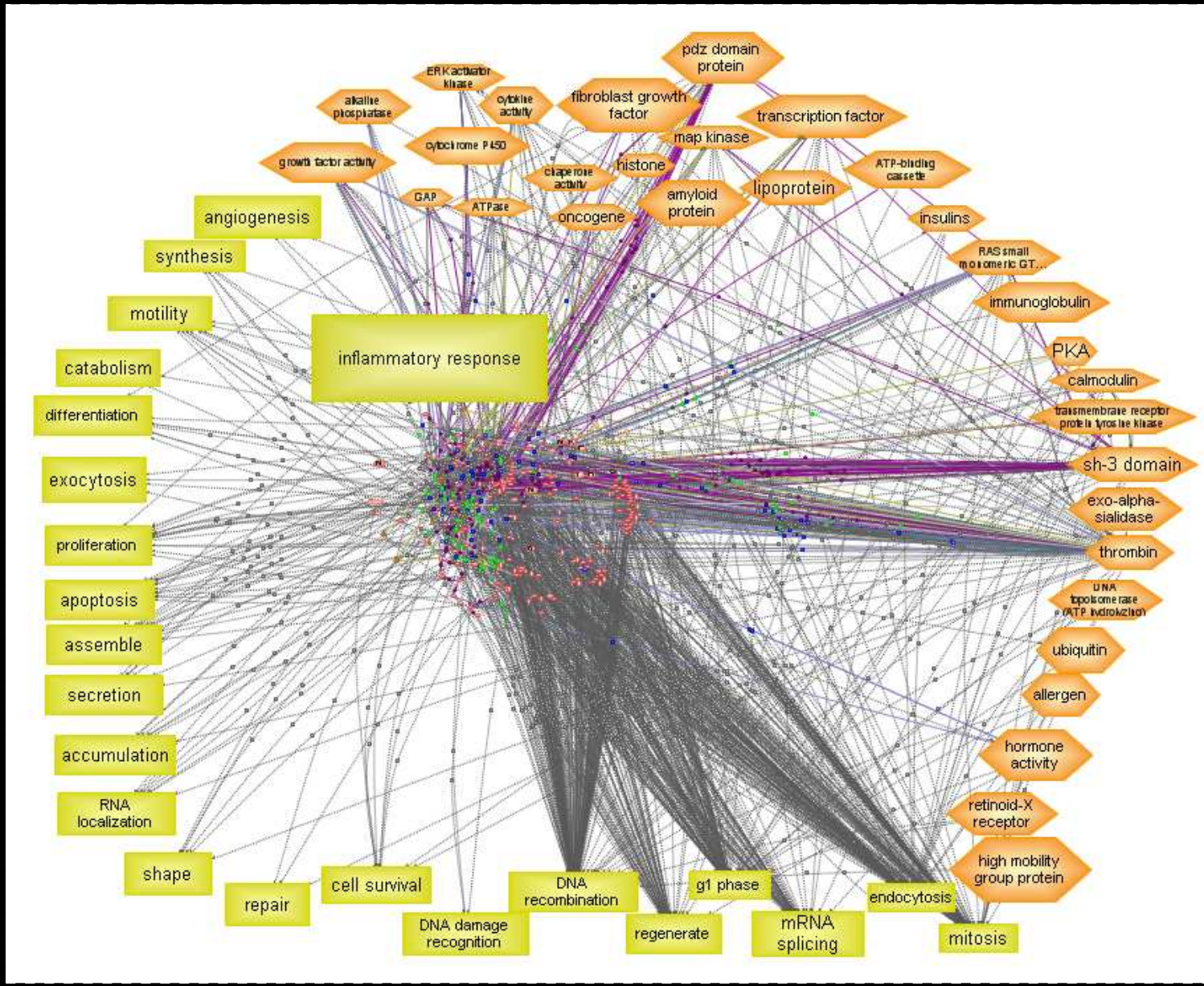
r=-0.32, p<0.0001

r=0.21, p=0.001

All correlations remain significant after controlling for relBMI

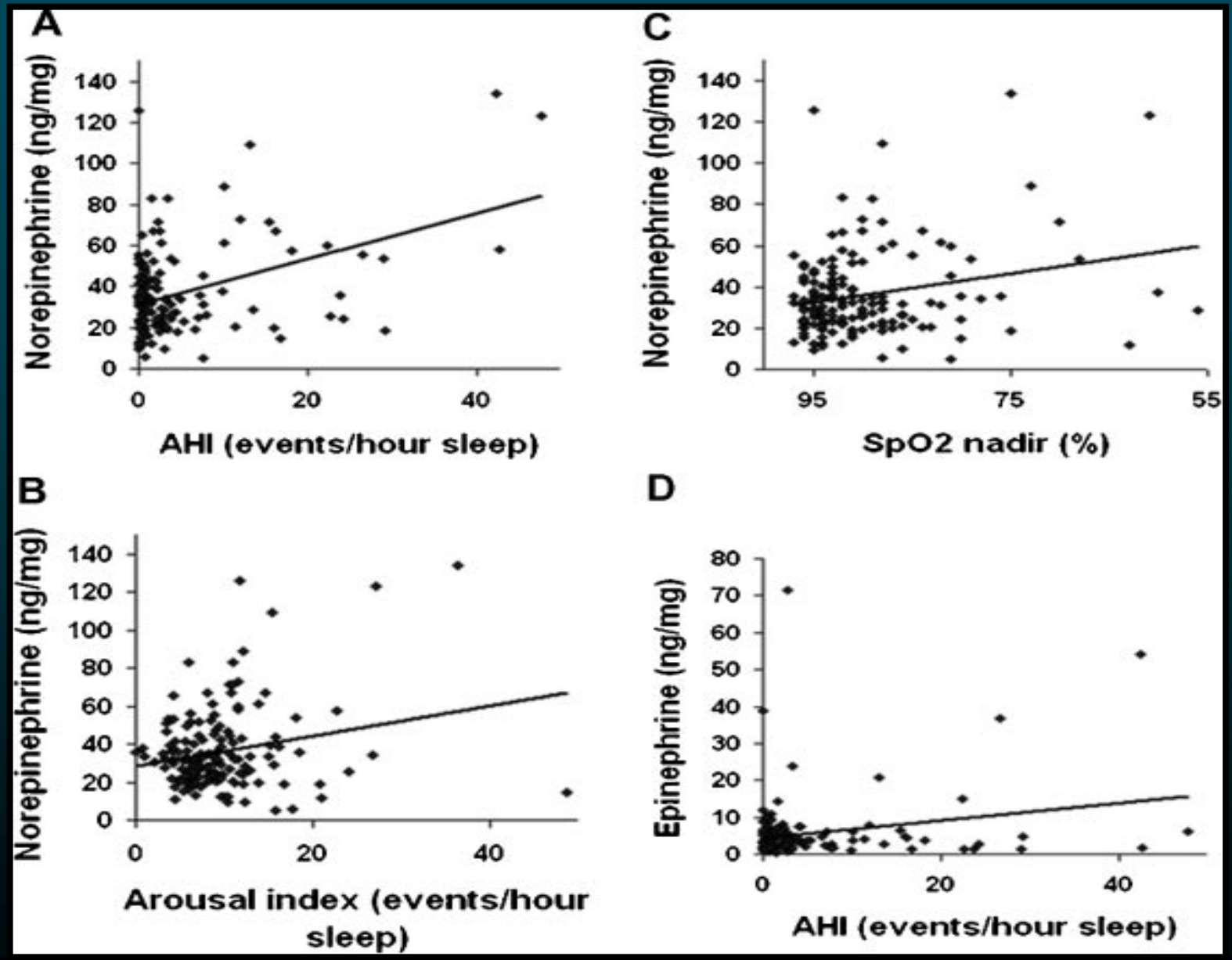
Tauman et al., 2004, 2006

Kheirandish-Gozal et al,J Clin Sleep Med,2006



Khalyfa, et al., Sleep Med 2009

CATECOLAMINAS



2D-DIGE Proteomic Approaches Reveal Urine Candidate Biomarkers in Pediatric Obstructive Sleep Apnea

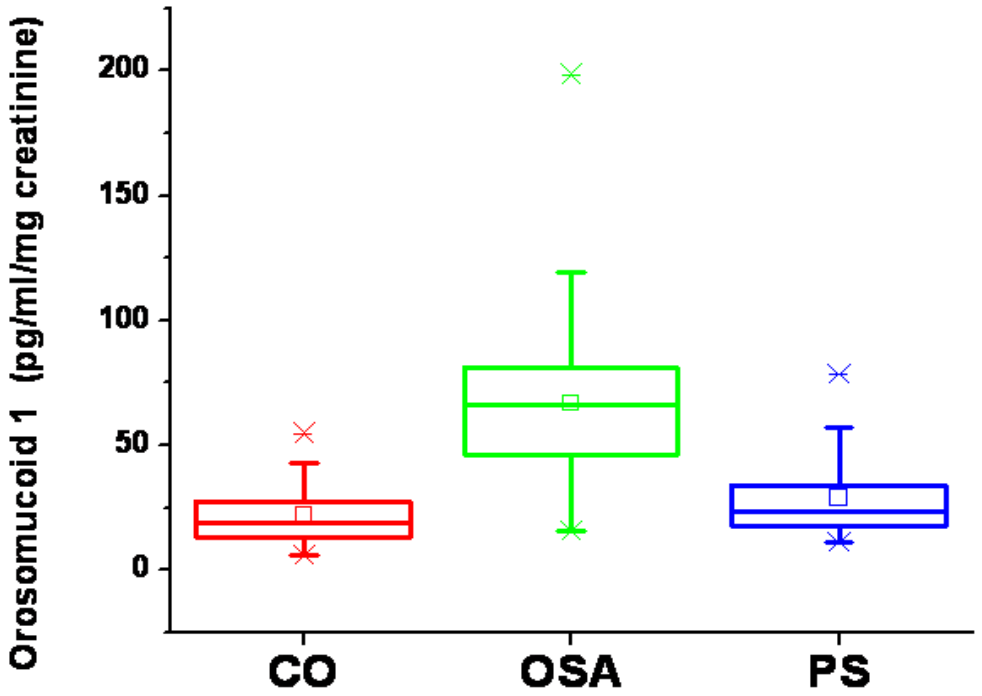
David Gozal, MD *, Saeed Jortani, PhD#, Ayelet B. Snow, MD, Leila Kheirandish-Gozal MD*,Rakesh Bhattacharjee, MD, Jinkwan Kim, PhD *, Oscar Sans Capdevila, MD

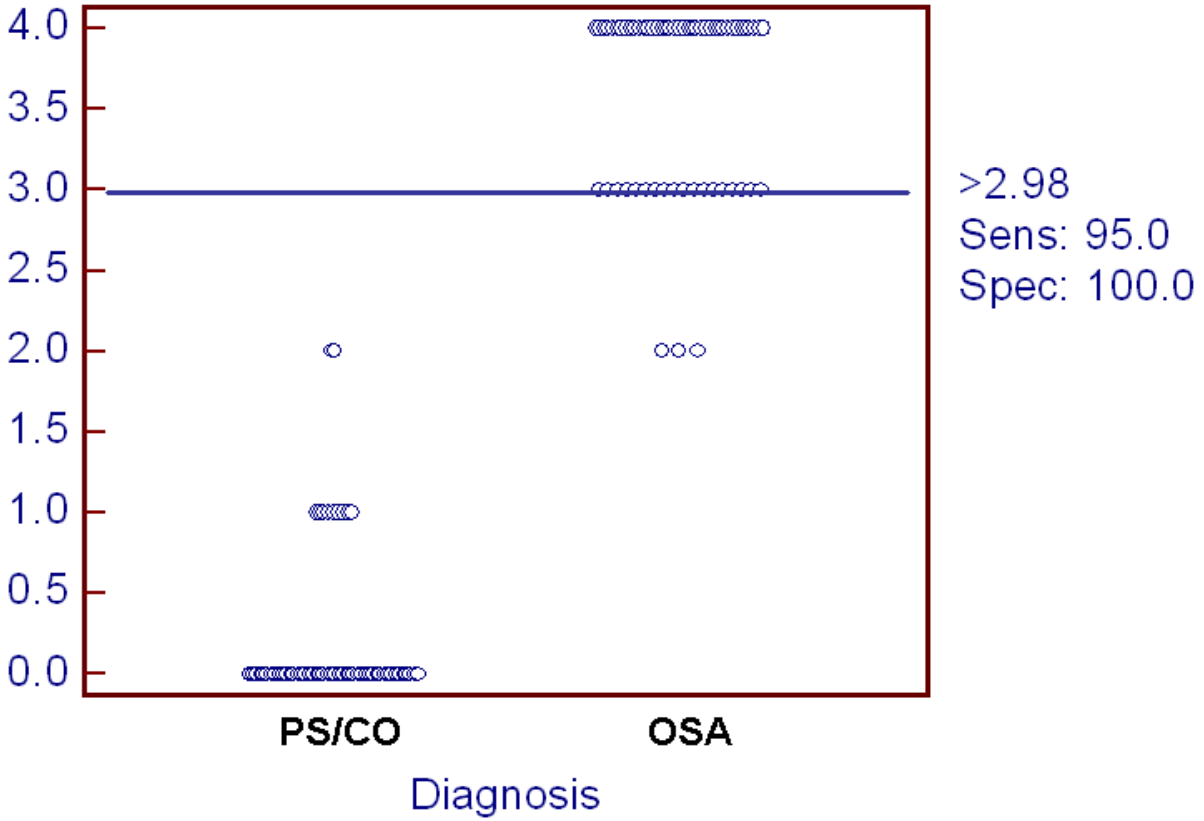
Am J Repir Crit Care Med 24 sept 2009

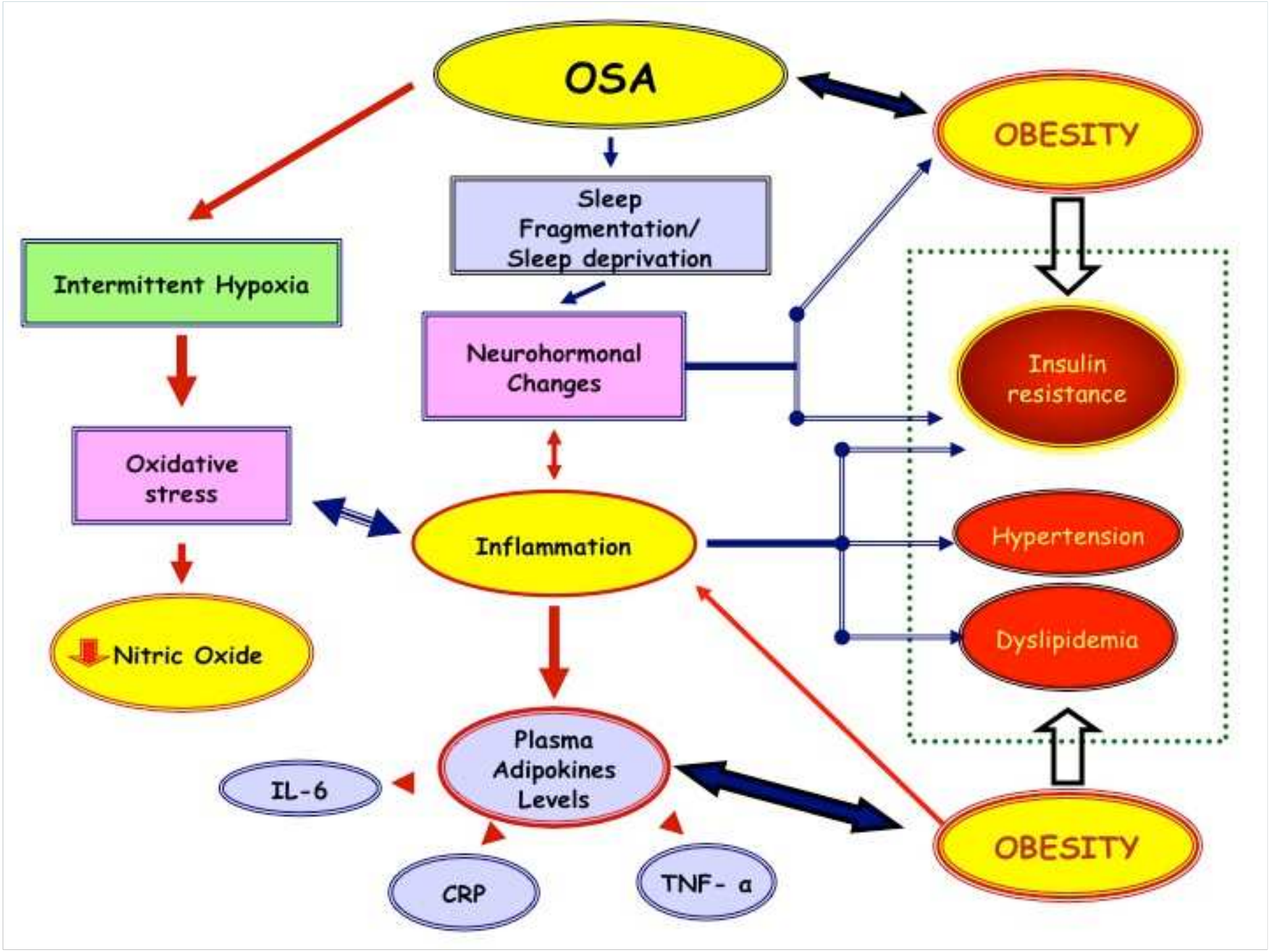
- *Subjects and Methods:* Morning urine proteins from 60 children with polysomnographicallyconfirmed OSA and matched children with either primary snoring (PS; n=30) or controls (CO; n=30) were assessed with 2D-DIGE and mass spectroscopy.

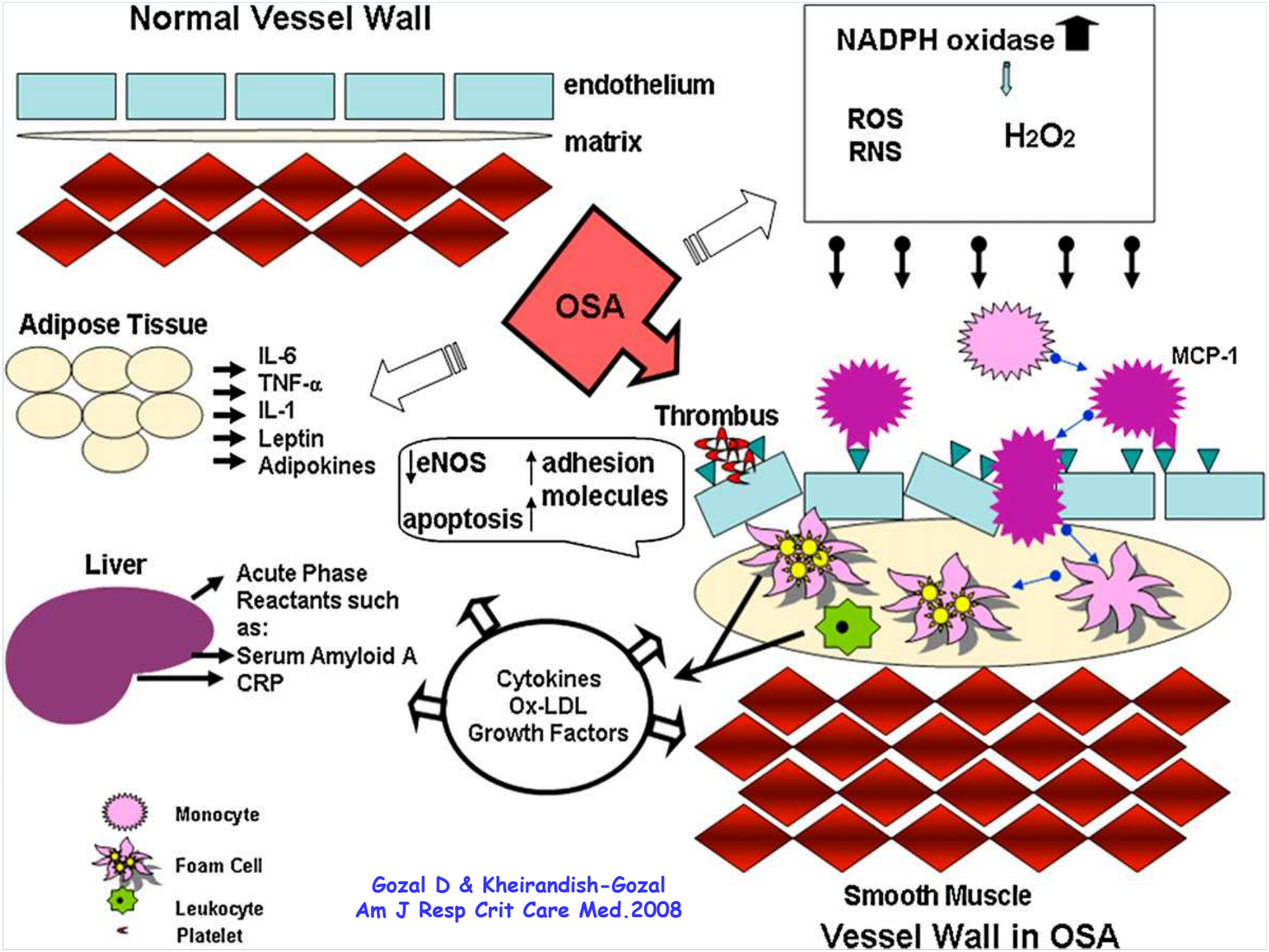
- A total of 16 proteins that are differentially expressed in OSA were identified, and 7 were confirmed by either immunoblots or ELISA.

- *Conclusions:* Proteomic approaches reveal that pediatric OSA is associated with specific and consistent alterations in urinary concentrations of specific protein clusters.(uromodulin, urocortin 3, orosomucoid 1, and Kallicrein)

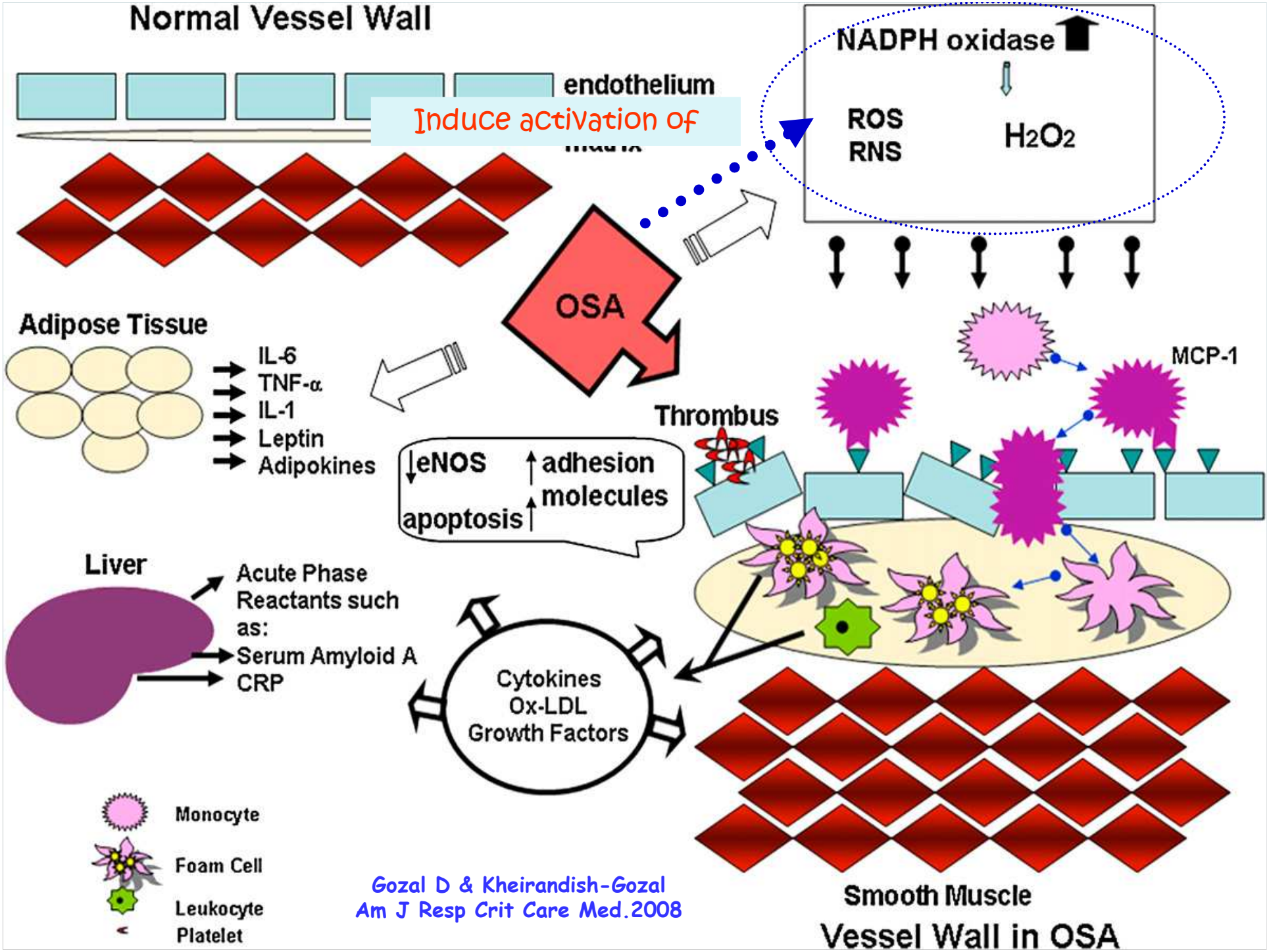

Orosomucoid 1 (pg/ml/mg creatinine)
200
150
100
50
0
CO
OSA
PS


4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
>2.98
Sens: 95.0
Spec: 100.0
PS/CO
OSA
Diagnosis

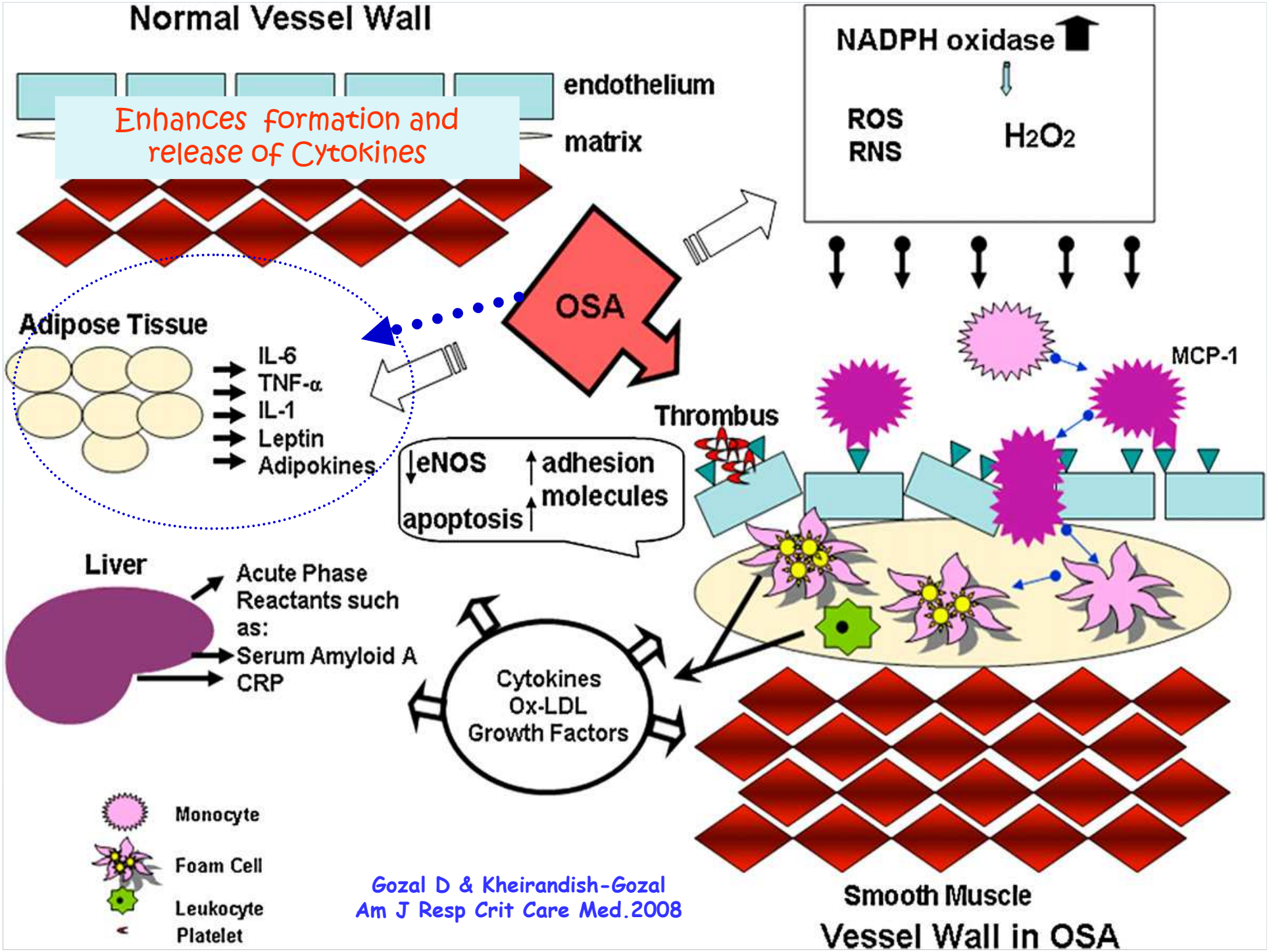

OSA
OBESITY
Sleep Fragmentation/ Sleep deprivation
Intermittent Hypoxia
Neurohormonal Changes
Insulin resistance
Oxidative stress
Inflammation
Hypertension
Dyslipidemia
Nitric Oxide
Plasma Adipokines Levels
IL-6
CRP
TNF- α
OBESITY

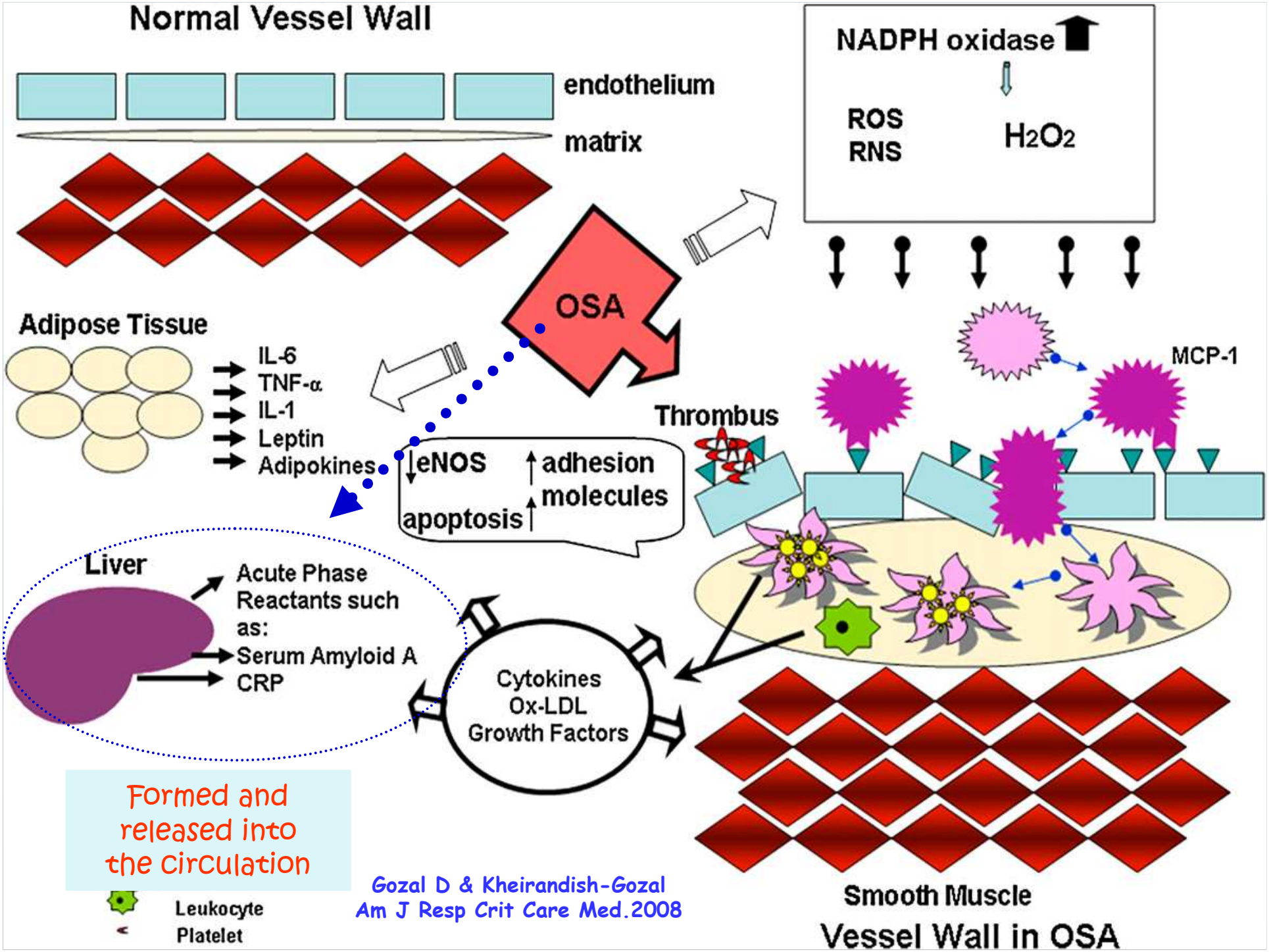


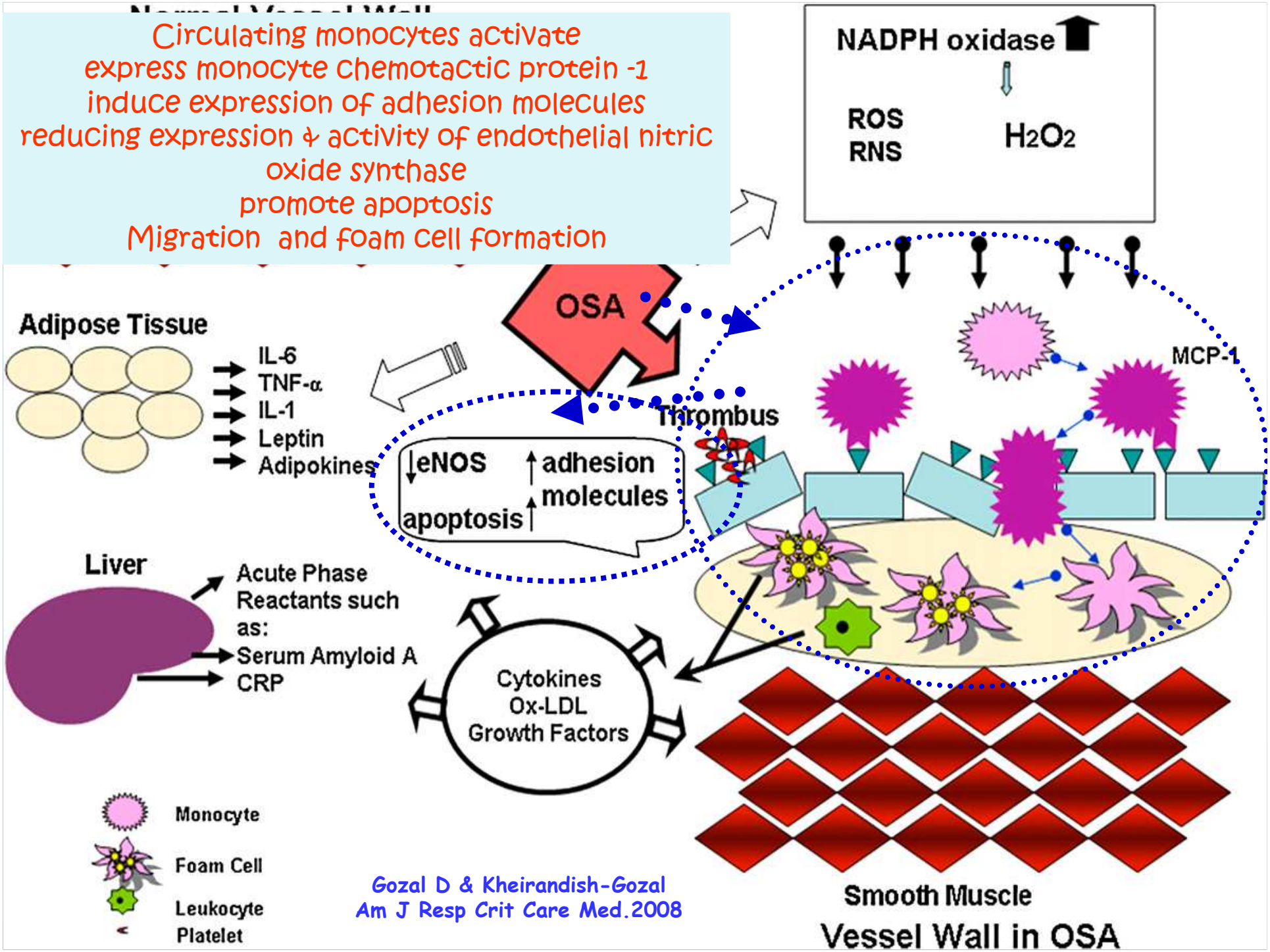
Gozal D & Kheirandish-Gozal
Am J Resp Crit Care Med.2008



Gozal D & Kheirandish-Gozal
Am J Resp Crit Care Med.2008


Normal Vessel Wall
endothelium
matrix
Enhances formation and release of Cytokines
NADPH oxidase
ROS
RNS
H2O2
OSA
Adipose Tissue
IL-6
TNF-α
IL-1
Leptin
Adipokines
MCP-1
Thrombus
↓eNOS
↑adhesion molecules
apoptosis↑
Liver
Acute Phase Reactants such as:
Serum Amyloid A
CRP
Cytokines
Ox-LDL
Growth Factors
Monocyte
Foam Cell
Leukocyte
Platelet
Gozal D & Kheirandish-Gozal
Am J Resp Crit Care Med.2008
Smooth Muscle
Vessel Wall in OSA


Normal Vessel Wall
endothelium
matrix
NADPH oxidase
ROS
RNS
H2O2
OSA
Adipose Tissue
IL-6
TNF-α
IL-1
Leptin
Adipokines
eNOS
adhesion molecules
apoptosis
MCP-1
Thrombus
Liver
Acute Phase Reactants such as:
Serum Amyloid A
CRP
Cytokines
Ox-LDL
Growth Factors
Formed and released into the circulation
Leukocyte
Platelet
Gozal D & Kheirandish-Gozal
Am J Resp Crit Care Med.2008
Smooth Muscle
Vessel Wall in OSA


Circulating monocytes activate
express monocyte chemotactic protein -1
induce expression of adhesion molecules
reducing expression & activity of endothelial nitric oxide synthase
promote apoptosis
Migration and foam cell formation
NADPH oxidase
ROS
RNS
H2O2
OSA
Adipose Tissue
IL-6
TNF-α
IL-1
Leptin
Adipokines
eNOS
adhesion molecules
apoptosis
Thrombus
MCP-1
Liver
Acute Phase Reactants such as:
Serum Amyloid A
CRP
Cytokines
Ox-LDL
Growth Factors
Monocyte
Foam Cell
Leukocyte
Platelet
Gozal D & Kheirandish-Gozal
Am J Resp Crit Care Med.2008
Smooth Muscle
Vessel Wall in OSA

GENETIC AND METABOLIC PARAMETERS IN SNORING CHILDREN

Peripheral Blood Leuko… Parameters in Habitually… Polysomnographic Findi…

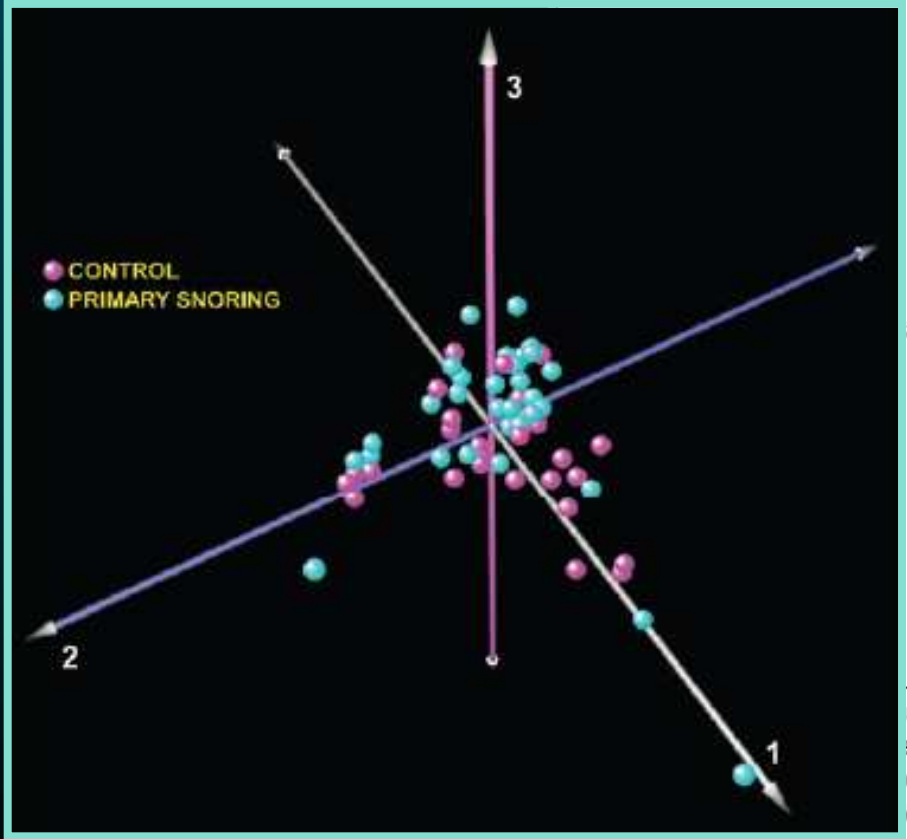
…Metabolic …with Normal

Abdelnaby Khalyfa, PhD[1]*; Sina A. Gharib, MD[2]; Rakesh Bhattacharjee, MD[3,5]; Mohamed Hegazi… …zal, MD[1];

*These authors contributed equally to the work.

Table 1—Demographic and polysomnographic characteristics of the initial cohort

	PS (n = 30)	Controls (n = 30)
Age (years)	6.9 ± 0.6	7.0 ± 0.5
Male (n)	16	15
African American (n)	10	10
BMI (z-score)	0.63 ± 0.22	0.47 ± 0.25
Sleep latency (min)	23.8 ± 15.4	23.4 ± 14.2
REM latency (min)	145.5 ± 43.2	146.2 ± 44.4



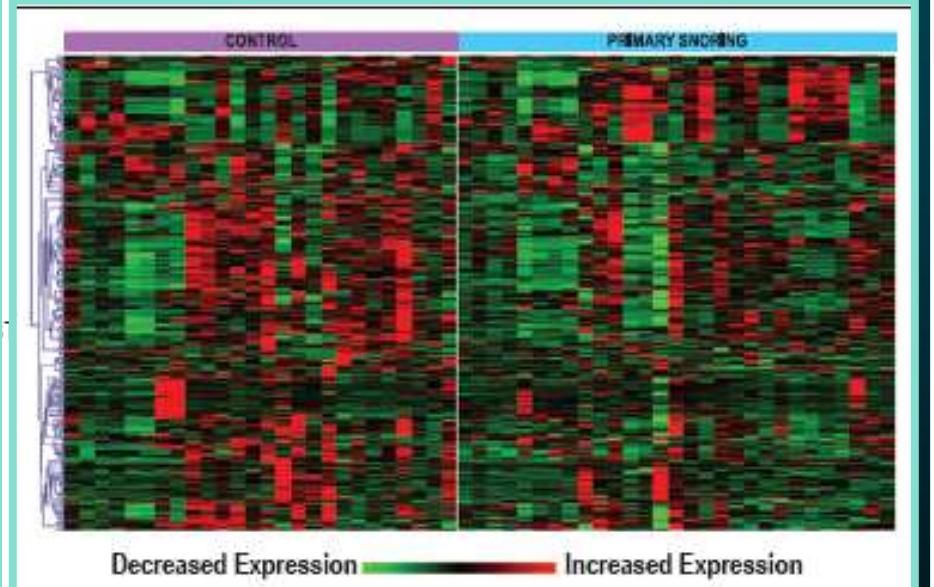


Figure 2—Gene expression heatmap of "leading edge" members of enriched gene sets in PBL of children with PS vs. controls. One-dimensional hierarchical clustering of expression values has been performed to better depict distinct transcriptional patterns between the phenotypes.

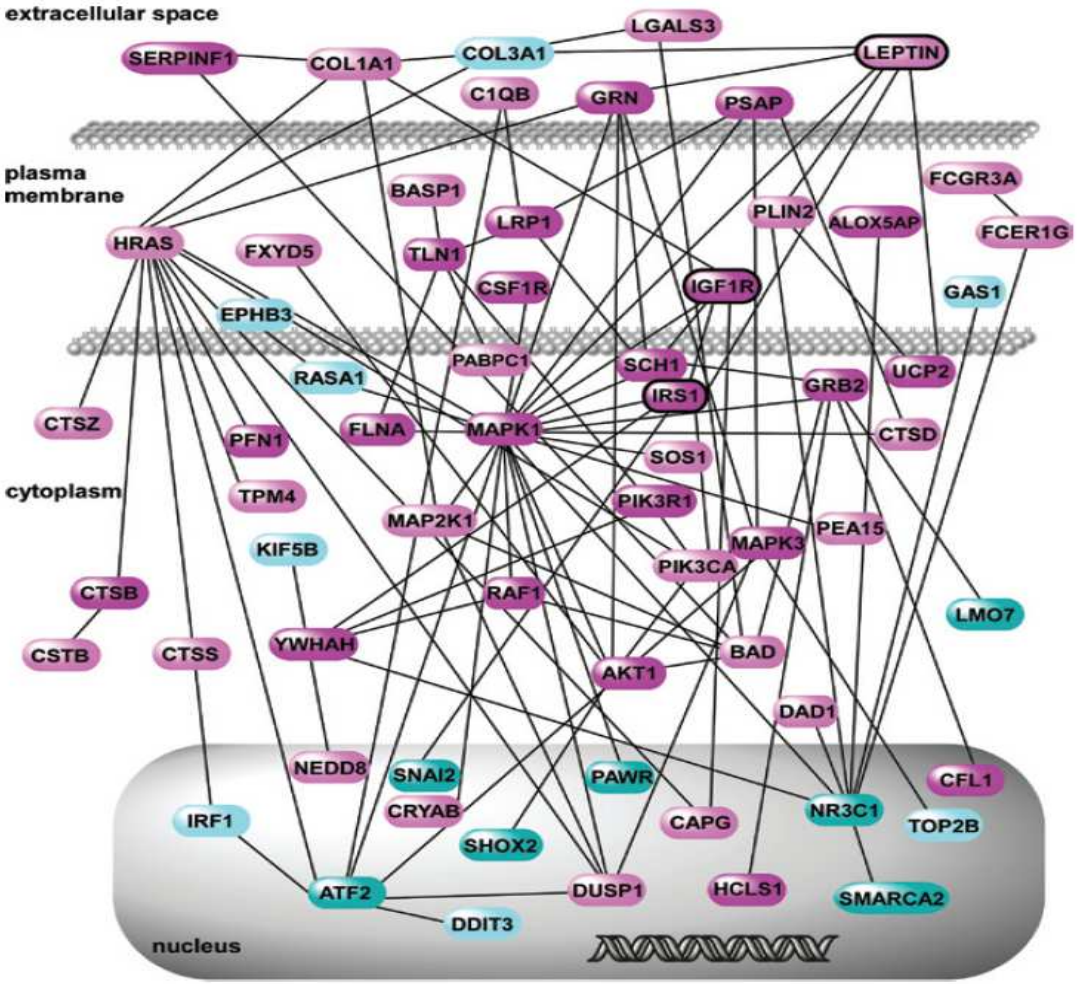
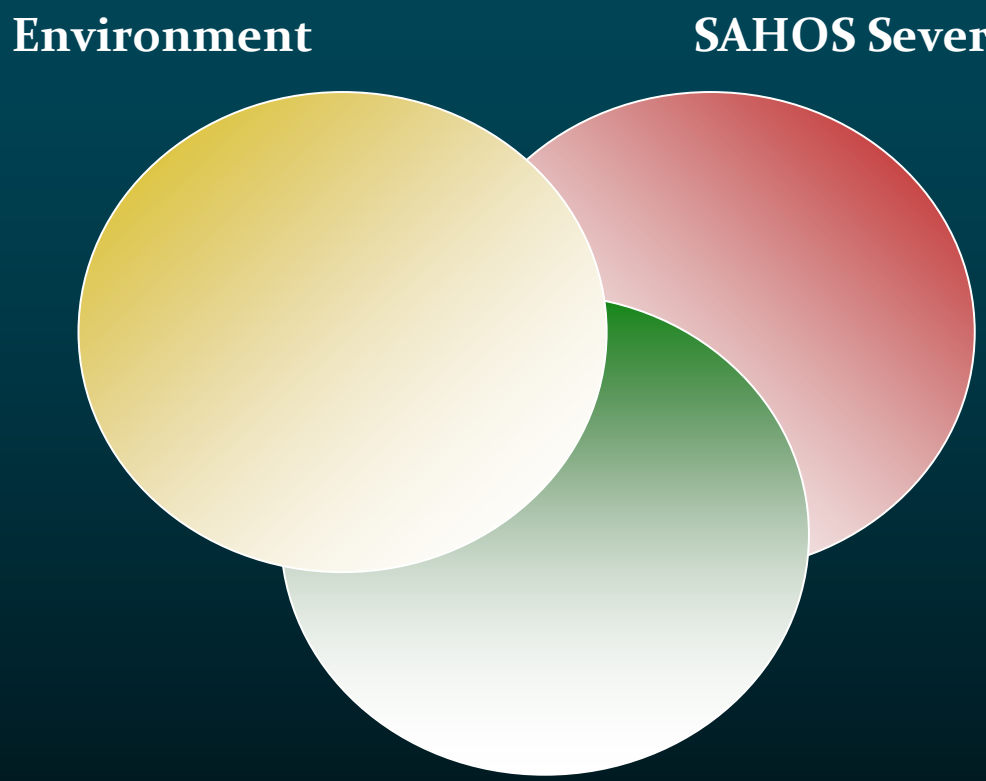


Figure 4—Gene product interaction network constructed from gene members mapping to the insulin signaling, adipocyte differentiation and obesity module (see Figure 3). Nodes up-regulated in PS are shown in cyan, and those up-regulated in controls are colored in magenta. Members of the leading edge are highlighted in darker shades. Among the complex interactions, note the relational links between leptin, IGF1R, and IRS1 as discussed in the text. A complete list of gene members is provided in the supplementary Table S2.

Modelo de Triple Riesgo de Morbilidad en SAHOS



Gozal & Kheirandish, 2006

CONCLUSIONES

- Los estudios de sueño son costosos y no es posible atender a toda la población pediátrica.
- Necesitamos nuevos métodos de diagnóstico (screening) para el SAHOS en niños.
- SAHOS en niños también produce marcadores biológicos en plasma y orina.
- Tenemos marcadores genéticos obtenidos mediante gene-array (técnicas complejas y caras.. **DISPONIBLES AQUÍ**).
- Estamos en fases iniciales , resultados PROMETEDORES aunque nos faltan más estudios (TRABAJO EN EQUIPO) de identificación de cuáles son el / los marcadores ideales.

Sant Joan de Déu
HOSPITAL MATERNOINFANTIL
UNIVERSITAT DE BARCELONA

GRACIAS