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Obesità infantile e rischio di futuro sviluppo di disfunzione renale

GLOBESITY

Negli ultimi 30 anni aumento esponenziale della prevalenza di sovrappeso e obesità nel mondo

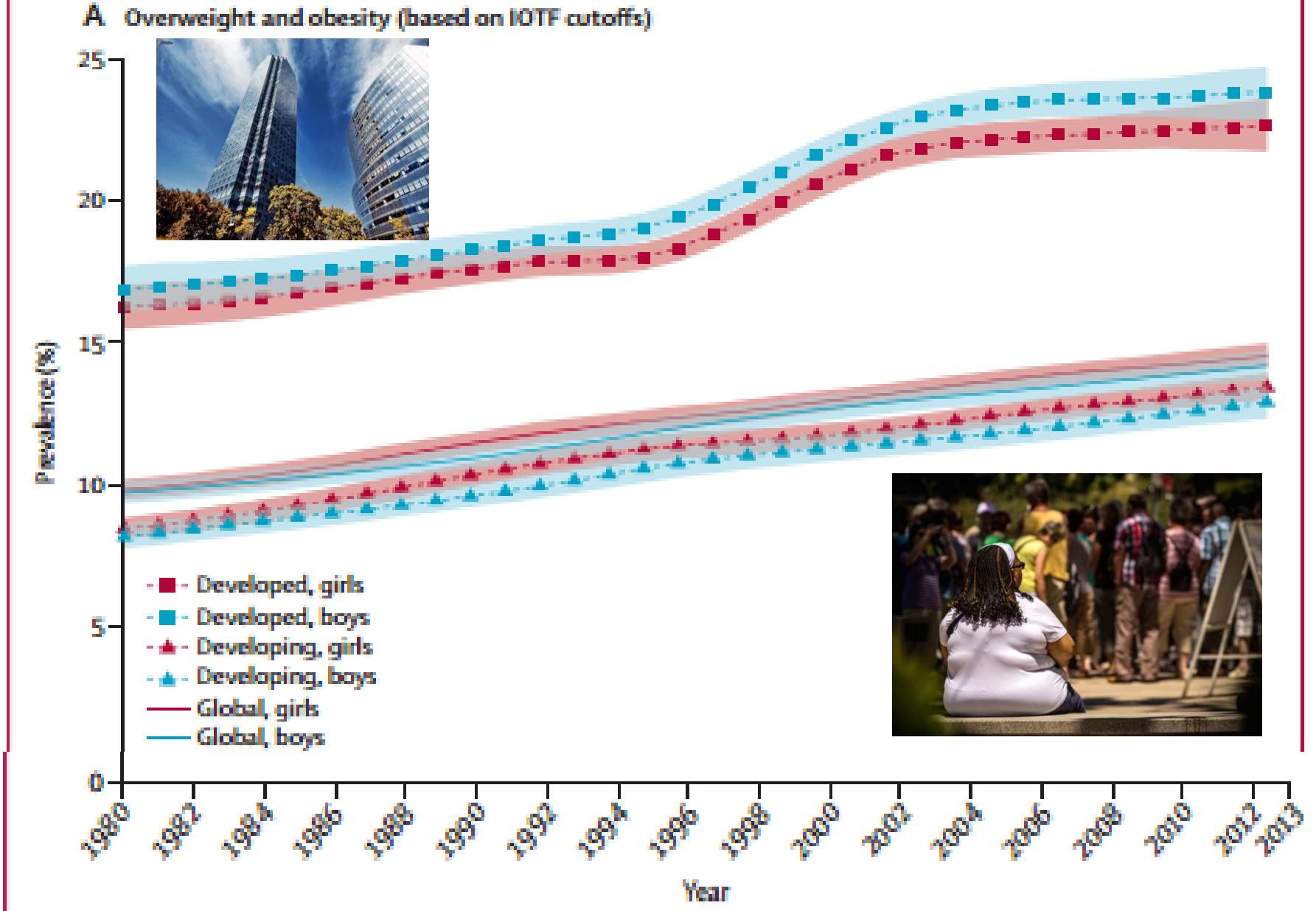
OBESITA' IN ETA' PEDIATRICA

A gennaio 2015 numero di obesi raddoppiato dal 1980

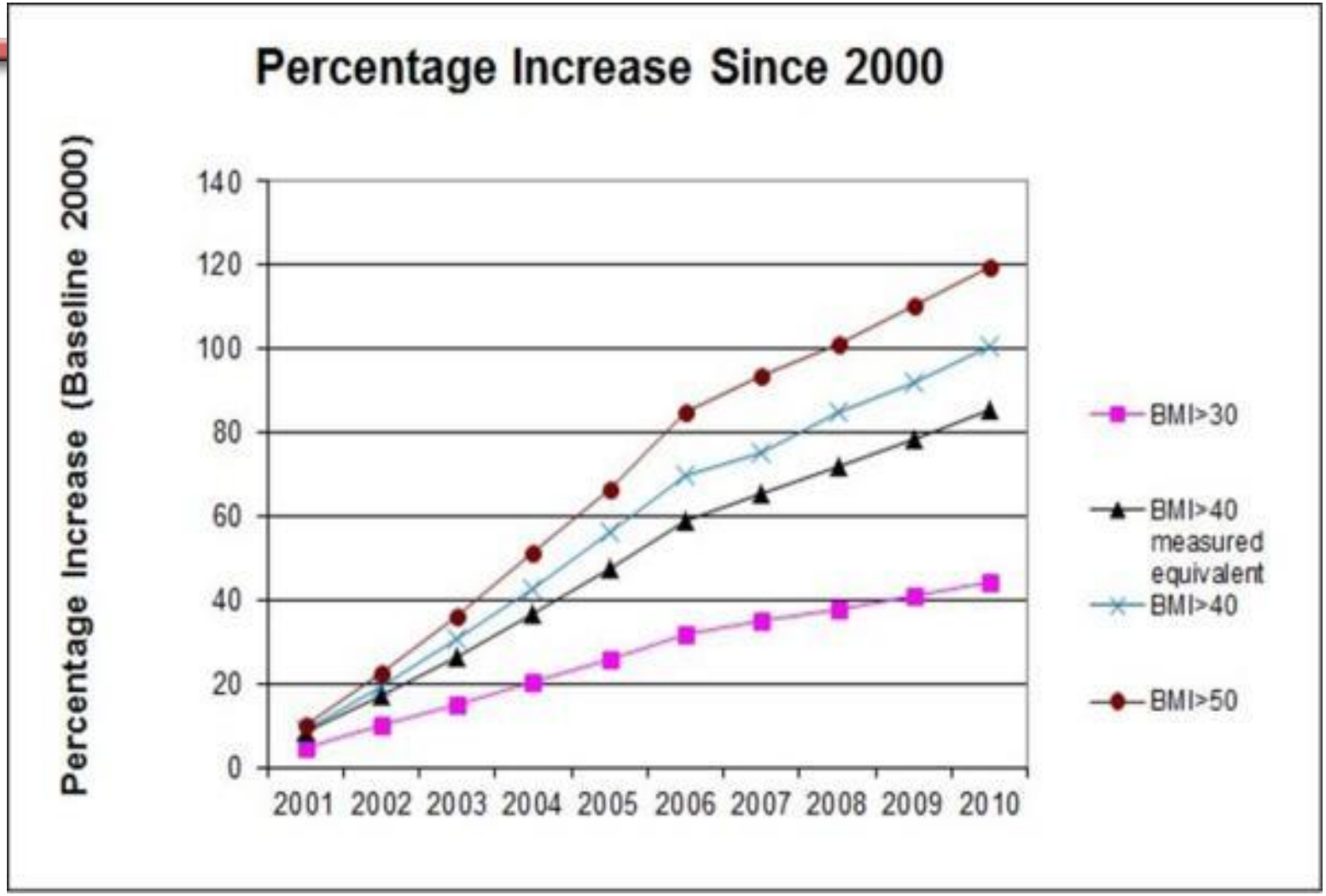
42 millioni di bambini < 5 anni obesi
(WHO 2015)

Nel **2020,** se non verranno prese delle misure drastiche, il 9% dei bambini in età prescolare sarà sovrappeso o obeso
60 milioni di bambini

Marie NG et al. Lancet 2014

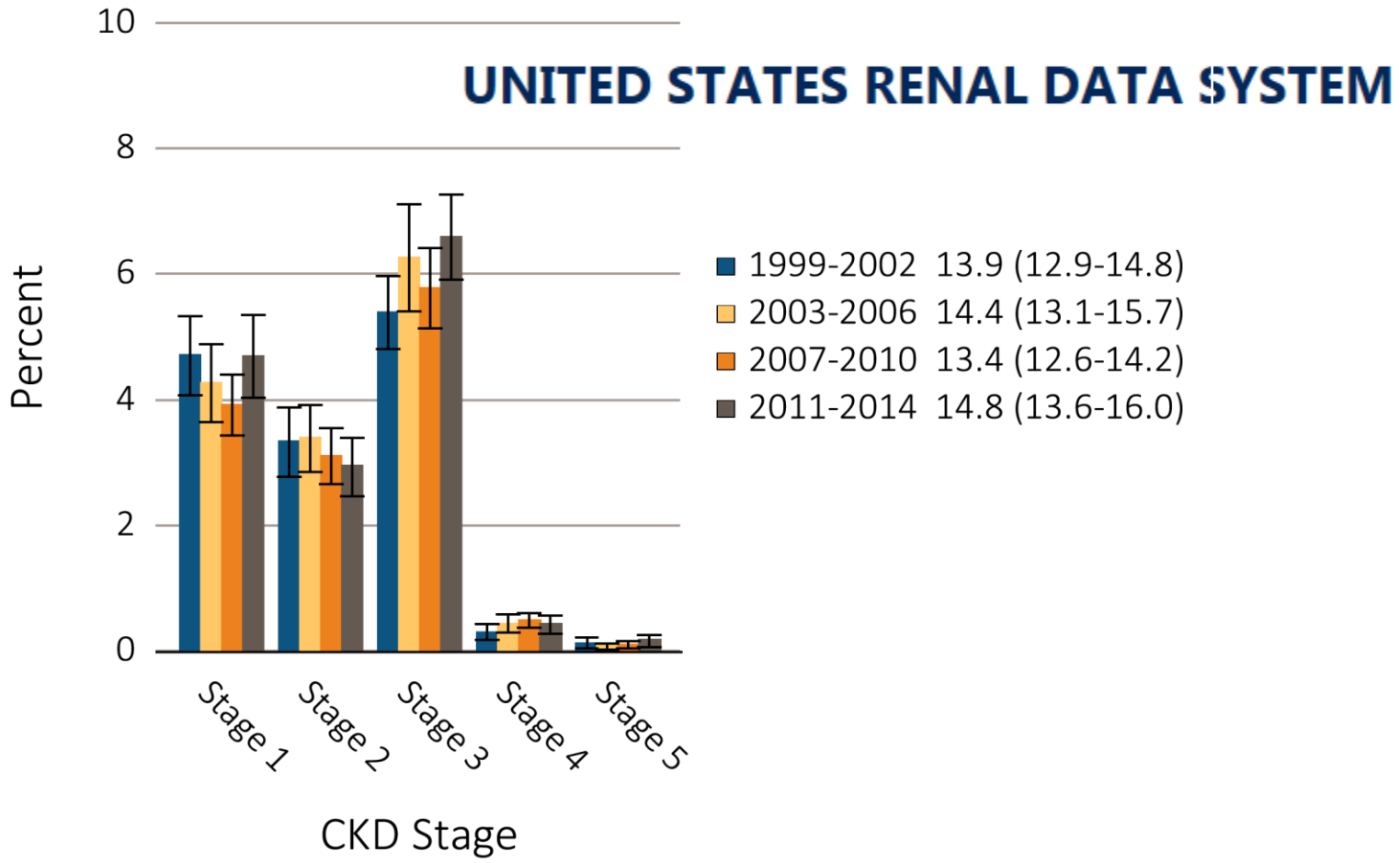


OBESITA' IN ETA' ADULTA



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3527647/

Prevalenza malattie renali croniche



The 2016 USRDS Annual Data Report, https://www.usrds.org/2016/view/Default.aspx

http://www.kidney-international.org review

Association between obesity and kidney disease: A systematic review and meta-analysis

http://www.kidney-international.org review

Association between obesity and kidney disease: A systematic review and meta-analysis

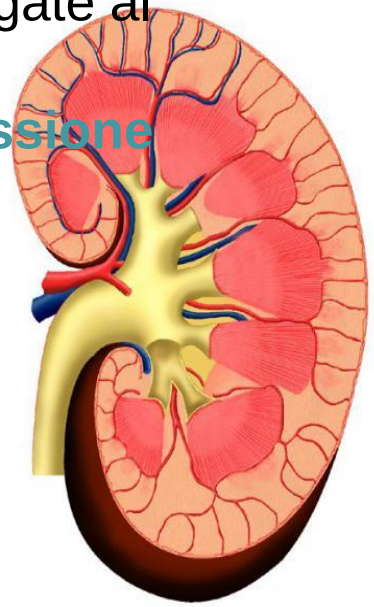
•I soggetti sovrappeso hanno un elevato rischio di sviluppare KD (RR¼1.40; 95% CI 1.30–1.50)

• Negli obesi il rischio é ancora maggiore (RR¼1.83 (1.57–2.13)

• **Nella donna obesa il rischio é il più alto**

• il 24.2% e il 33.9% delle nefropatie possono essere legate al sovrappeso/obesità.

• **Obesità influisce in maniera negativa sulla progressione** della patologia renale in soggetti con nefropatia



http://www.kidney-international.org review

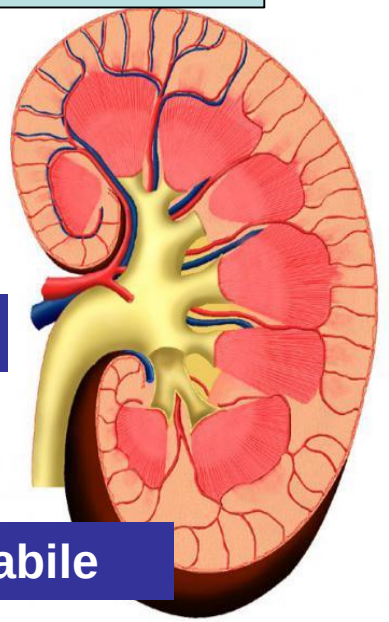
Association between obesity and kidney disease: A systematic review and meta-analysis

Adjusted for potential confounders (age, gender, ethnicity, smoking, alcohol, physical activity)

Also adjusted for diabetes, dyslipidemia, and hypertension.

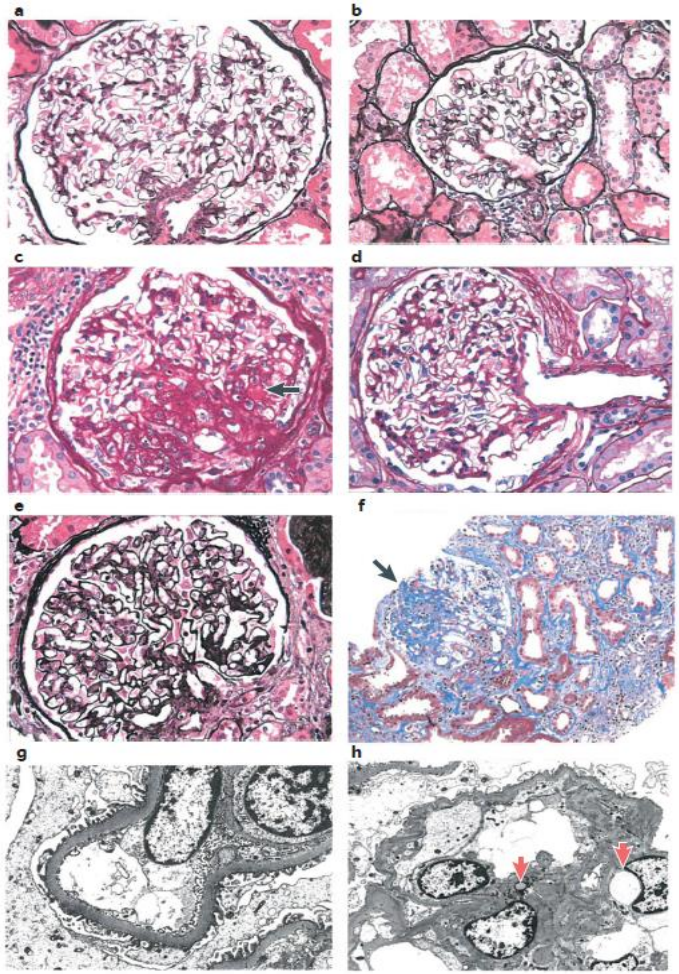
Impact of obesity on KD risk is independent of these major risk factors

Correla con il BMI



Fattore di rischio modificabile

Obesity-related glomerulopathy: clinical and pathologic characteristics and pathogenesis



Descritta nel 1975 da Cohen in grandi obesi con f. renale nella norma

Glomerulomegalia
Presenza di aree di glomerulosclerosi focale
Proliferazione delle cellule mesangiali
Accumulo di matrice

Proteinuria lieve/moderata (raramente nefrosica)
Lieve edema
Lenta progressione
Basso rischio di sviluppare S.nefrosica

D'Agati V et a. 2016

Obesity-related glomerulopathy: An emerging epidemic

Biopsia eseguita per proteinuria o proteinuria +IR in soggetti obesi

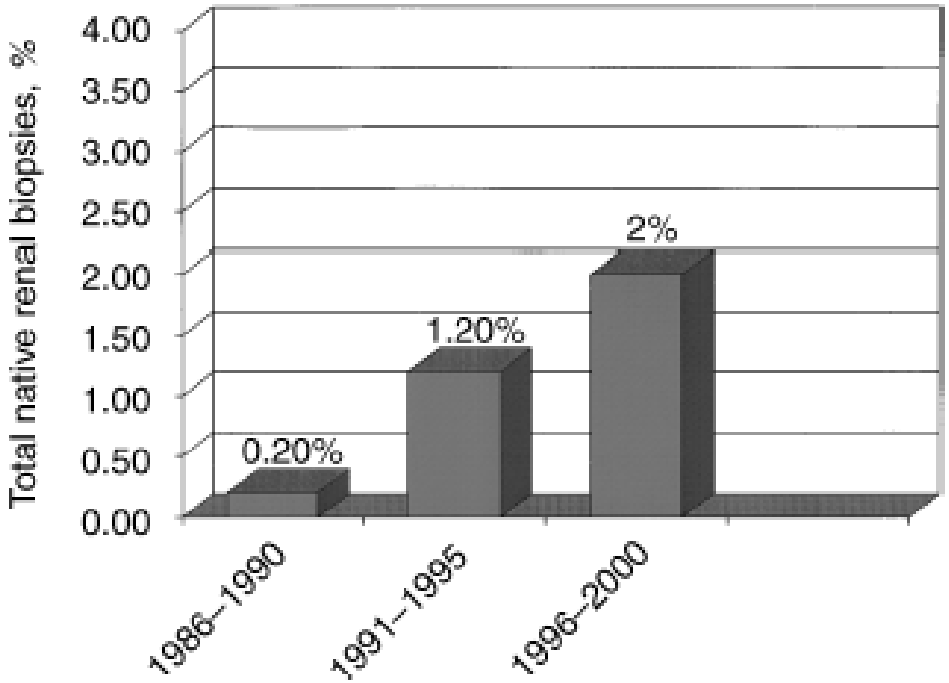


Fig. 1. The increased incidence of obesity-related glomerulopathy (ORG) is plotted as a percentage of total native renal biopsies received over a 15-year period.

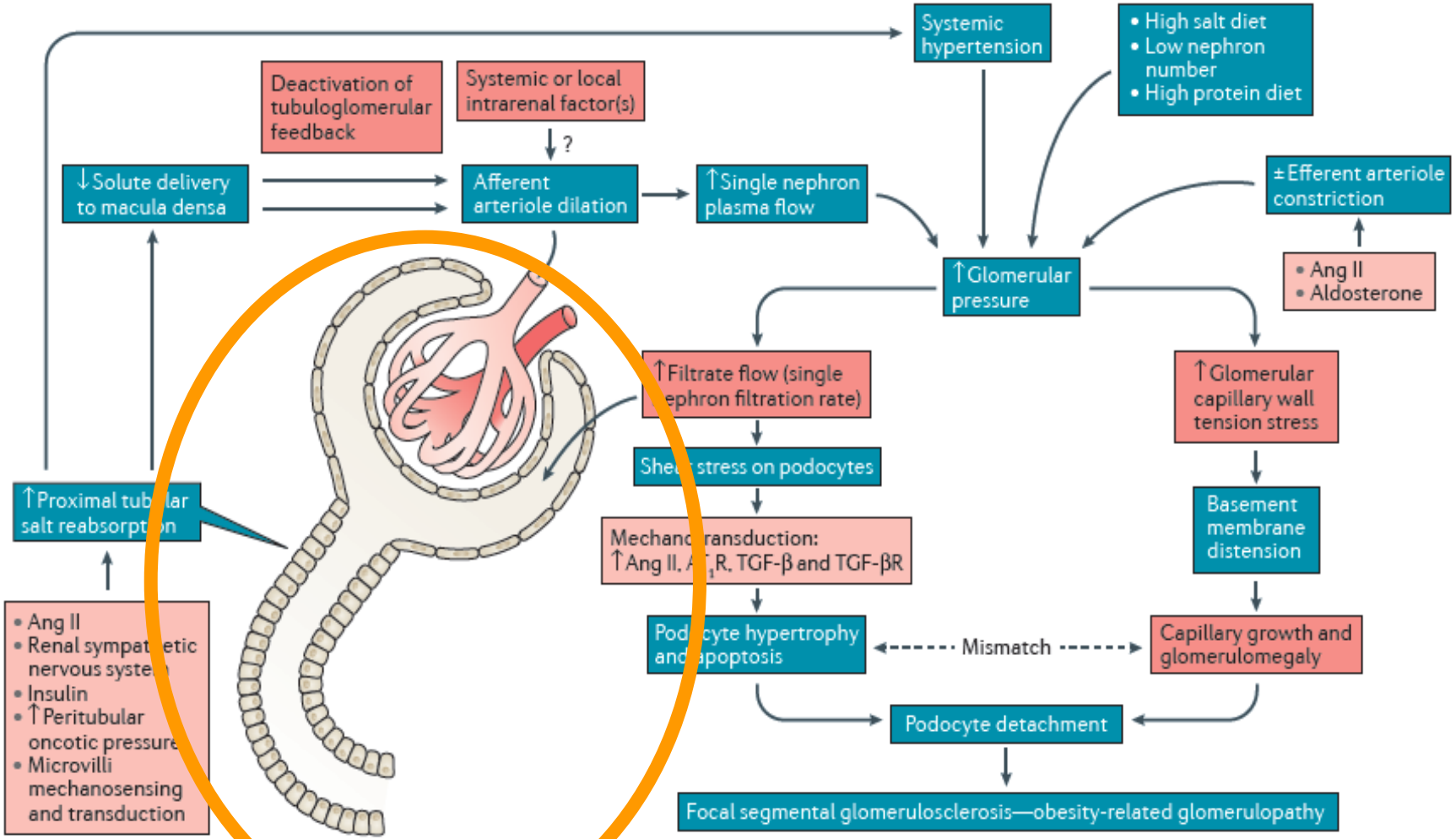


Figure 2 | **Haemodynamic alterations in obesity.** Primary dilatation of the afferent arteriole and variable constriction of the efferent arteriole via activation of angiotensin II (Ang II) and aldosterone contribute to increases in single nephron plasma flow, glomerular intracapillary hydrostatic pressure, and filtration rate. The major driver of afferent arteriolar dilatation is unknown, but deactivation of tubuloglomerular feedback via increased proximal tubular salt reabsorption and decreased delivery to the macula densa likely has a role. A host of factors, including Ang II, the renal sympathetic nervous system, insulin, an increase in postglomerular oncotic pressure due to increased filtration fraction, and mechanosensors of tubular flow rates, mediate the increased tubular reabsorption of sodium. The increase in filtrate flow (single nephron filtration rate) in turn promotes glomerular capillary wall stretch tension, glomerulomegaly, and maladaptive podocyte stress leading to obesity-related glomerulopathy and focal segmental glomerulosclerosis. AT_1R, type 1 angiotensin II receptor; TGF-β, transforming growth factor β; TGF-βR, TGF-β receptor.

D'Agati V et a. 2016

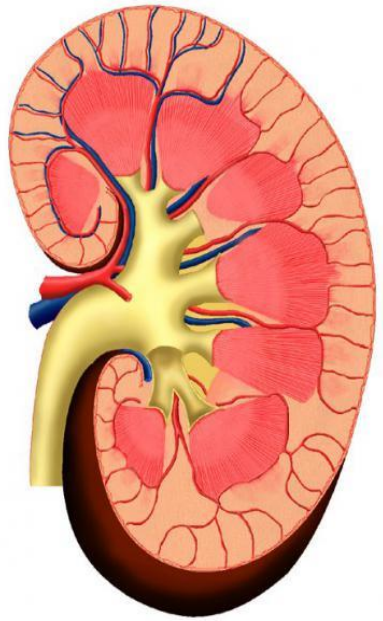
Modificazioni glomerulari determinate dall'obesità

Aumento di dimensione dei glomeruli

fase di iperfiltrazione
(adattamento del rene all'aumento della BMI)

Stato cronico di iperfiltrazione potenzia il danno renale

Perdita di proteine
Rimodellamento cellulare
Cicatrici fibrose
Tubulo-interstizioapatia
Aumento della componente fibrosa
Distruzione progressiva del parenchima renale

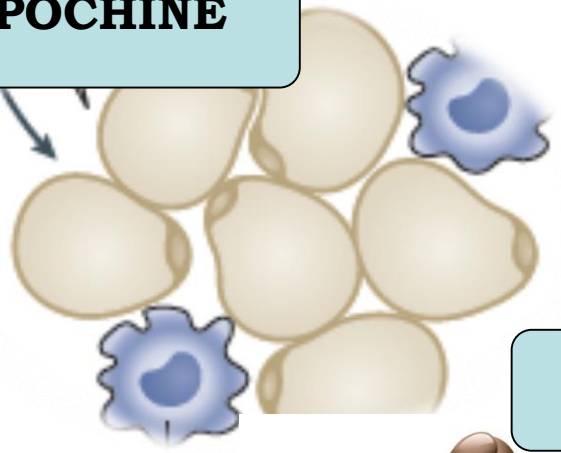


D'Agati V et a. 2016

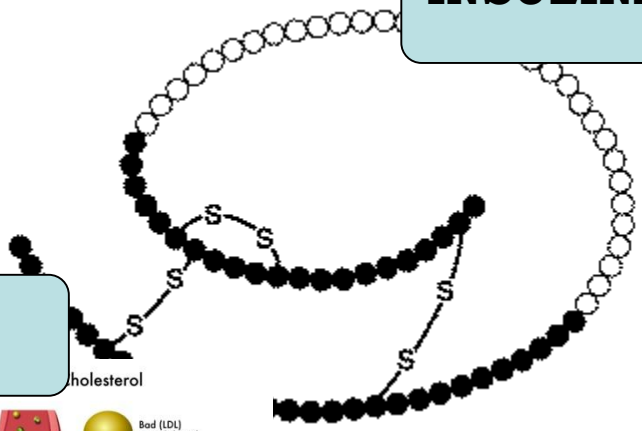
Obesità e nefrotossine

Il meccanismo non è ancora completamene noto ma sembra coinvolgere diverse molecole

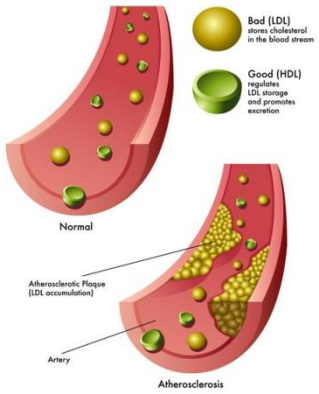
ADIPOCHINE



INSULINA



LIPIDI

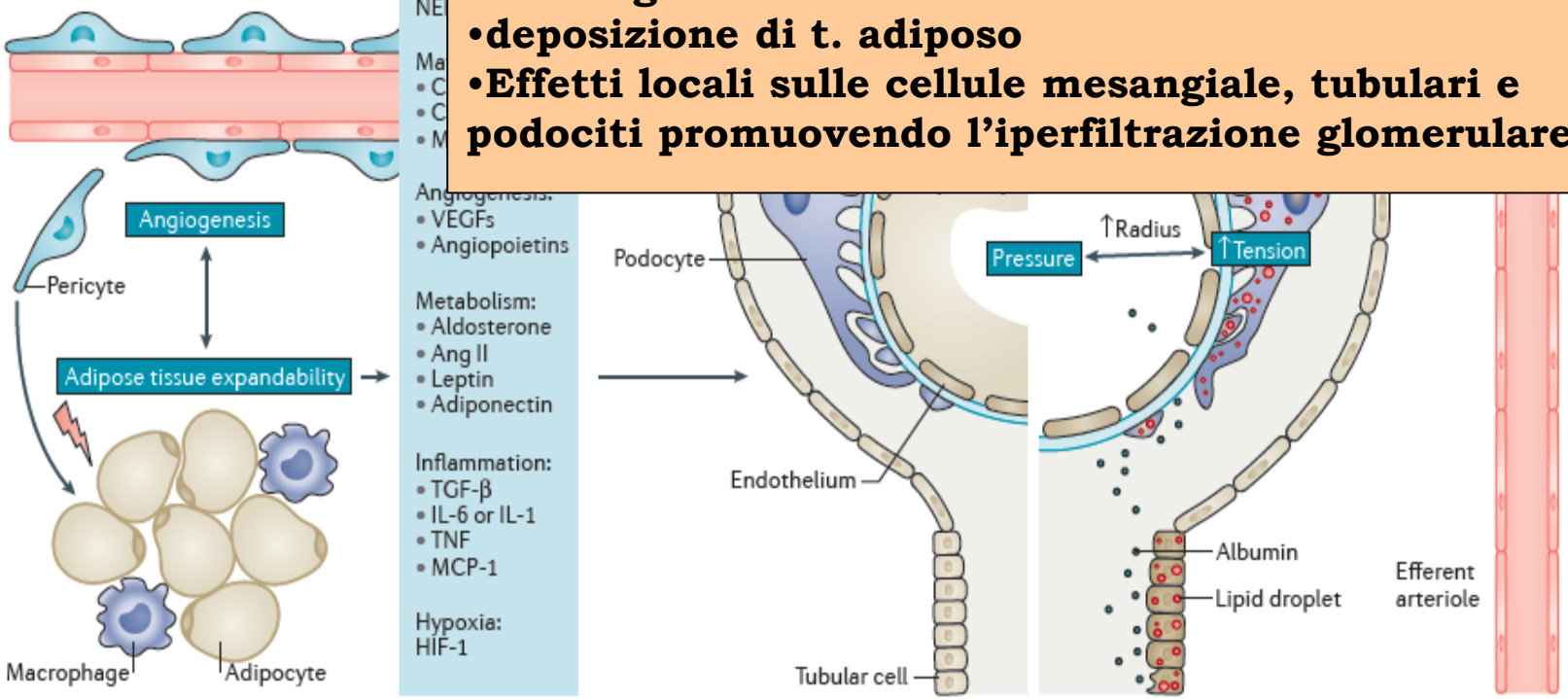


D'Agati V et a. 2016

T. adiposo come organo endocrino

Adipochine

- **angiogenesi**
- **riarrangimanenti stromali**
- **deposizione di t. adiposo**
- **Effetti locali sulle cellule mesangiale, tubulari e podociti promuovendo l'iperfiltrazione glomerulare**



D'Agati V et a. 2016; Gunta S et A. Pediatrc Nefrology 2013

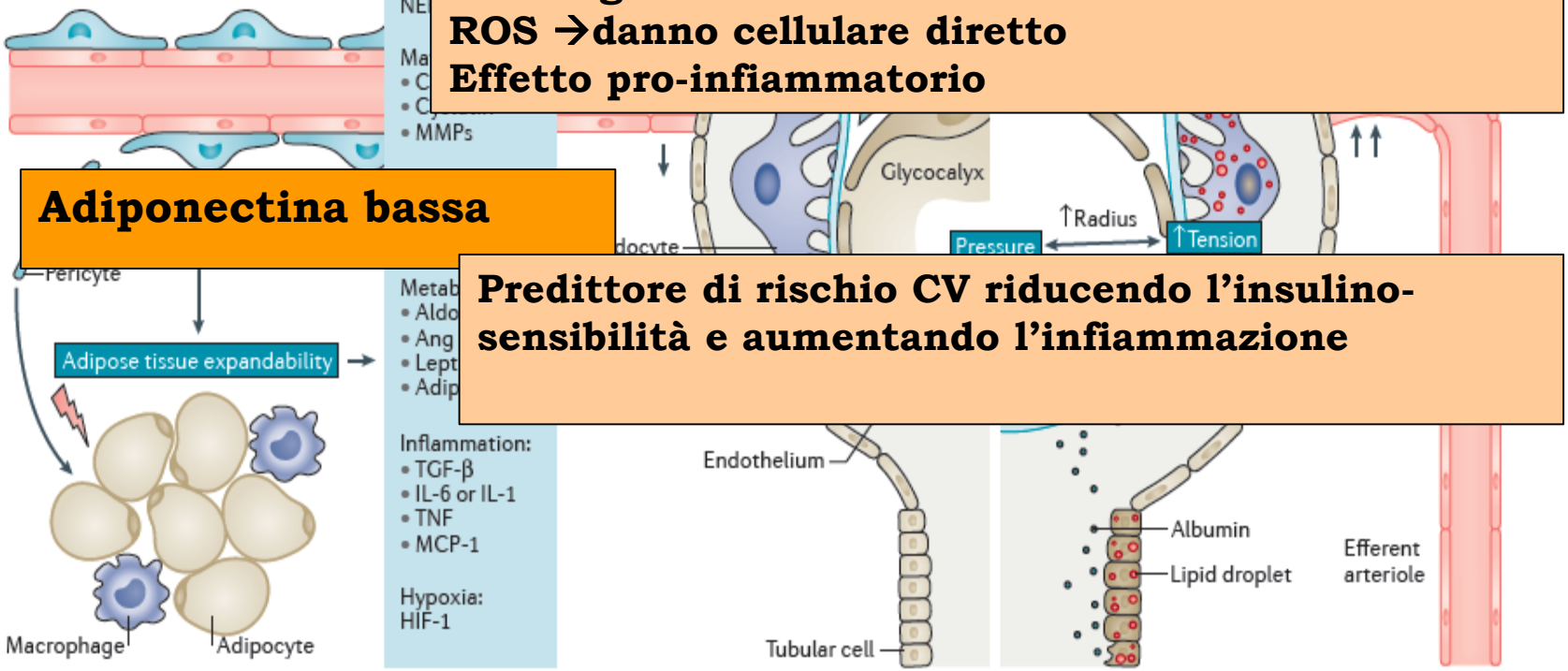
T. adiposo come organo endocrino

Leptina elevata

Stimola la proliferazione del collagene tipo IV nelle cellule glomerulari
ROS →danno cellulare diretto
Effetto pro-infiammatorio

Adiponectina bassa

Predittore di rischio CV riducendo l'insulino-sensibilità e aumentando l'infiammazione

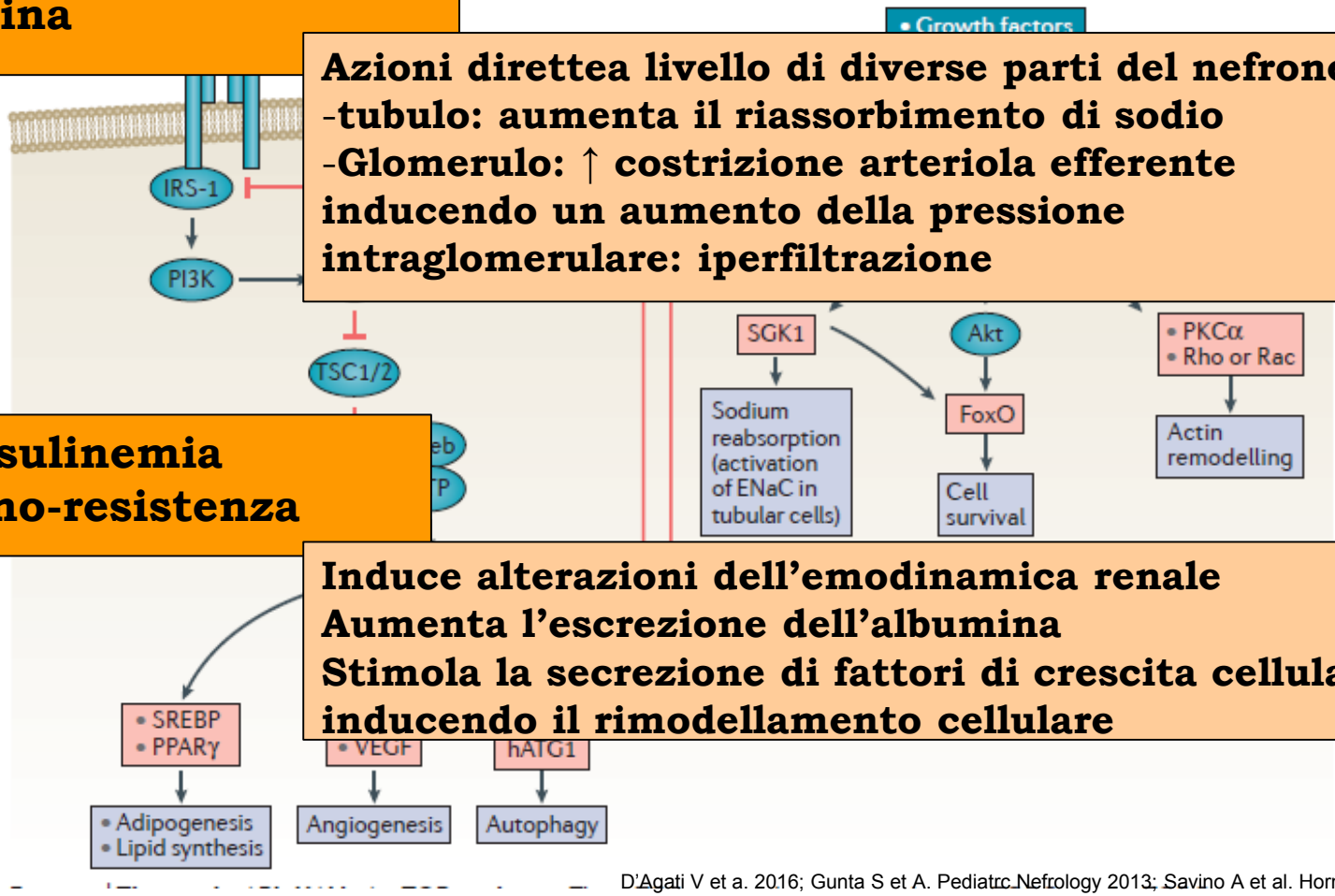


D'Agati V et a. 2016; Gunta S et A. Pediatrc Nefrology 2013; Correia Costa et al. Port J Nephrol Hypert 2016

Obesità e nefrotossine

Insulina

Azioni direttea livello di diverse parti del nefrone
-tubulo: aumenta il riassorbimento di sodio
-Glomerulo: ↑ costrizione arteriola efferente inducendo un aumento della pressione intraglomerulare: iperfiltrazione

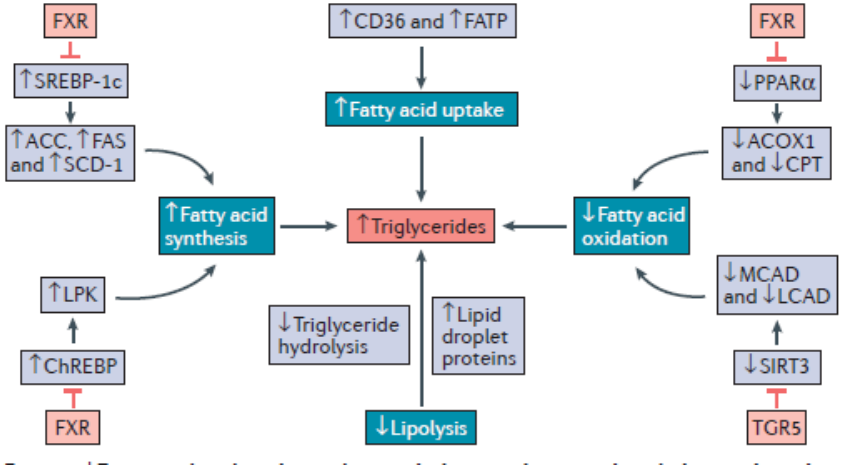


Iperinsulinemia
Insulino-resistenza

Induce alterazioni dell'emodinamica renale
Aumenta l'escrezione dell'albumina
Stimola la secrezione di fattori di crescita cellulari inducendo il rimodellamento cellulare

D'Agati V et a. 2016; Gunta S et A. Pediatric Nefrology 2013; Savino A et al. Horm Res Ped 2009

Obesità e nefrotossine



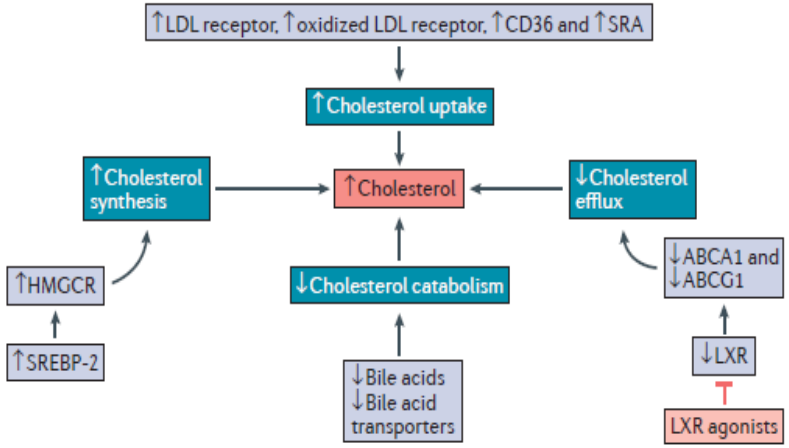
Dislipidemia

Correlazione tra ↑livelli di colesterolo tot e TGL per ogni 10ml/min/1.73m2 di ↓ GFR

↑ proteinuria nefrosica

Accumulo cellulare di acidi grassi liberi nel rene

Induce danno mesangiale ed epiteliale



D'Agati V et a. 2016; Gunta S et A. Pediatrc Nefrology 2013; Savino A et al. Horm Res Ped 2009

Da dove nasce il problema?

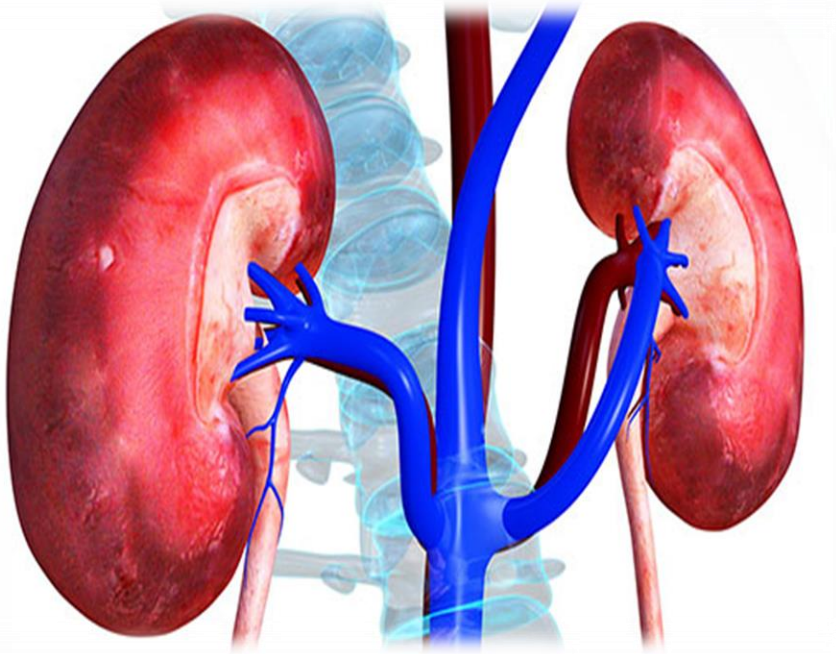
In età pediatrica sono disponibili **pochissimi studi** sull'impatto dell'obesità sul rene

La glomerulopatia obesità-correlata sembra essere **un'entità virtuale** - non diagnosticata

Correia- Costa. Port J Nephrol Hypert 2016

•Le alterazioni iniziano a svilupparsi **molti anni prima della comparsa di diabete e ipertensione,** noti fattori di rischio di CKD

•Difficile evidenziare e quantificare queste alterazioni senza procedure invasive (biopsia)



Correia- Costa. Port J Nephrol Hypert 2016

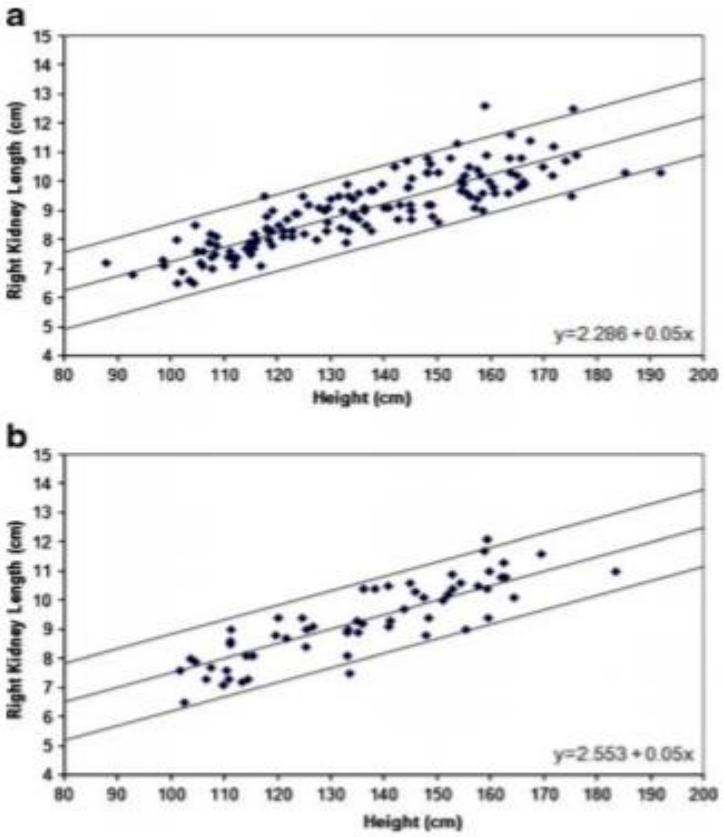


Fig. 1 Renal length nomogram based on height for (**a**) NW and (**b**) obese children for the right kidney, with 95% confidence intervals

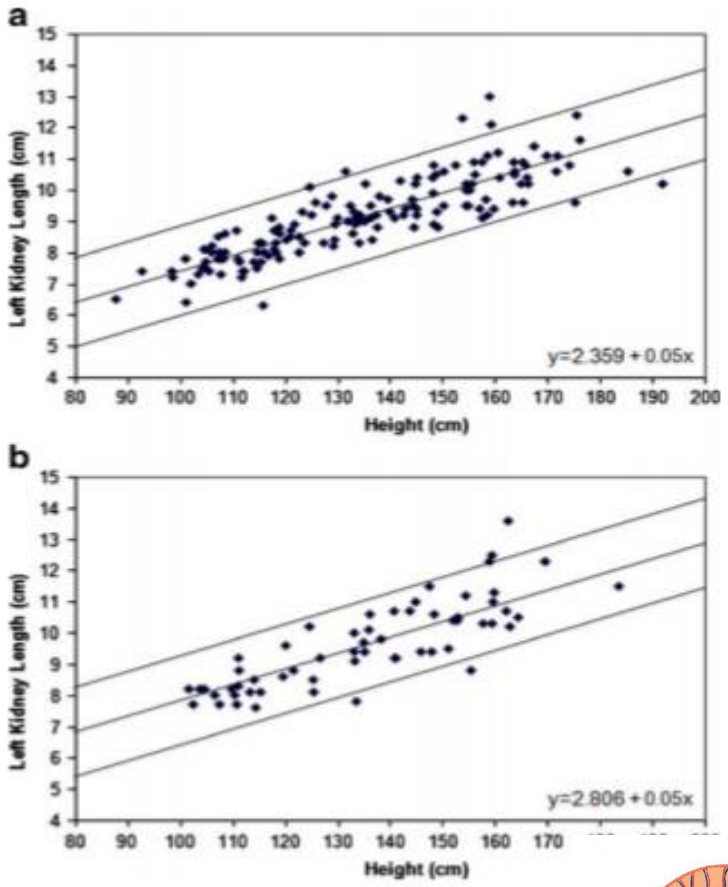
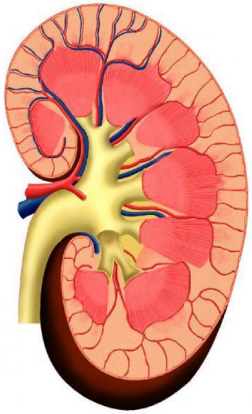


Fig. 2 Renal length nomogram based on height for (a
obese children for the left kidney, with 95% confidence

I **bambini obesi** rispetto ai normopeso hanno
- **reni dimensionalmente più grandi**
- **aumento del flusso renale**



Pediatr Nephrol (2009) 24:2023–2027

Obesità infantile e proteinuria

- Bambini e adolescenti obesi possono avere **proteinuria**
- Correla con **il BMI** e la presenza di **ipertensione arteriosa**
- Non tutti gli autori sono concordi nell'utilizzare **l'albuminuria come marker di screening per il danno renale**: nei bambini normopeso può anche essere elevata (maggio livello di attività fisica)

Impact of obesity on childhood kidney. Pediatr Rep 2011. Proteinuria and focal segmental glomerulosclerosis in severely obese adolescents. J Pediatr 2001; Is albuminuria associated with obesity in school children? Pediatric Diabetes 2009

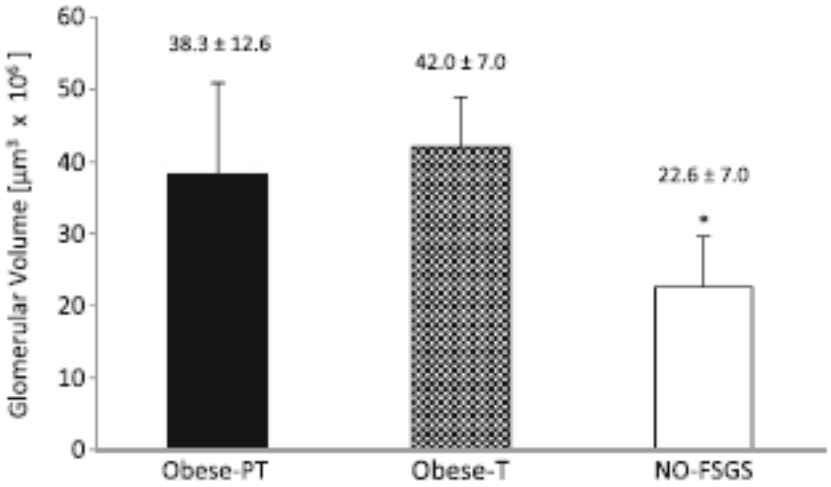
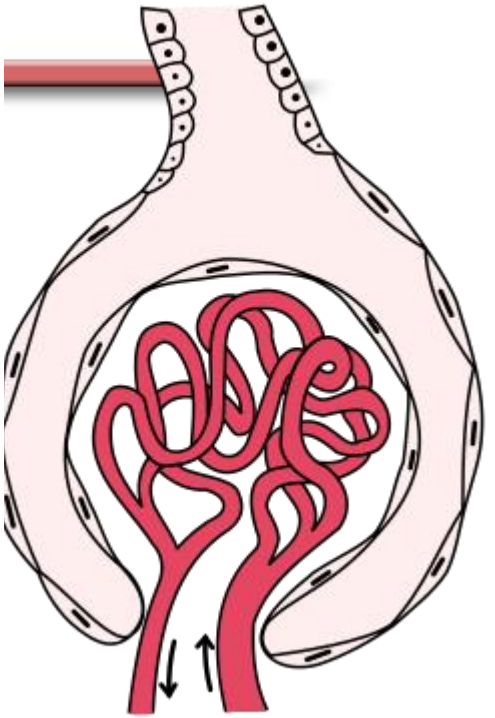


Fig. 1 Average glomerular volume in obese preterm (PT) and obese term (T) children is significantly higher than in nonobese (NO) focal segmental glomerular sclerosis (FSGS) children. Used with permission from [14]



I bambini obesi con proteinuria hanno un aumento del volume del glomerulo rispetto ai bambini normopeso

Pediatr Nephrol (2009) 24:2023–2027

Articles | Clinical Investigation

Decreased renal function in overweight and obese prepubertal children

Table 2. Mean changes in renal function markers and estimated glomerular filtration rates per unit of BMI z-score

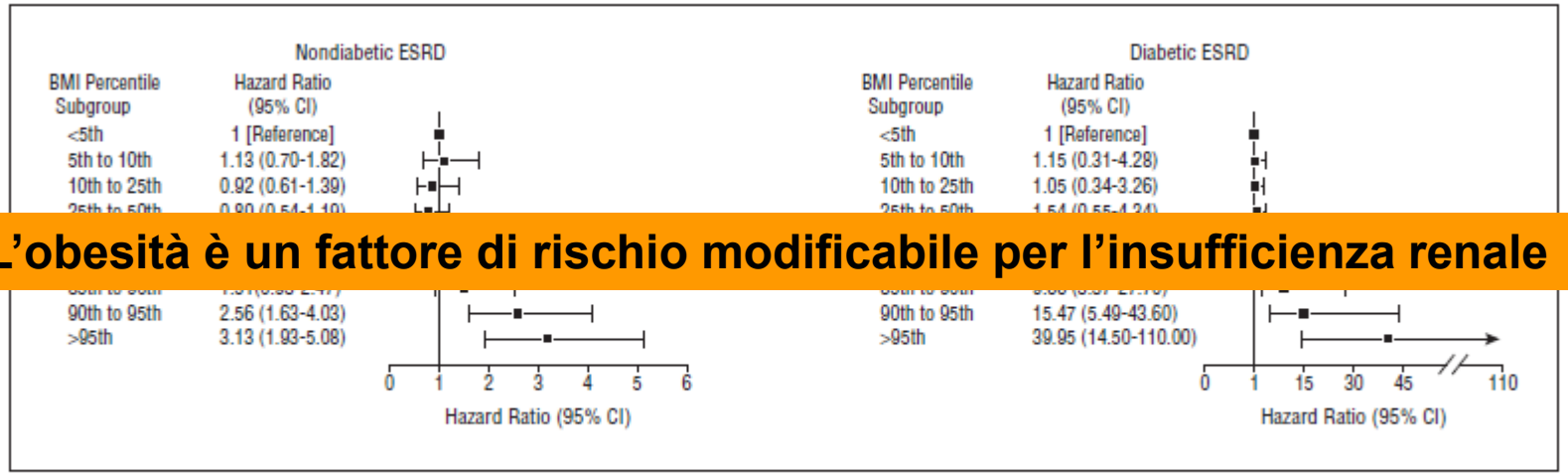
	Creatinine (mg/dl)	Cystatin C (mg/l)	eGFR Schwartz-R (ml/min/1.73m²)	eGFR Filler (ml/min/1.73m²)	eGFR Zappitelli-Comb (ml/min/1.73m²)	eGFR Schwartz-Comb (ml/min/1.73m²)	CrCl (ml/min/1.73 m²)
BMI z-score	0.007 (0.002 to 0.013); $P = 0.004$	0.017 (0.011 to 0.023); $P < 0.001$	−0.51 (−2.17 to 1.16); $P = 0.548$	−4.26 (−5.77 to −2.74); $P < 0.001$	−2.77 (−4.16 to −1.38); $P < 0.001$	−1.10 (−2.01 to −0.18); $P = 0.014$	−3.54 (−6.52 to −0.57); $P = 0.020$

The values presented are β and 95% confidence intervals, estimated by multiple linear regression, with renal function markers as dependent variable and BMI z-score (continuous) as independent variable, adjusting for sex and age in months. In the model with 24-h creatinine clearance only 298 cases with valid 24-h urine samples were included.
eGFR, estimated glomerular filtration rate.

CONCLUSION: Young prepubertal children with overweight/obesity already present significantly lower GFR estimations that likely represent some degree of renal impairment associated with the complex deleterious effects of adiposity.

Bambini obesi dall'età di 4 anni
Valutati all'età di 8-9 anni

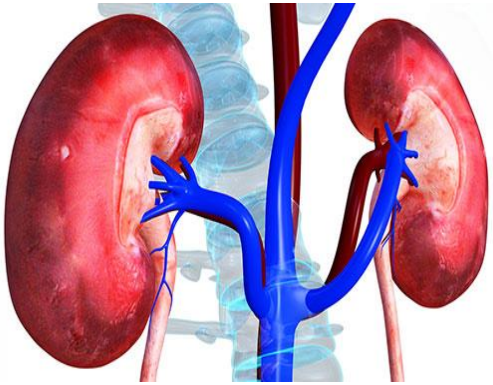
Body Mass Index in 1.2 Million Adolescents and Risk for End-Stage Renal Disease

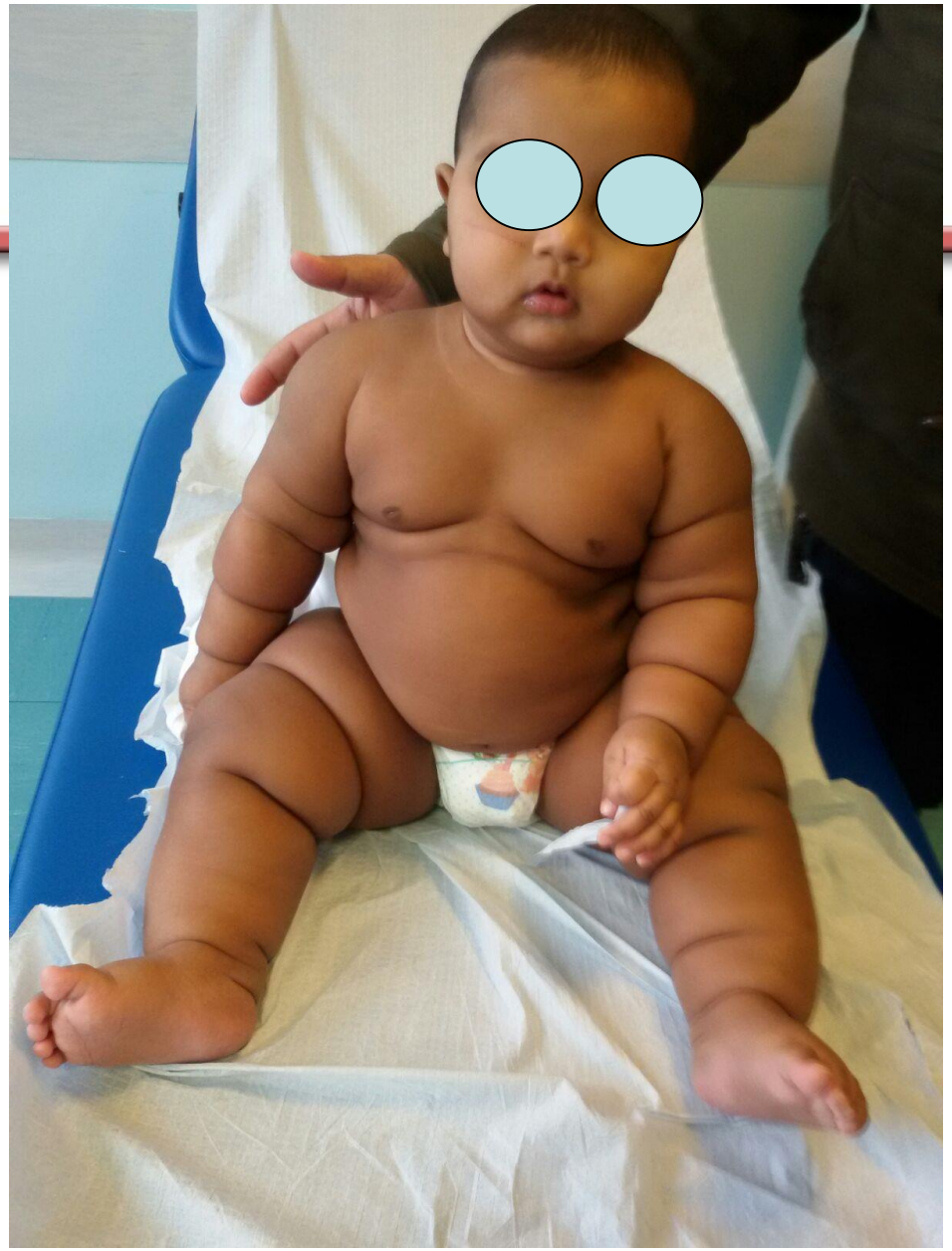


L'obesità è un fattore di rischio modificabile per l'insufficienza renale

Figure 2. Hazard ratios for diabetic and nondiabetic end-stage renal disease (ESRD) by body mass index (BMI) percentile subgroup. Model 2 is adjusted for sex, country of origin, period of enrollment in the study, and systolic blood pressure (above or below the 95th age-specific and sex-specific percentiles). Black boxes indicate significant results ($P < .001$).

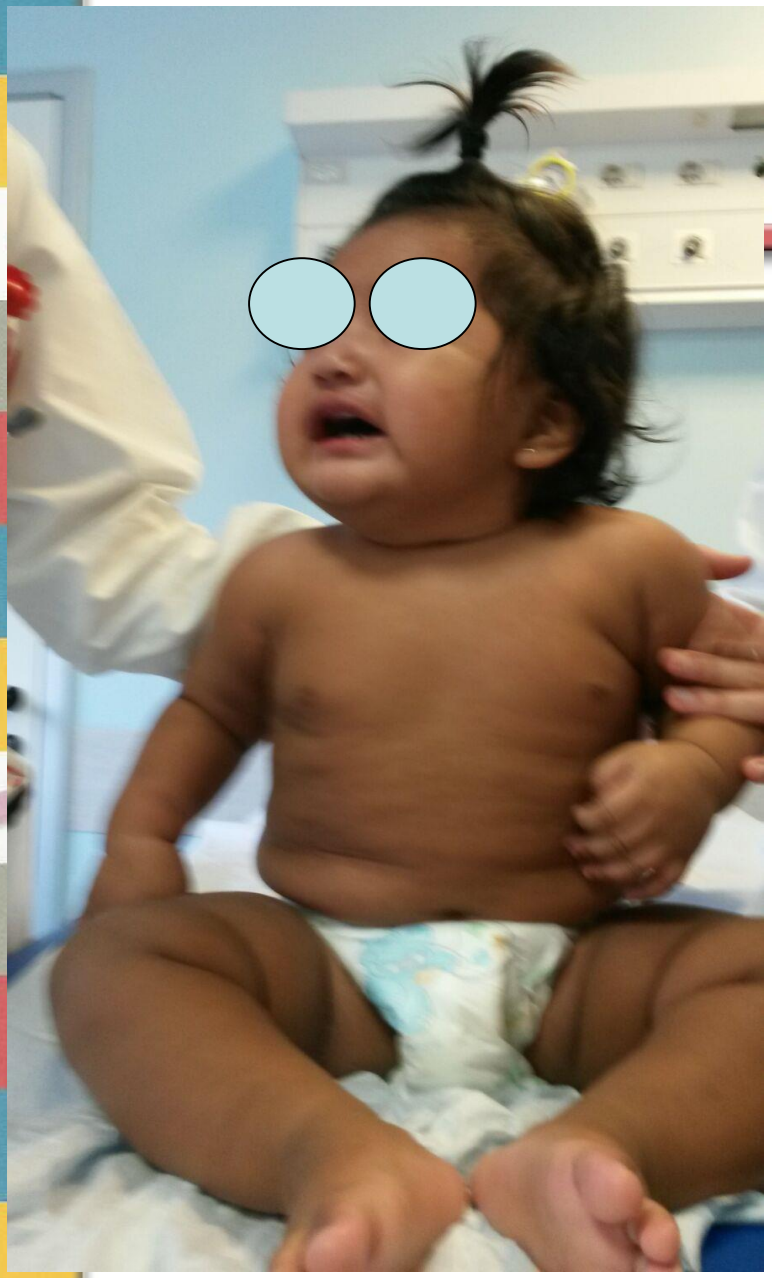
Conclusions: Overweight and obesity in adolescents were associated with significantly increased risk for all-cause treated ESRD during a 25-year period. Elevated BMI constitutes a substantial risk factor for diabetic and nondiabetic ESRD.



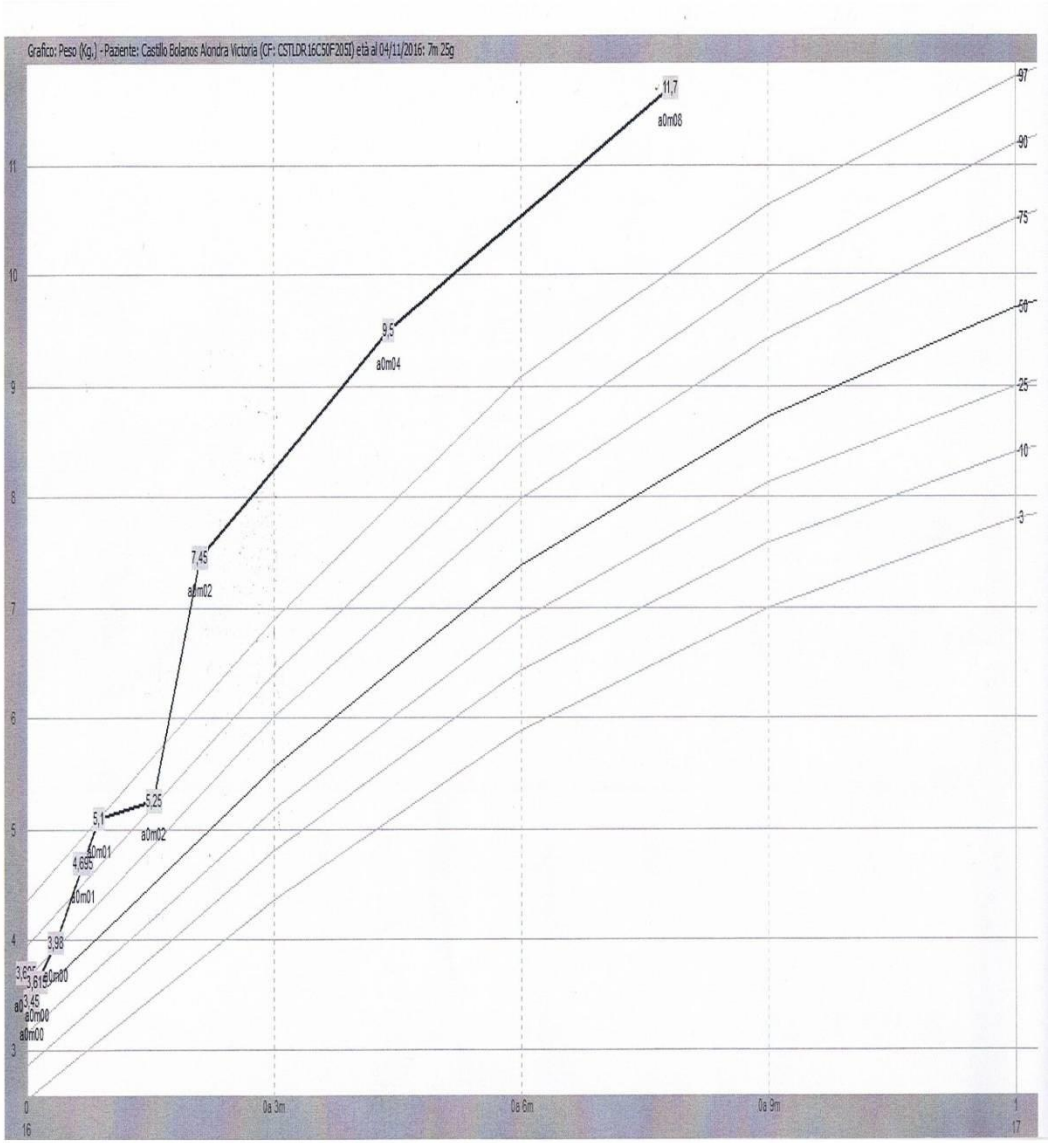


R. 7 mesi Femmina

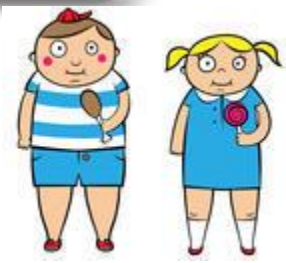
- Inviata all'Ambulatorio di Endocrinologia pediatrica per obesità a precoce insorgenza
- 7 mesi: peso 14 kg (>>97°centile)
- Nessuna causa accertata di obesità secondaria o genetica
- Riscontro di Ipertensione arteriosa inizialmente in duplice terapia, attualmente monoterapia

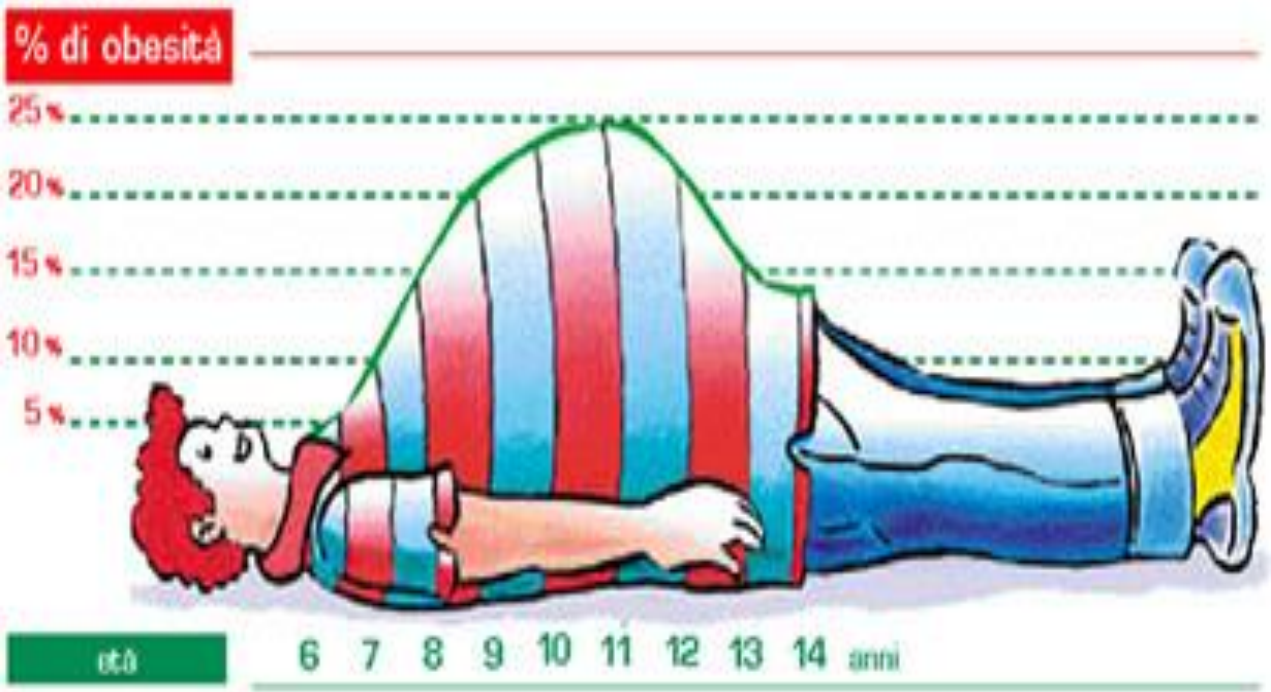


A , 8 mesi, Femmina
11.7 KG



Cosa ne sarà di loro e del loro rene da adulti?





Grazie

ENDING
CHILDHOOD
OBESITY