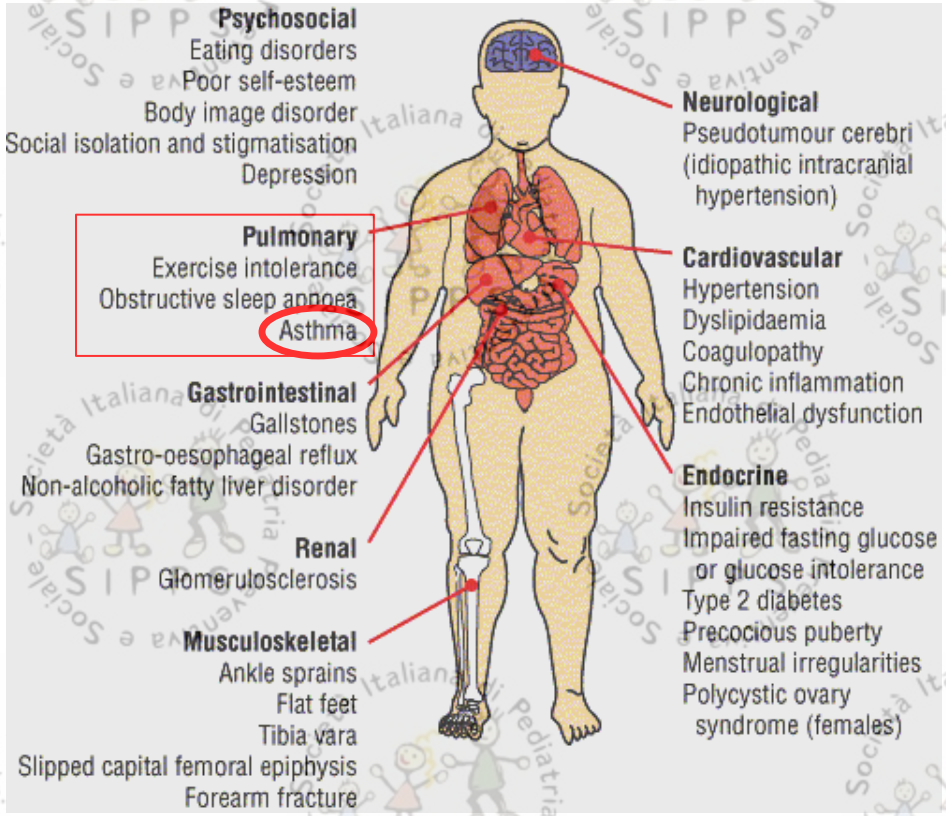
Respiratorie

Michele Miraglia del Giudice
Dipartimento della Donna, del Bambino e di Chirurgia Generale e Specialistica
Università della Campania "Luigi Vanvitelli"

OBESITY

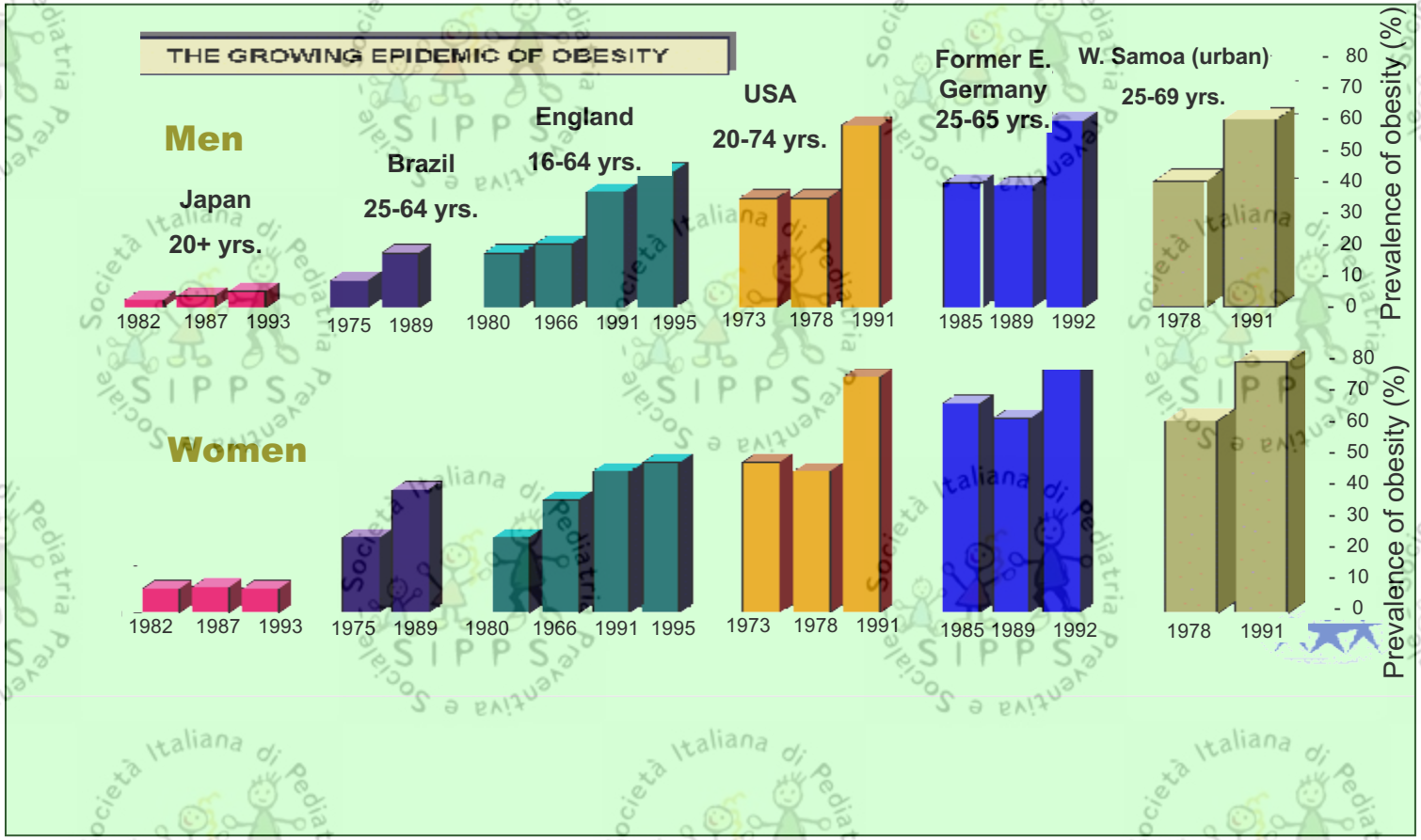
OBESITY AS A RISK FACTOR:

* Obesity increases the risk of developing many health conditions:



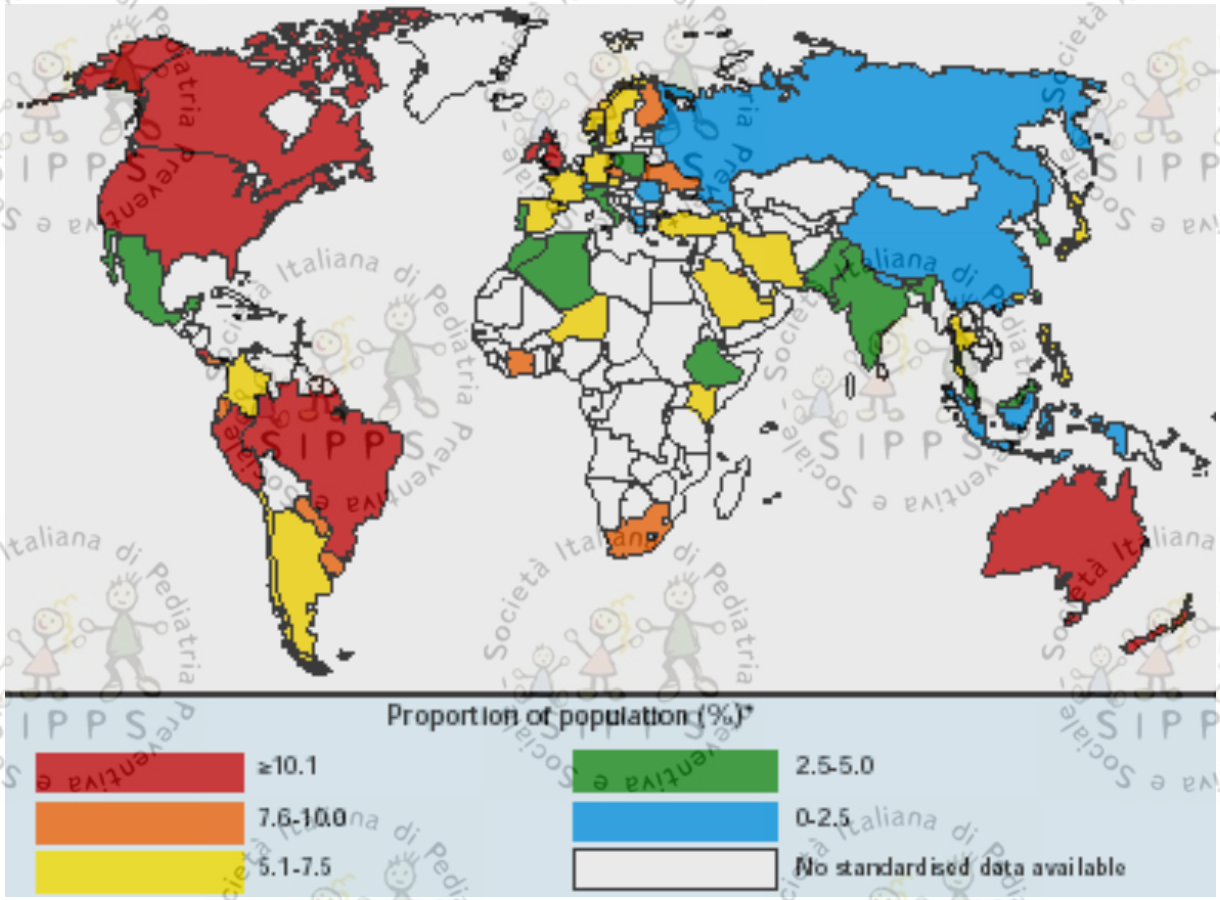
OBESITY

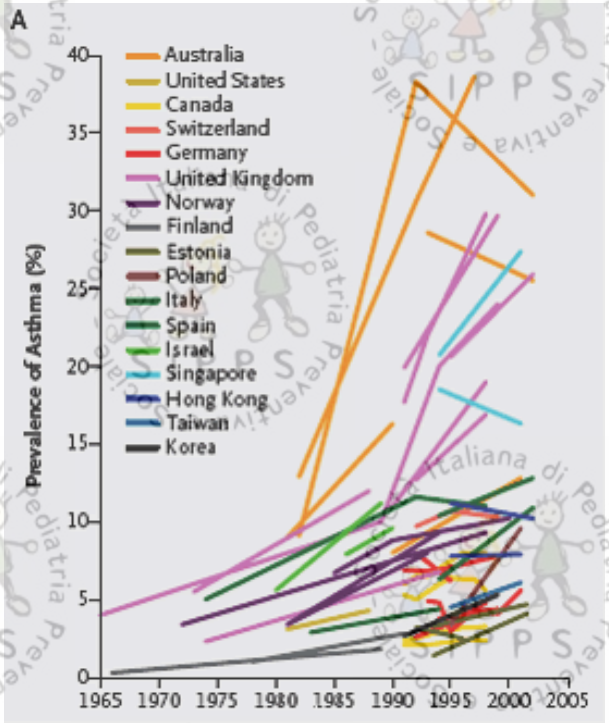
INCREASING PREVALENCE IN WESTERN COUNTRIES:



ASTHMA

INCREASING PREVALENCE IN WESTERN COUNTRIES:



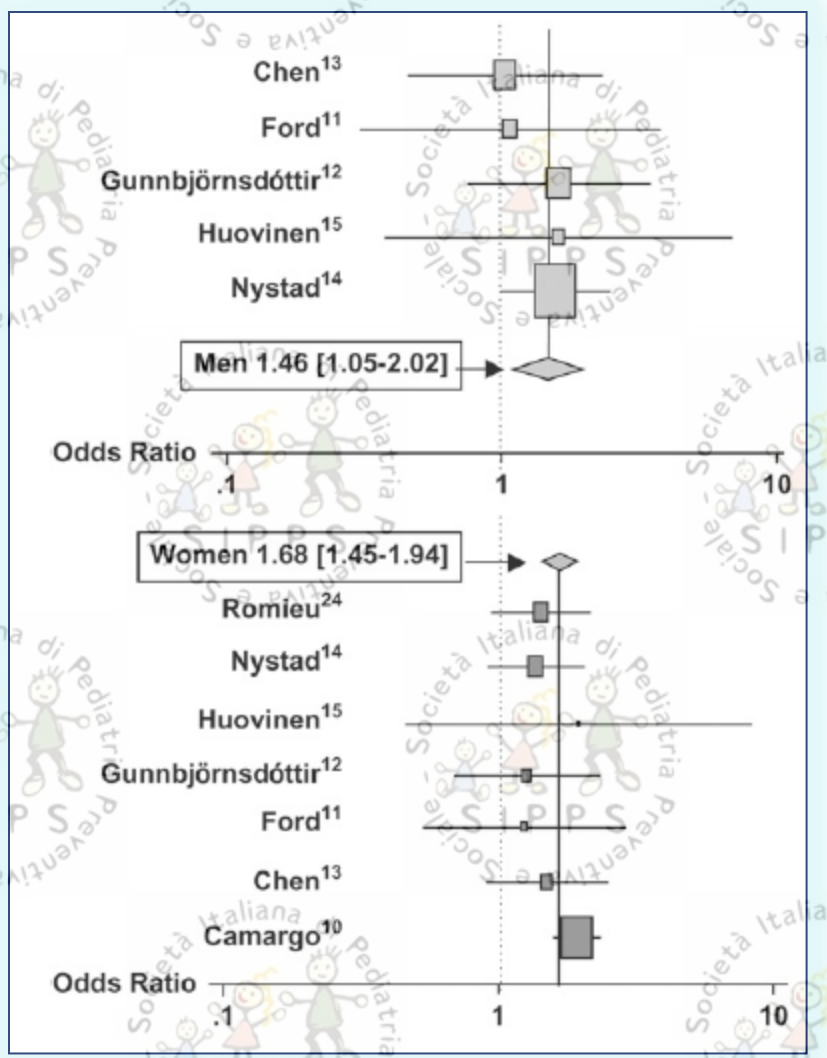


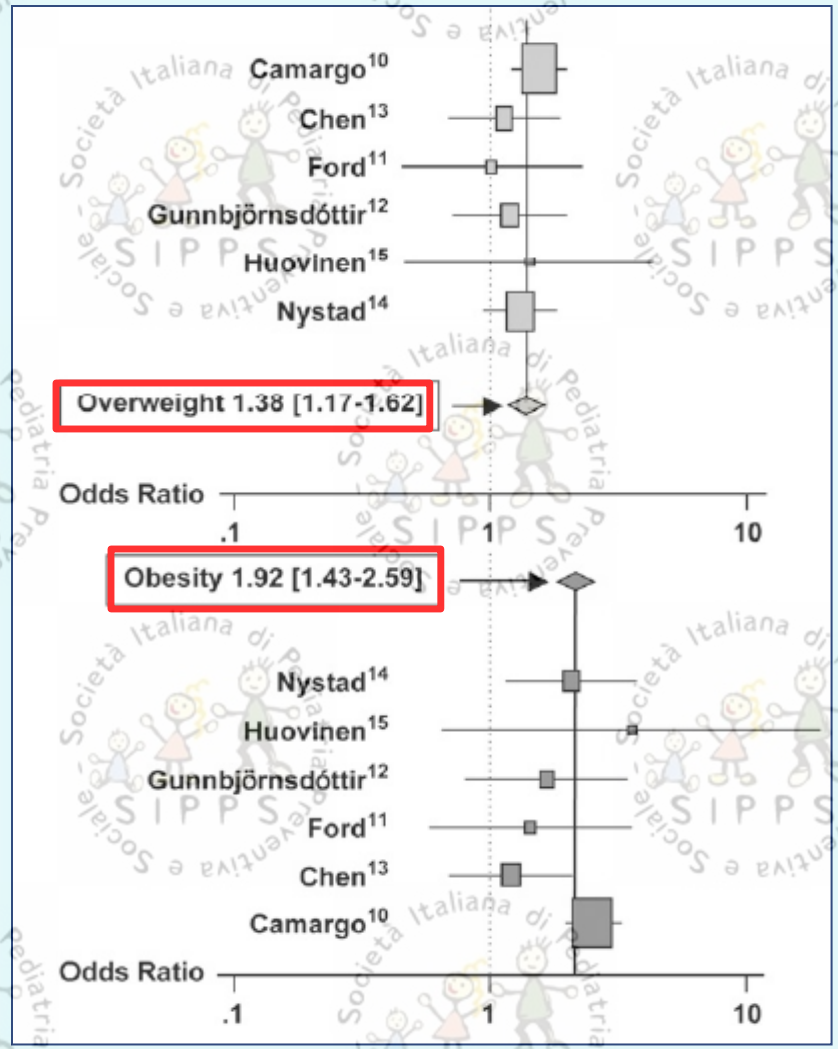
OBESITY & ASTHMA

EVIDENCE OF ASSOCIATION BETWEEN OBESITY AND ASTHMA:

* Studies have shown 1.5-3-0 fold increase in prevalence of asthma amongst obese patients.

OBESITY & ASTHMA





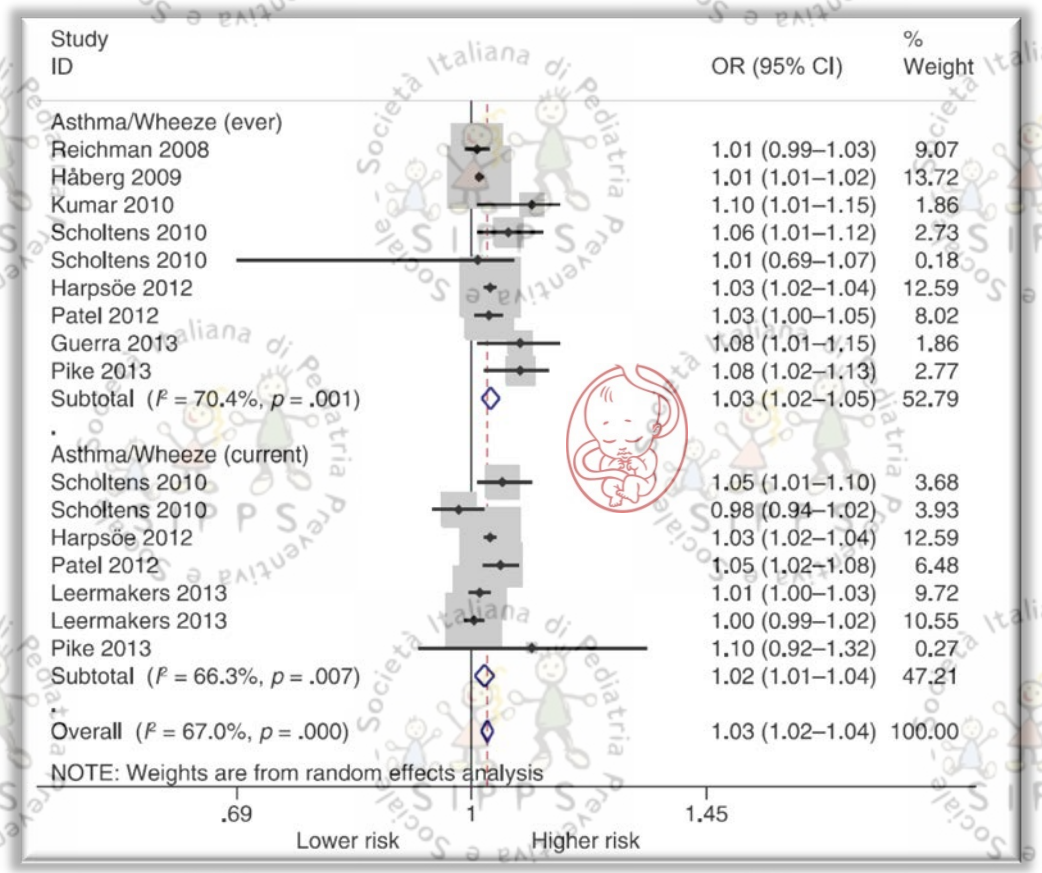
Beuther DA & Sutherland ER – Overweight, obesity, and incident asthma. A meta-analysis of prospective epidemiologic studies. *Am J Respir Crit Care Med* 2007;175:661.666

Maternal obesity in pregnancy, gestational weight gain, and risk of childhood asthma.

Forno E et al Pediatrics 2014; 134:e535-46

Obesity-induced increases in asthma risk can start in utero.

In a meta-analysis of more than 108,000 participants, we found that **maternal obesity and weight gain during pregnancy** are independently associated with approximately **15% to 30% increased risk of asthma in the offspring**

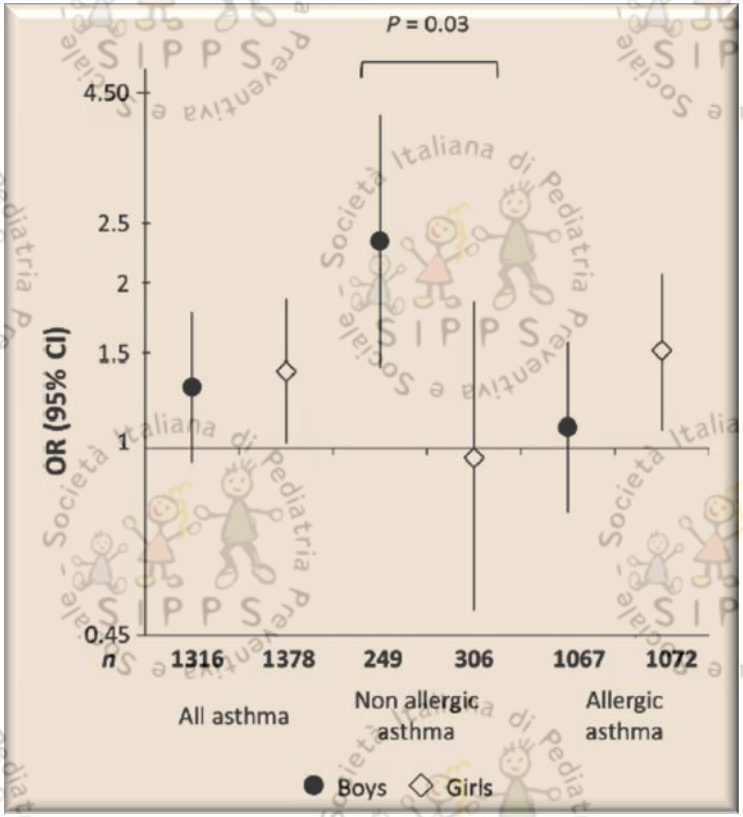


Longitudinal study of maternal body mass index, gestational weight gain, and offspring asthma

Dumas O et al Allergy 2016; 71: 1295–1304.

In a longitudinal study of 12 963 adolescents (9-14 y.) and their mothers, we examined the association of (i) maternal prepregnancy body mass index (BMI) and (ii) gestational weight gain (GWG), with incidence of allergic and nonallergic asthma in offspring.

- We observed a positive association between maternal prepregnancy BMI and offspring asthma
- The association appeared stronger for nonallergic asthma than for allergic asthma
- A suggestive association between low birthweight and asthma was observed with a stronger and significant association for nonallergic asthma.



Associations (adjusted odds ratio and 95% confidence intervals) between maternal prepregnancy obesity (body mass index ≥30 kg/m2) and incidence of allergic and nonallergic asthma in childhood, according to the child's sex.

OBESITY & ASTHMA

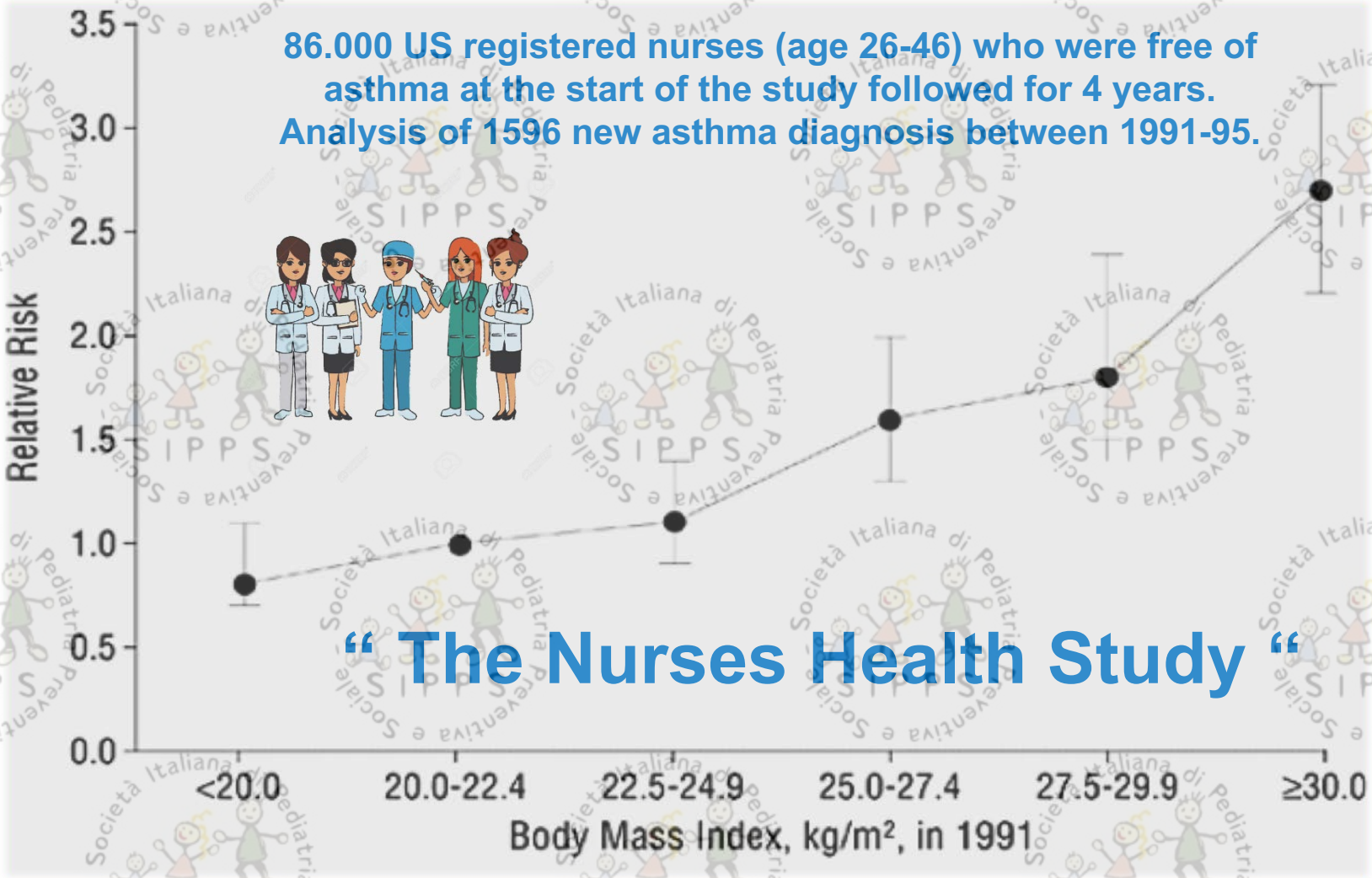
EVIDENCE OF ASSOCIATION BETWEEN OBESITY AND ASTHMA:

* Studies have shown 1.5-3-0 fold increase in prevalence of asthma amongst obese patients.

* Weight gain is associated with incident cases of asthma.

OBESITY & ASTHMA

86.000 US registered nurses (age 26-46) who were free of asthma at the start of the study followed for 4 years. Analysis of 1596 new asthma diagnosis between 1991-95.

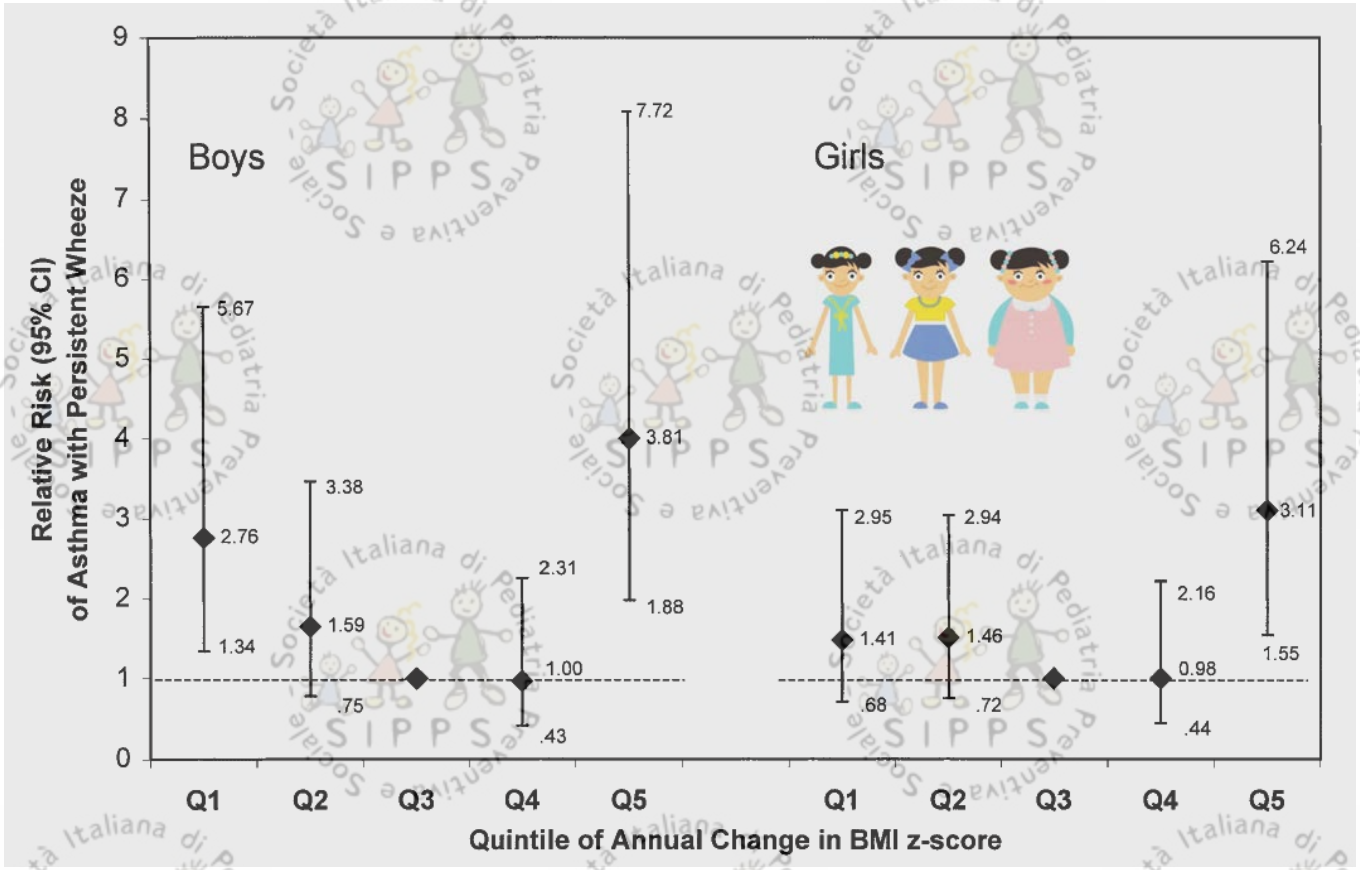


“ The Nurses Health Study “

Camargo CA et al – Prospective study of Body Mass Index, weight change and risk of adult-onset of asthma in women. *Arch Internal Med* 1999;159:2582-2588

Body-Mass Index as a Predictor of Incident Asthma in a Prospective Cohort of Children *Gold DR et al Pediatric Pulmonology 2003: 36:514–521*

Studio prospettico longitudinale sulla variazione dell'indice di massa corporea (BMI) vs l'incidenza di asma in 9828 bambini (6-14 anni) valutati annualmente per 5 anni



An increased risk of a new asthma diagnosis was associated with higher BMI at entry into the study (P=0.009) and **greater increase in BMI during follow-up** (P=0.0003).

OBESITY & ASTHMA

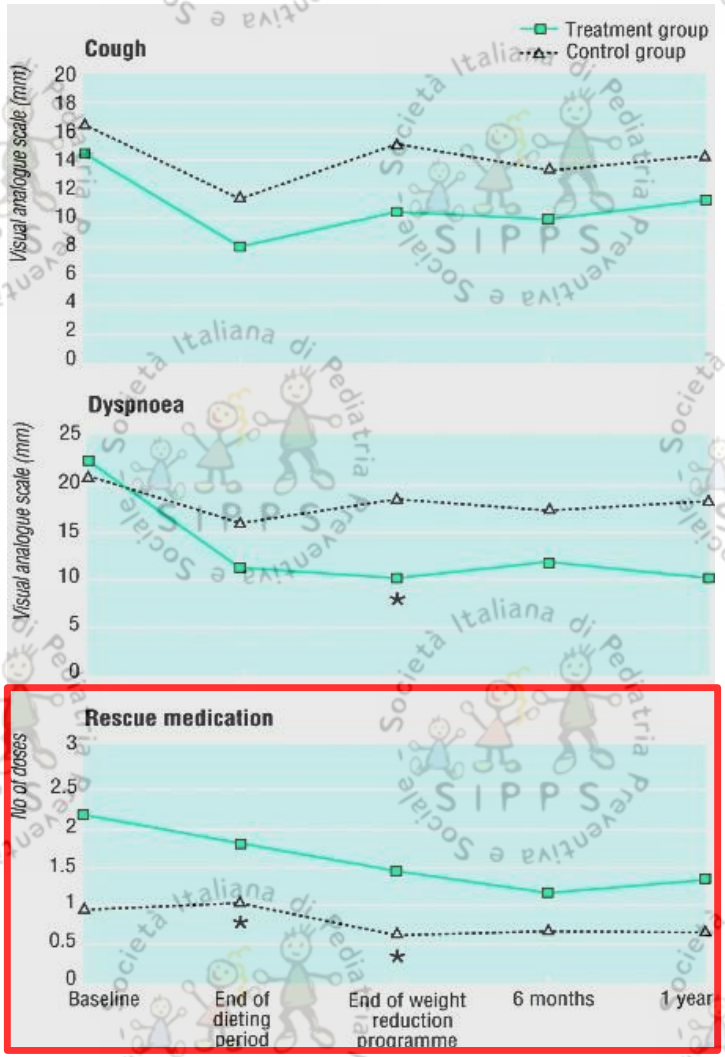
EVIDENCE OF ASSOCIATION BETWEEN OBESITY AND ASTHMA:

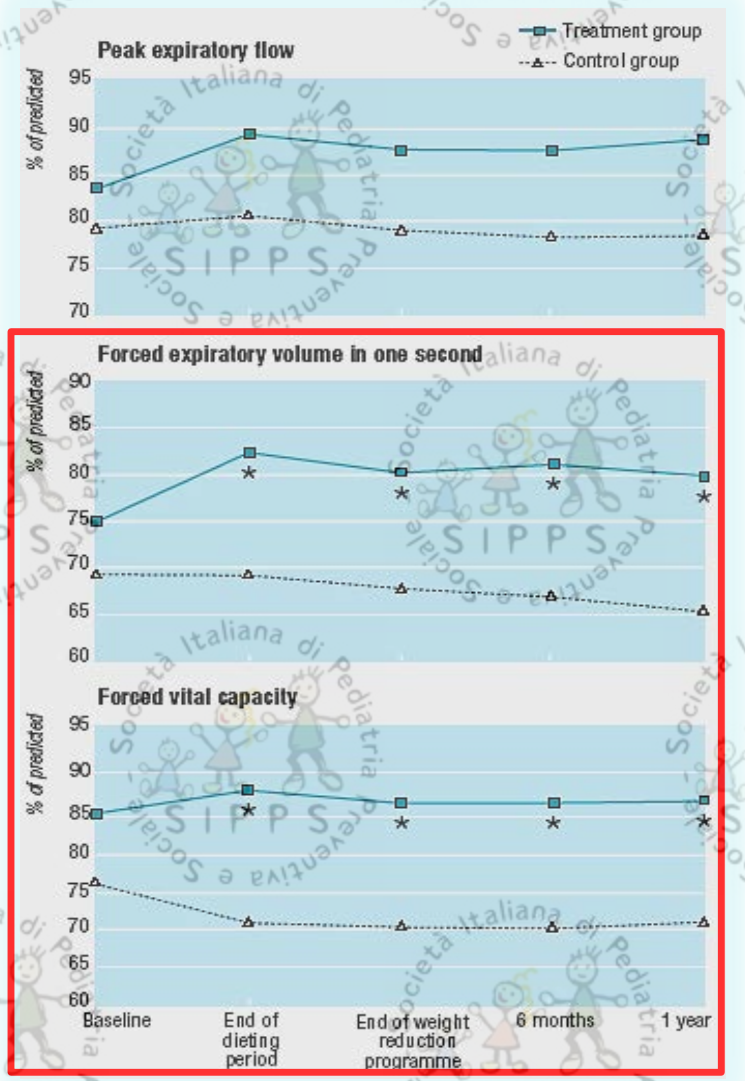
* Studies have shown 1.5-3-0 fold increase in prevalence of asthma amongst obese patients.

* Weight gain is associated with incident cases of asthma.

* Weight loss is associated with improved asthma outcomes.

OBESITY & ASTHMA





Stenius-Aarniala B et al. – **Immediate and long term effects of weight reduction in obese people with asthma: randomised controlled study.** *BMJ* 2000

OBESITY & ASTHMA

EVIDENCE OF ASSOCIATION BETWEEN OBESITY AND ASTHMA:

* Studies have shown 1.5-3-0 fold increase in prevalence of asthma amongst obese patients.

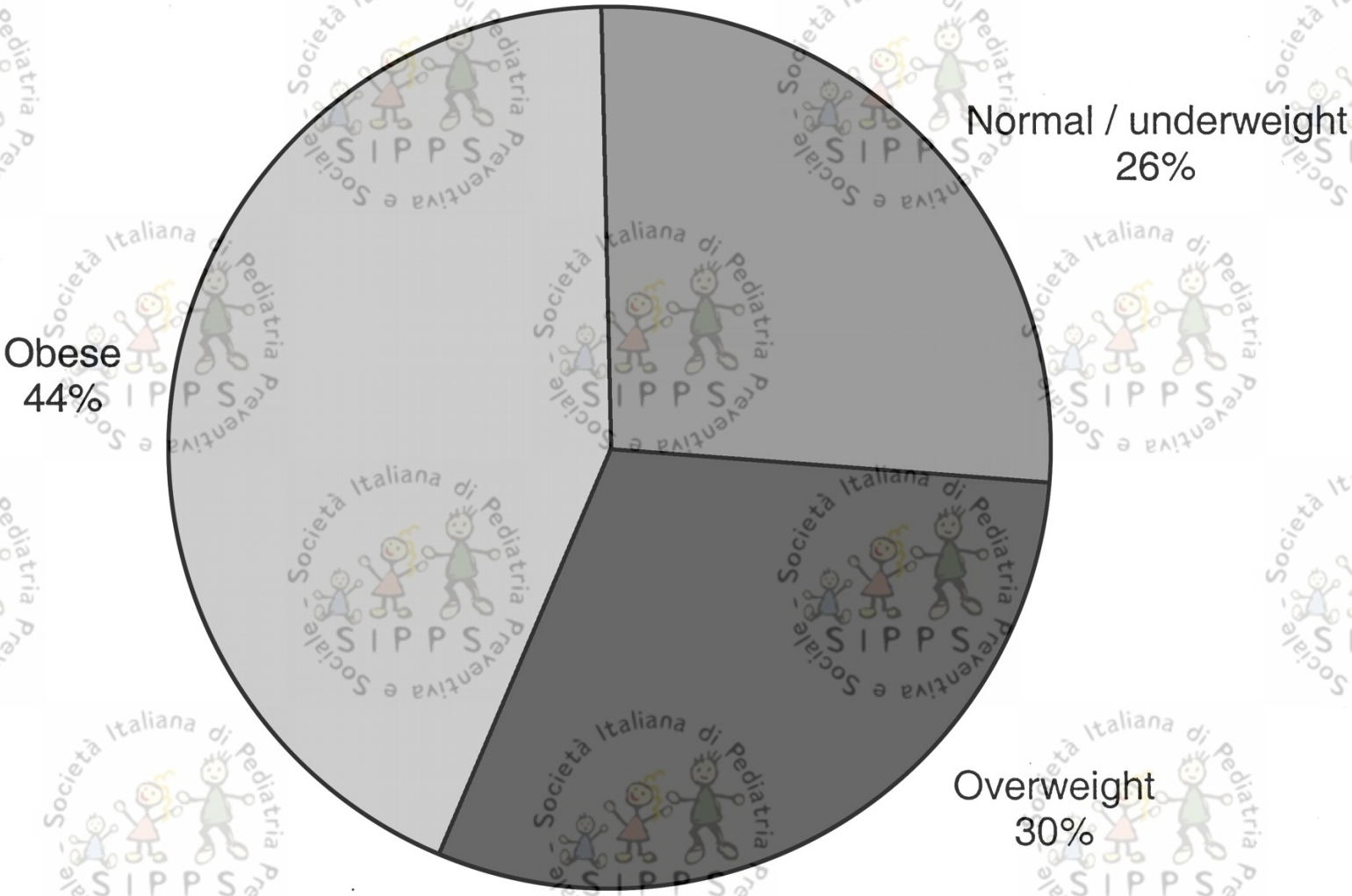
* Weight gain is associated with incident cases of asthma.

* Weight loss is associated with improved asthma outcomes.

* Obesity is associated with more severe asthma and more difficult asthma control.

OBESITY & ASTHMA

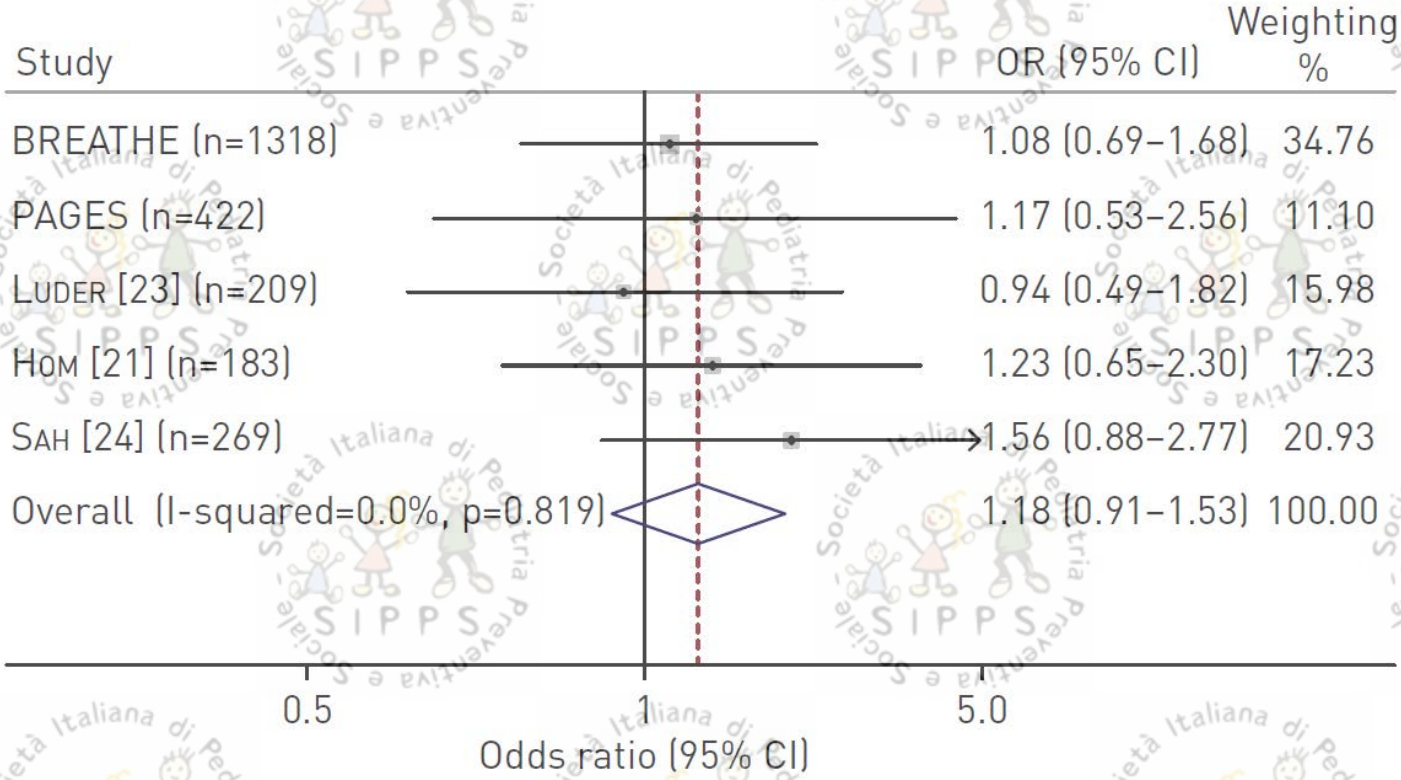
Distribution of BMI among adults presenting to the ED with acute asthma.



Childhood obesity in relation to poor asthma control and exacerbation: a meta-analysis *Ahmadizar F et al Eur Respir J 2016; 48: 1063–1073*

In a meta-analysis of 46070 asthmatic children and adolescents, obese children were compared with non-obese

Pooled odds ratio of the association combined overweight and obesity with hospitalisation due to asthma.



i bambini obesi e in sovrappeso hanno un rischio più elevato per le esacerbazioni gravi di asma

Obesity and adiposity indicators, asthma, and atopy in Puerto Rican children *Forno E et al J Allergy Clin Immunol 2014;133:1308-14*

In a study of Puerto Rican children with (n 5 351) and without (n 5 327) asthma, we measured BMI, percent of body fat, waist circumference, and waist-to-hip ratio

TABLE II. Indicators of adiposity, allergy markers, and indicators of asthma severity or control

	BMI	PBF	WC	WHR
Asthma status	**1.27 (1.1-1.5)***	1.24 (0.99-1.6)†	1.18 (0.98-1.4)†	1.12 (0.93-1.35)‡
Lung function in cases				
FEV_1 (mL)§	**68.8 (34.7-103.0)***	37.5 (−10.5 to 84.5)‡	20.1 (−18.3 to 60.2)‡	27.3 (−19.4 to 74.0)‡
FVC (mL)§	**98.0 (59.0-137.1)***	**63.4 (8.9-117.8)***	**61.1 (15.9-106.2)***	50.1 (−4.0 to 104.3)†
FEV_1/FVC (%)	−0.6 (−1.5 to 0.5)‡	−0.6 (−1.9 to 0.7)‡	−1.0 (−2.1 to 0.0)†	−0.7 (−2.1 to 0.7)‡
Asthma severity				
Urgent care visits, ever	**3.0 (0.01-6.1)***	**4.6 (0.50-8.79)***	3.4 (−0.01 to 6.8)†	2.4 (−2.0 to 6.9)‡
>1 urgent care visit, last year	1.23 (0.96-1.59)†	1.40 (0.99-1.97)*	0.99 (0.75-1.31)‡	1.01 (0.70-1.45)‡
Severity scores				
Prednisone courses	0.08 (−0.01 to 0.17)†	**0.15 (0.03-0.28)***	0.07 (−0.03 to 0.14)‡	0.07 (−0.05 to 0.20)‡
Missed school days	**0.13 (0.02-0.25)***	**+0.17 (0.01-0.33)***	**0.13 (0.005-0.26)***	0.10 (−0.05 to 0.26)‡
Exercise symptoms	0.09 (−0.02 to 0.11)‡	**0.15 (0.03-0.29)***	**0.18 (0.07-0.29)***	**0.18 (0.04-0.32)***
Atopy measures in cases				
Allergic rhinitis	1.19 (0.96-1.49)‡	1.33 (0.97-1.81)†	**1.36 (1.05-1.77)***	1.31 (0.95-1.90)†
Total IgE level (IU/mL)‖	0.99 (0.84-1.18)‡	1.04 (0.83-1.31)‡	**1.2 (1.002-1.45)***	1.03 (0.83-1.29)‡
STR to¶				
Dust mite	0.97 (0.77-1.23)‡	1.17 (0.85-1.61)‡	1.07 (0.83-1.39)‡	0.95 (0.70-1.30)‡
Cockroach	**1.37 (1.04-1.79)***	**1.57 (1.11-2.24)***	**1.49 (1.11-2.01)***	1.41 (0.99-2.01)†
Alternaria	**1.46 (1.08-1.97)***	**1.80 (1.20-2.70)***	**1.76 (1.26-2.45)***	**1.44 (1.01-2.06)***
Mold	**2.54 (1.54-4.19)***	**2.08 (1.23-3.52)***	**1.80 (1.20-2.71)***	1.17 (0.73-1.88)‡
Mouse	**1.36 (1.02-1.83)***	**1.70 (1.15-2.51)***	**1.38 (1.01-1.88)***	1.21 (0.85-1.74)‡
Any STR+	**1.30 (1.02-1.64)***	**1.54 (1.10-2.17)***	**1.36 (1.03-1.78)***	1.35 (0.96-1.91)†

*$P < .05$. †$P < .10$. ‡$P > .10$.

Adiposity indicators are associated with asthma, asthma severity/control, and atopy.

OBESITY & ASTHMA

EVIDENCE OF ASSOCIATION BETWEEN OBESITY AND ASTHMA:

* Studies have shown 1.5-3-0 fold increase in prevalence of asthma amongst obese patients.

* Weight gain is associated with incident cases of asthma.

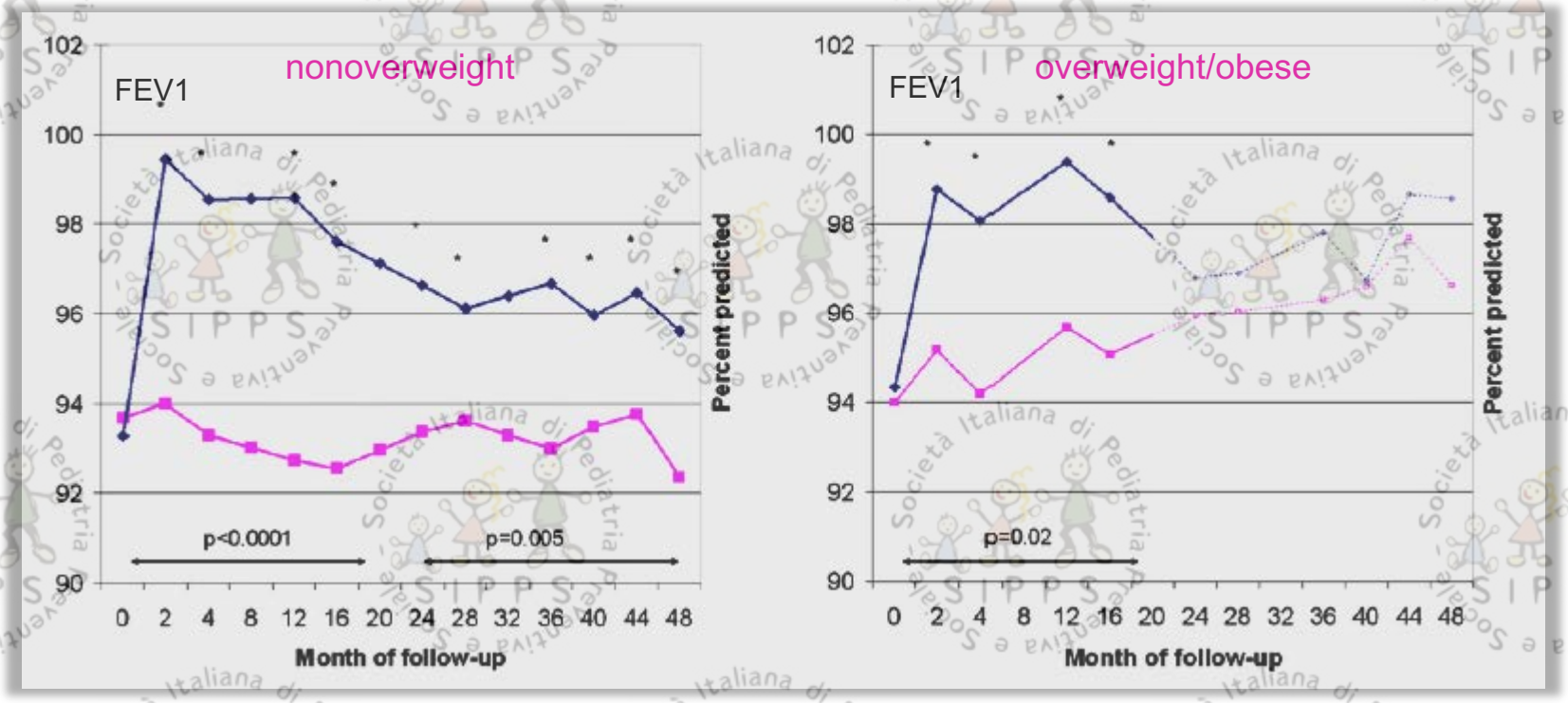
* Weight loss is associated with improved asthma outcomes.

* There is particularly compelling association between obesity and more severe asthma and asthma control.

* Obesity decreased response to inhaled steroids

Decreased response to inhaled steroids in overweight and obese asthmatic children *Forno E et al J Allergy Clin Immunol 2011;127:741-9*

We performed a post hoc analysis to evaluate the interaction between body mass index (BMI) and treatment with inhaled budesonide on lung function in the CAMP study (1041 children; mean age 8.9 years; 31.4% were overweight/obese)

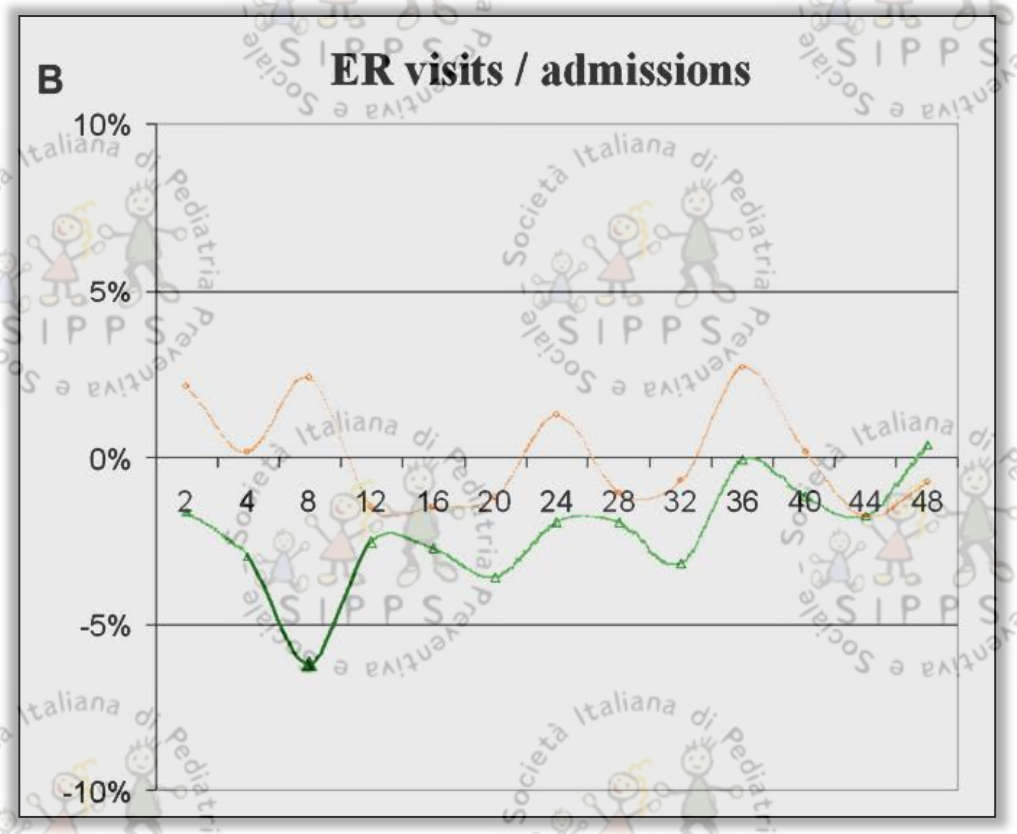


Nonoverweight children showed a significant improvement in all of the outcomes (FEV1, FEV1/FVC ratio, and BDR) during the early (months 0-20) and late (months 24-48) stages of the trial.
Among overweight/obese children, there was significant improvement in FEV1 and BDR during the early stage of the trial but not thereafter.

Decreased response to inhaled steroids in overweight and obese asthmatic children *Forno E et al J Allergy Clin Immunol 2011;127:741-9*

We performed a post hoc analysis to evaluate the interaction between body mass index (BMI) and treatment with inhaled budesonide on lung function in the CAMP study (1041 children; mean age 8.9 years; 31.4% were overweight/obese)

Nonoverweight children had a 44% reduction in the risk of emergency department visits or hospitalizations throughout the trial *(P = .001)*; there was **no reduction in risk among overweight/obese children** *(P= .97)*.



OBESITY & ASTHMA

EVIDENCE OF ASSOCIATION BETWEEN OBESITY AND ASTHMA:

* Studies have shown 1.5-3-0 fold increase in prevalence of asthma amongst obese patients.

* Weight gain is associated with incident cases of asthma.

* Weight loss is associated with improved asthma outcomes.

* There is particularly compelling association between obesity and more severe asthma and asthma control.

* Obesity decreased response to inhaled steroids

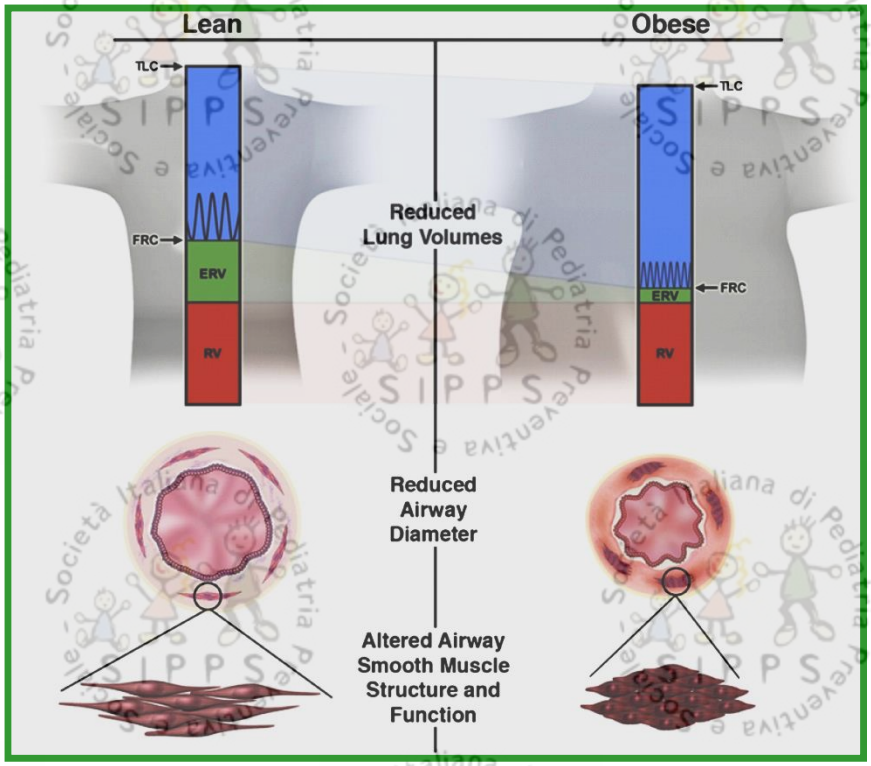
* **Mechanisms of the link between obesity and asthma**

OBESITY & ASTHMA

MECHANISMS OF THE LINK BETWEEN OBESITY AND ASTHMA:

Possible mechanism	Brief explanation
Comorbidities	There may be an indirect link between obesity and asthma due to the role of obesity in other disease processes (e.g. increased risk of gastro-oesophageal reflux disease, sleep-disordered breathing, type 2 diabetes, and hypertension)
Foetal programming	Asthma may be the result of events occurring during development (e.g. obesity-related abnormalities in lung development)
Genetics	There may be an overlap in the genes responsible for asthma and obesity (e.g. TNF-α)
Effects on lung volume	Obesity produces negative effects on the residual capacity of the lung and the flexibility of airway smooth muscle, making the muscle stiffer and reducing airway volume
Chronic systemic inflammation	The expression of inflammatory genes (e.g. TNF-α, which causes airway hyperresponsiveness) is upregulated in the adipose tissue of obese individuals, leading to chronic, low-level systemic inflammation
Action of adipokines	There are changes in the serum concentrations of adipokines (e.g. leptin, adiponectin, and PAI-1) that could modify airway function and lead to asthma

PAI = plasminogen activator inhibitor; TNF-α = tumour necrosis factor alpha.



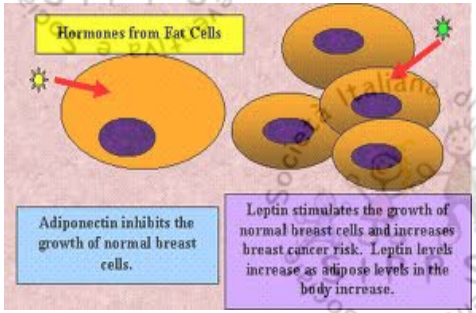
OBESITY & ASTHMA

MECHANISMS OF THE LINK BETWEEN OBESITY AND ASTHMA:

Possible mechanism	Brief explanation
Comorbidities	There may be an indirect link between obesity and asthma due to the role of obesity in other disease processes (e.g. increased risk of gastro-oesophageal reflux disease, sleep-disordered breathing, type 2 diabetes, and hypertension)
Foetal programming	Asthma may be the result of events occurring during development (e.g. obesity-related abnormalities in lung development)
Genetics	There may be an overlap in the genes responsible for asthma and obesity (e.g. TNF-α)
Effects on lung volume	Obesity produces negative effects on the residual capacity of the lung and the flexibility of airway smooth muscle, making the muscle stiffer and reducing airway volume
Chronic systemic inflammation	The expression of inflammatory genes (e.g. TNF-α, which causes airway hyperresponsiveness) is upregulated in the adipose tissue of obese individuals, leading to chronic, low-level systemic inflammation
Action of adipokines	There are changes in the serum concentrations of adipokines (e.g. leptin, adiponectin, and PAI-1) that could modify airway function and lead to asthma

PAI = plasminogen activator inhibitor; TNF-α = tumour necrosis factor alpha.

Adiponectin: the link between obesity and asthma in women? *Wood G. L et al AJRCCM 2012;186(1):1-10*



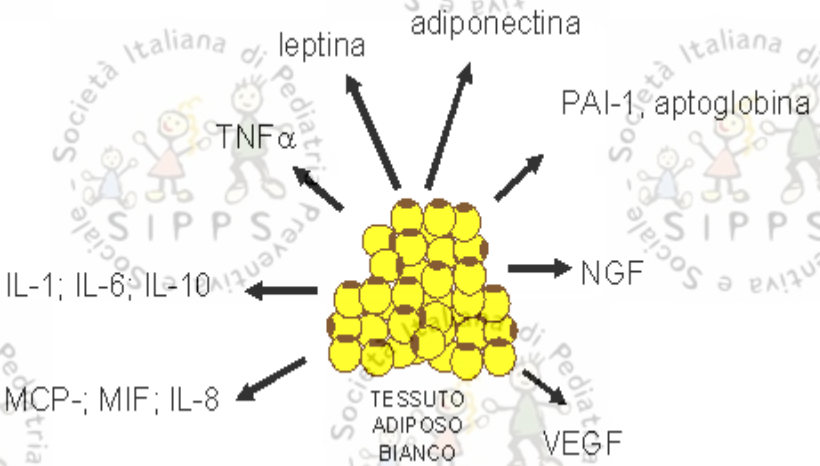
- **L'adiponectina** è un ormone secreto dal tessuto adiposo
- Altri ormoni derivati dal tessuto adiposo comprendono la **leptina** e la **resistina**
- **La leptina** e **la resistina** sono aumentate nell'obesità e **hanno effetti proinfiammatori**, compresa l'attivazione del fattore nucleare - kB (NF - kB), l'upregolazione dei livelli del fattore di necrosi tumorale a (TNFα) e l'aumento dell'**infiammazione neutrofilica delle vie aeree**
- **L'adiponectina,** d'altra parte, agisce generalmente come un **ormone antinfiammatorio** nell'obesità è ridotta, molto probabilmente a causa del rilascio di TNFα e IL-6 da parte dei macrofagi, che inibisce la produzione di adipociti di adiponectina
- **L'adiponectina** regola negativamente i toll-like receptors, inibisce l'attività di NF-kB, sopprime la produzione di citochine, compreso IL-6 e TNFα, e ha dimostrato di ridurre sia l'iperreattività delle vie aeree che la neutrofilia delle vie aeree in modello animale

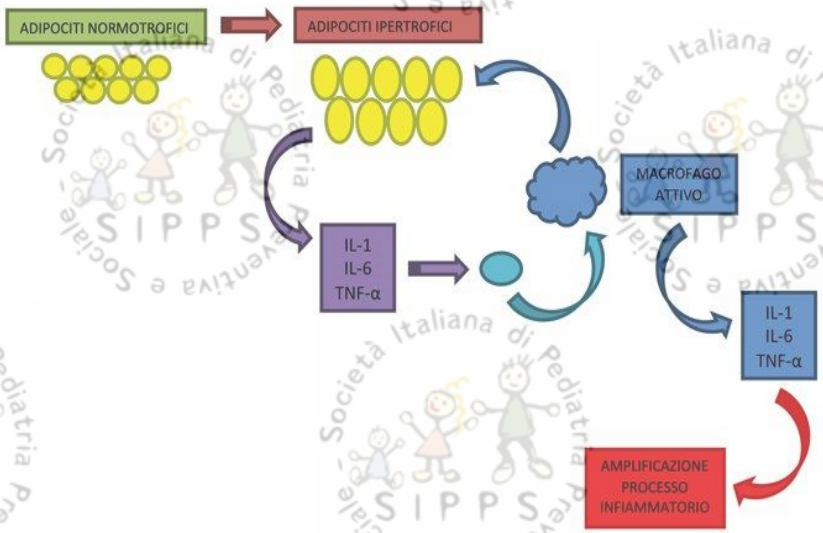
Low serum adiponectin predicts future risk for asthma in women *Sood A,* Am J Respir Crit Care Med *2012;186(1):41*

- Sebbene **gli adipociti viscerali siano la fonte più importante di adiponectina**, le concentrazioni sieriche di adiponectina si riducono nei soggetti obesi.

- Una possibile spiegazione è che **la necrosi correlata all'ipossia degli adipociti attiva i macrofagi** in soggetti obesi

- Questi macrofagi attivati **producono fattori di necrosi tumorale a e IL-6, che a loro volta possono inibire direttamente la produzione locale di adiponectina** in modo paracrino.



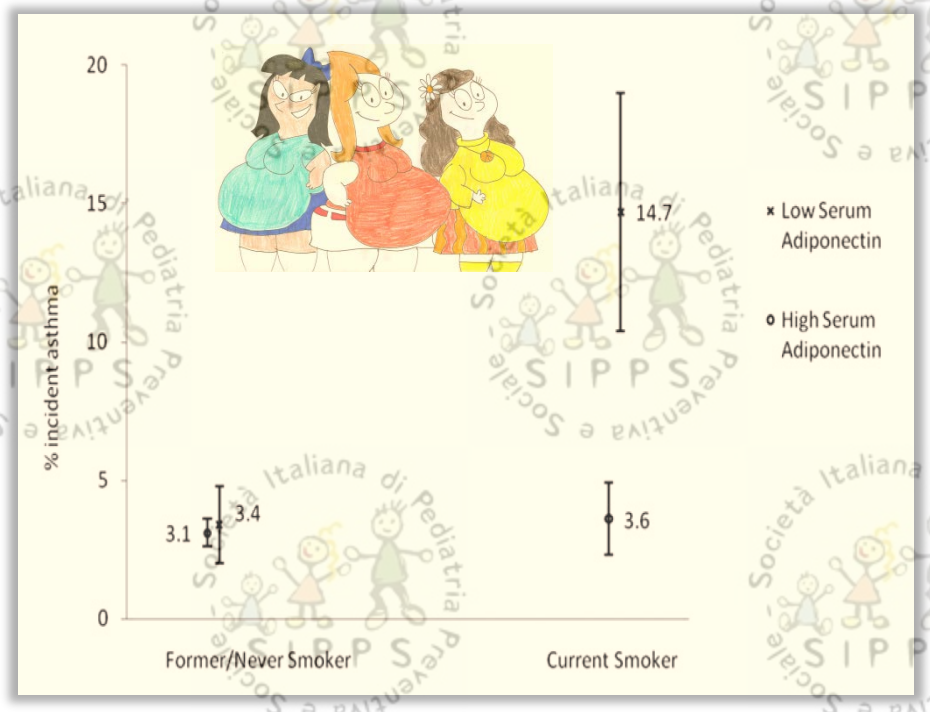


Low serum adiponectin predicts future risk for asthma in women

Sood A, Am J Respir Crit Care Med *2012;186(1):41*

- Examinations 1,450 women at Years 10, 15, and 20 of the Coronary Artery Risk Development in Young Adults (CARDIA) cohort

- Multivariable analyses demonstrated that the lowest tertile of Year 15 serum adiponectin concentration (<7 mg/L) predicted significantly higher risk for incident asthma at Year 20 among women and particularly among current smokers.

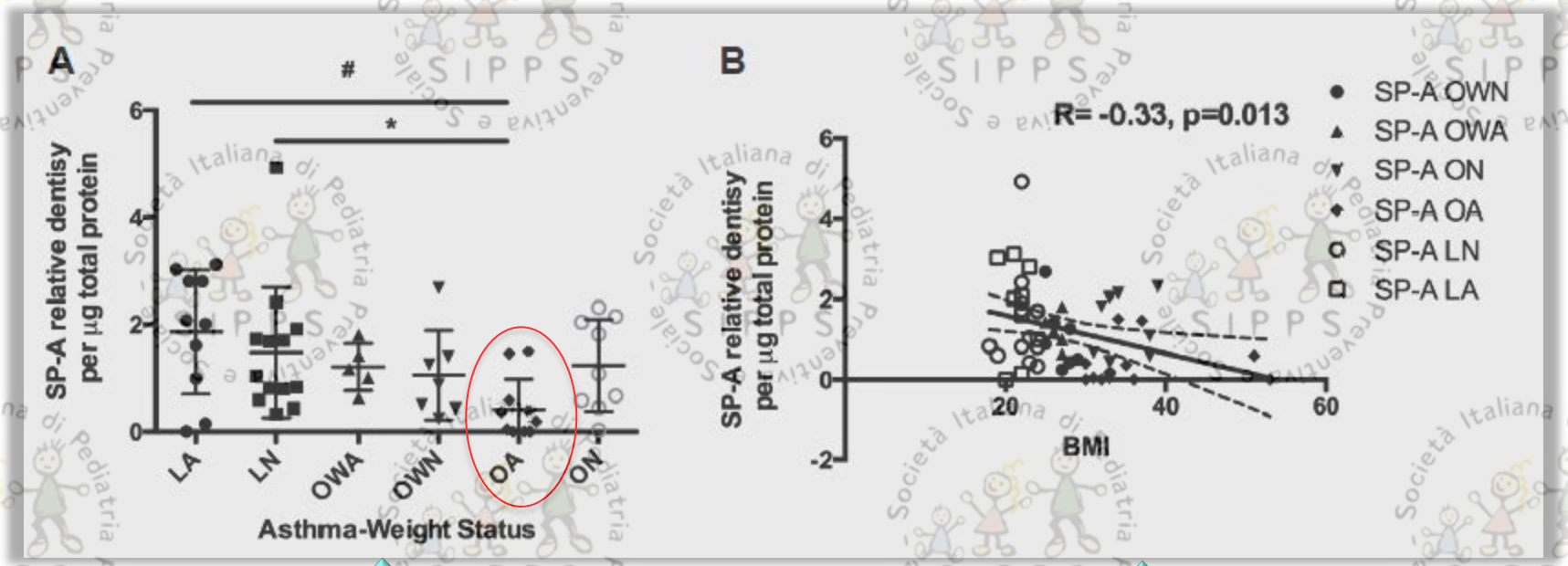


Further, low serum adiponectin was more important than body mass index in predicting the risk for incident asthma among women

Obese asthmatic patients have decreased surfactant protein A levels: Mechanisms and implications *Lugogo N et al J Allergy Clin Immunol 2018;141:918-26.*

Sono stati valutati i livelli di Proteina A del Surfattante (SP-A) in pazienti obesi con asma (Oas).
Il liquido di lavaggio broncoalveolare di 23 soggetti magri, 12 sovrappeso e 20 obesi sono stati esaminati per valutare i livelli di SP-A

LA: Lean patient with asthma; LN: Lean healthy subject; OA: Obese patient with asthma; ON: obese healthy subjects

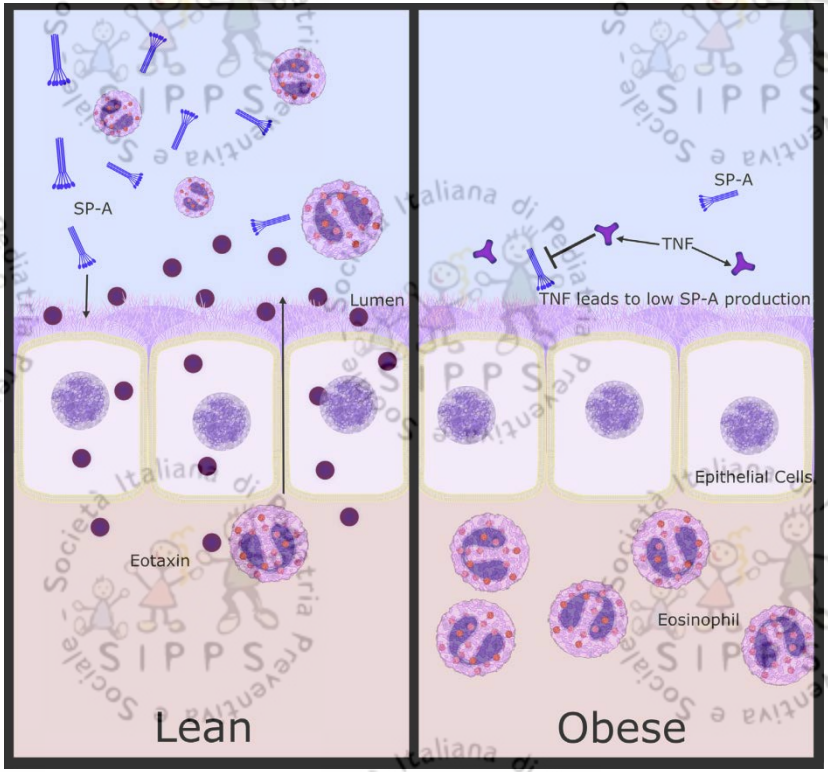


Significantly less SP-A (P =.002) was detected in samples from OAs compared with those from control subjects

SP-A levels are negatively correlated with increasing BMI

Obese asthmatic patients have decreased surfactant protein A levels: Mechanisms and implications *Lugogo N et al J Allergy Clin Immunol 2018;141:918-26.*

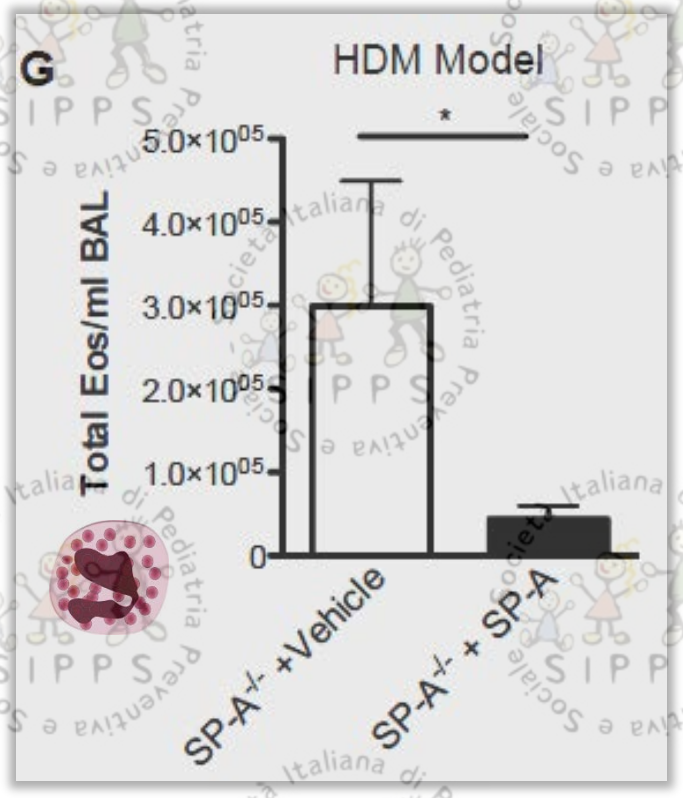
Addition of exogenous TNF-α to mouse tracheal epithelial cells was sufficient to **attenuate SP-A and eotaxin secretion**.



In vitro studies support the concept that SP-A promotes movement of eosinophils from the tissue indirectly by enhancing eotaxin production from airway epithelial cells.

Obese asthmatic patients have decreased surfactant protein A levels: Mechanisms and implications *Lugogo N et al J Allergy Clin Immunol 2018;141:918-26.*

- **Allergen-challenged** SP-A $^{-/-}$ mice that received SP-A therapy had significantly less tissue eosinophilia compared with mice receiving vehicle



La riduzione dei livelli di SP-A negli Obesi Asmatici potrebbe essere dovuta all'aumento dei livelli locali di TNF-α, favorendo la migrazione eosinofila potrebbe contribuire al fenotipo dell'asma eosinofilo

OBESITY & ASTHMA

MECHANISMS OF THE LINK BETWEEN OBESITY AND ASTHMA:

Possible mechanism	Brief explanation
Comorbidities	There may be an indirect link between obesity and asthma due to the role of obesity in other disease processes (e.g. increased risk of gastro-oesophageal reflux disease, sleep-disordered breathing, type 2 diabetes, and hypertension)
Foetal programming	Asthma may be the result of events occurring during development (e.g. obesity-related abnormalities in lung development)
Genetics	There may be an overlap in the genes responsible for asthma and obesity (e.g. TNF-α)
Effects on lung volume	Obesity produces negative effects on the residual capacity of the lung and the flexibility of airway smooth muscle, making the muscle stiffer and reducing airway volume
Chronic systemic inflammation	The expression of inflammatory genes (e.g. TNF-α, which causes airway hyperresponsiveness) is upregulated in the adipose tissue of obese individuals, leading to chronic, low-level systemic inflammation
Action of adipokines	There are changes in the serum concentrations of adipokines (e.g. leptin, adiponectin, and PAI-1) that could modify airway function and lead to asthma

PAI = plasminogen activator inhibitor; TNF-α = tumour necrosis factor alpha.

OBESITY & ASTHMA

Obesity is associated with low circulating vitamin D levels

Earthman CP et al. The link between obesity and low circulating 25-hydroxyvitamin D concentrations: considerations and implications. Int J Obes (Lond) 2012;36:387-96..

Vitamin D deficiency might be a risk factor for the development of both obesity and asthma: prenatal vitamin D insufficiency has been associated with obesity in the offspring

Boyle VT et al. The relationship between maternal 25-hydroxyvitamin D status in pregnancy and childhood adiposity and allergy: an observational study. Int J Obes (Lond) 2017;14:1755-60.

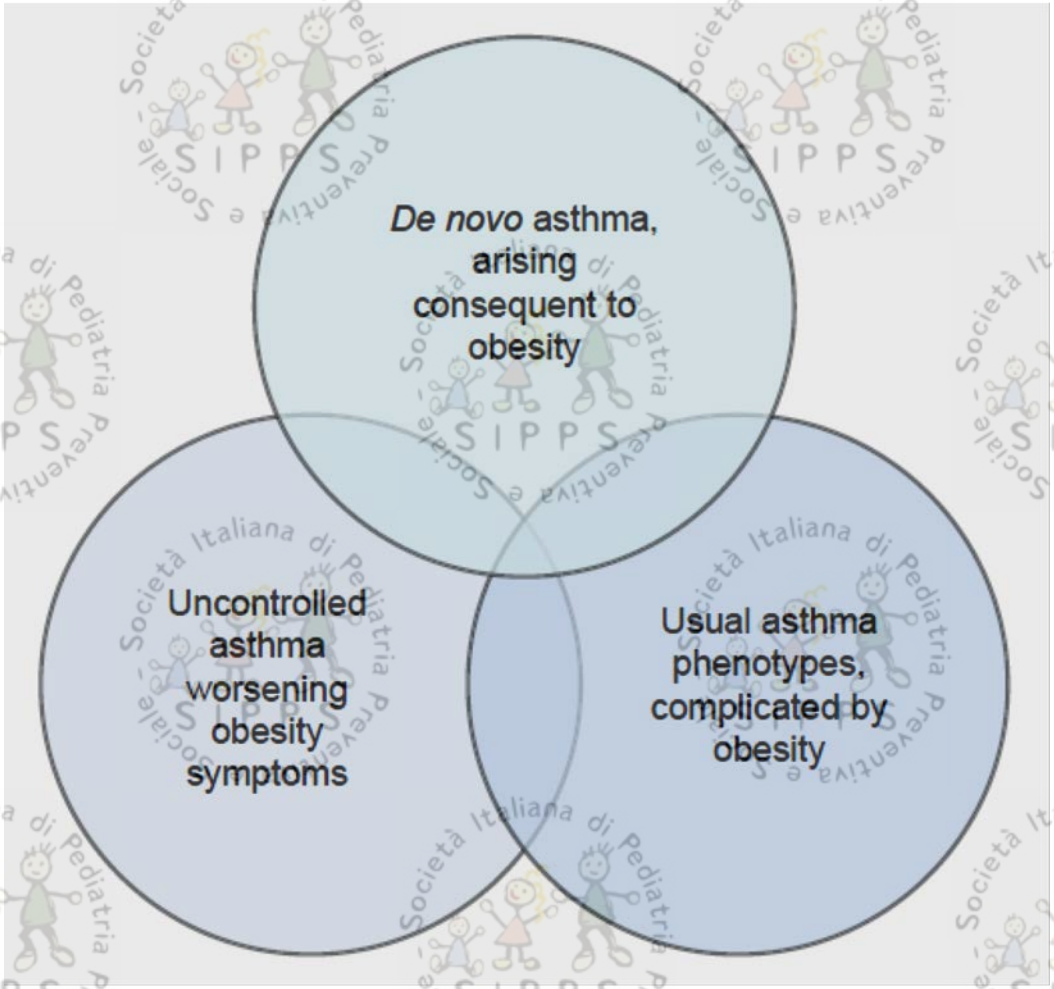
The efficacy of supplementation of vitamin D specifically on asthma in obesity is not known

Peters U et al Obesity and asthma J Allergy Clin Immunol 2018;141:1169-79

OBESITY & ASTHMA

CONCLUSIONS:

The syndrome of obese asthma likely includes many phenotypes



OBESITY & ASTHMA

CONCLUSIONS:

In clinical settings, **physicians should be cautious about diagnosing asthma in obese children** on the basis of self-reported symptoms alone and should confirm the diagnosis **by using objective measurements and marker evaluations** that can better identify asthma phenotype and exclude overdiagnosis

Asthma and obesity in childhood: on the road ahead.
Peroni D, *Int J Obes (Lond). 2010*