

# 14°

## CONGRESSO NAZIONALE SINut

**SINut**  
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# SINDROME METABOLICA E MENOPAUSA: RUOLO POTENZIALE DELLA PALMITOILETANOLAMIDE

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Il sottoscritto **Alessandro MEDORO**  
ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg.  
Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

**dichiara**

che negli ultimi due anni NON ha avuto rapporti diretti di  
finanziamento con soggetti portatori di interessi commerciali in  
campo sanitario

# Definizione di Menopausa

La menopausa è un evento prevalentemente spontaneo e naturale, definito come l'ultimo periodo mestruale, confermato dopo 1 anno di assenza di sanguinamento mestruale

Rappresenta la cessazione permanente delle mestruazioni causata dalla perdita della funzione follicolare ovarica, solitamente dovuta all'invecchiamento.

Table 1 | Geographical variation in age at menopause\*

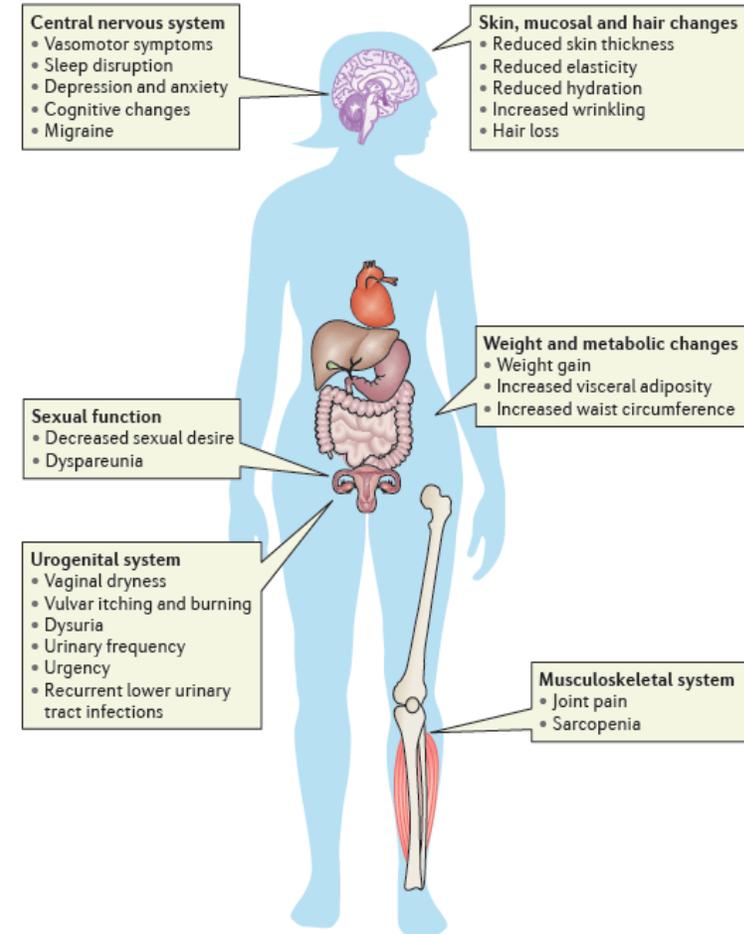
Region or country	n	Number of studies	Mean age at menopause (95% CI)	Heterogeneity (I-squared; %)
Africa	1,175	3	48.4 (48.1–48.6)	0.0
Asia	39,158	8	48.8 (48.1–49.4)	98.9
Australia	9,268	2	51.3 (49.8–52.8)	99.1
Europe	18,692	6	50.5 (50.0–51.1)	96.6
Latin America	18,073	3	47.2 (45.9–48.6)	99.1
Middle East	7,733	8	47.4 (46.9–47.8)	97.2
United States	15,690	6	49.1 (48.8–49.4)	94.6
Total	109,789	36	48.8 (48.3–49.2)	99.6

# Sintomi della Menopausa

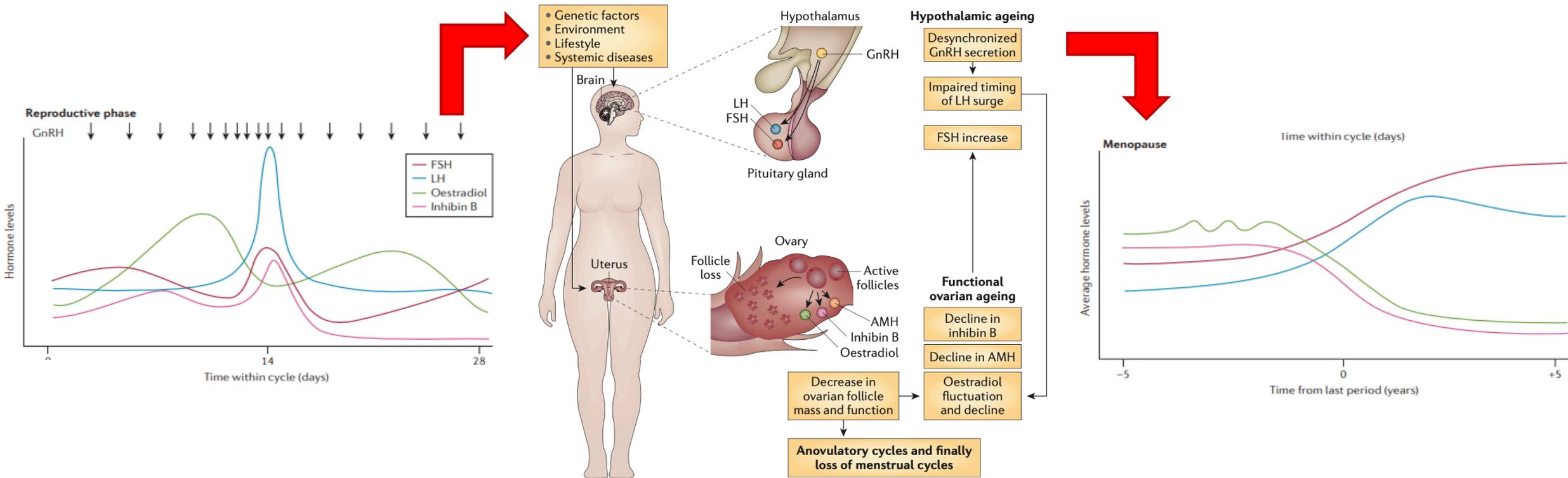
## Key points

- Menopausal symptoms have a substantial effect on the quality of life of women and on performance at the workplace; increased awareness of symptoms and acquisition of coping strategies might help
- Certain menopausal symptoms might serve as markers for future health; severe vasomotor symptoms and sleep disorders might increase cardiovascular risk, whereas severe vasomotor symptoms and depression might affect cognitive function
- The nature of menopausal symptoms is common to all women; however, geographical location and ethnicity influence the prevalence of certain symptoms
- Individual factors such as personal history, current health status (particularly obesity) and socioeconomic status considerably worsen a woman's experience of menopause

Symptom	Typical age at onset (years)	Peak severity	Average duration (years)
Hot flashes	47	Late transition	6–10
Poor sleep	40–50	Late transition	Variable
Adverse mood	49	Late transition	2–4
Vaginal dryness	49	Early to late transition	Persists lifelong if untreated

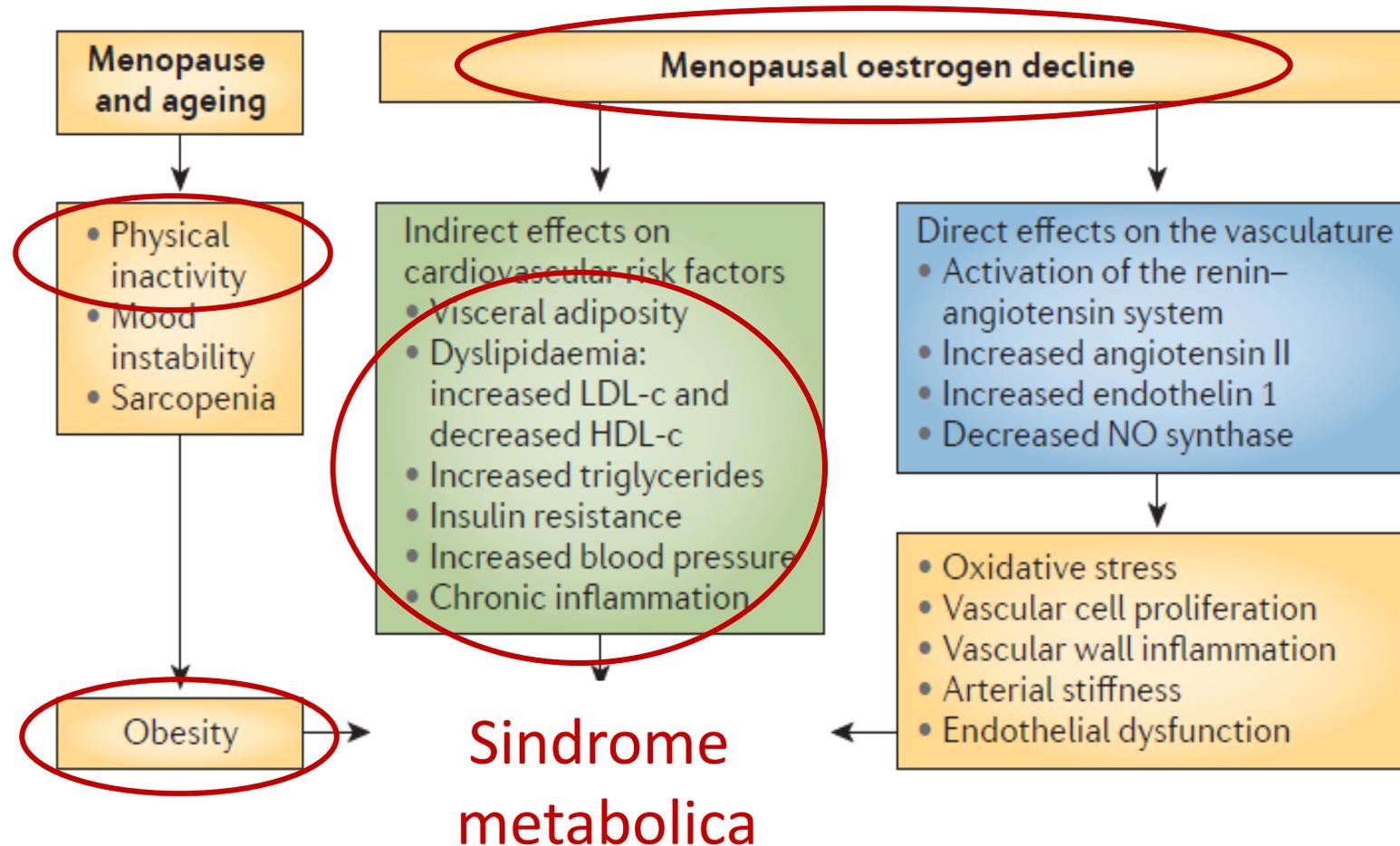


# Regolazione Ormonale del Ciclo Riproduttivo e Transizione alla Menopausa

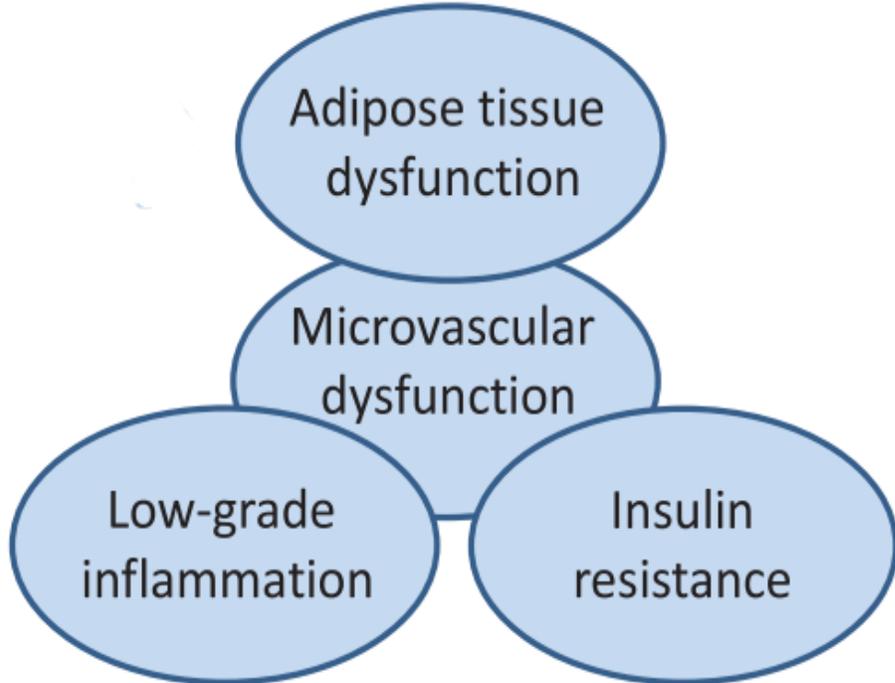


Questo processo biologico è associato a una diminuzione dei livelli di estrogeni, che può avere numerose implicazioni per la salute metabolica, cardiovascolare e ossea.

# Fattori di Rischio della Sindrome Metabolica durante la Menopausa



# La Sindrome Metabolica



## Metabolic Syndrome

defined as 3 or more of the following

- Abdominal obesity



- Elevated plasma triglycerides



- Low plasma HDL cholesterol



- Elevated blood pressure



- Elevated fasting blood glucose



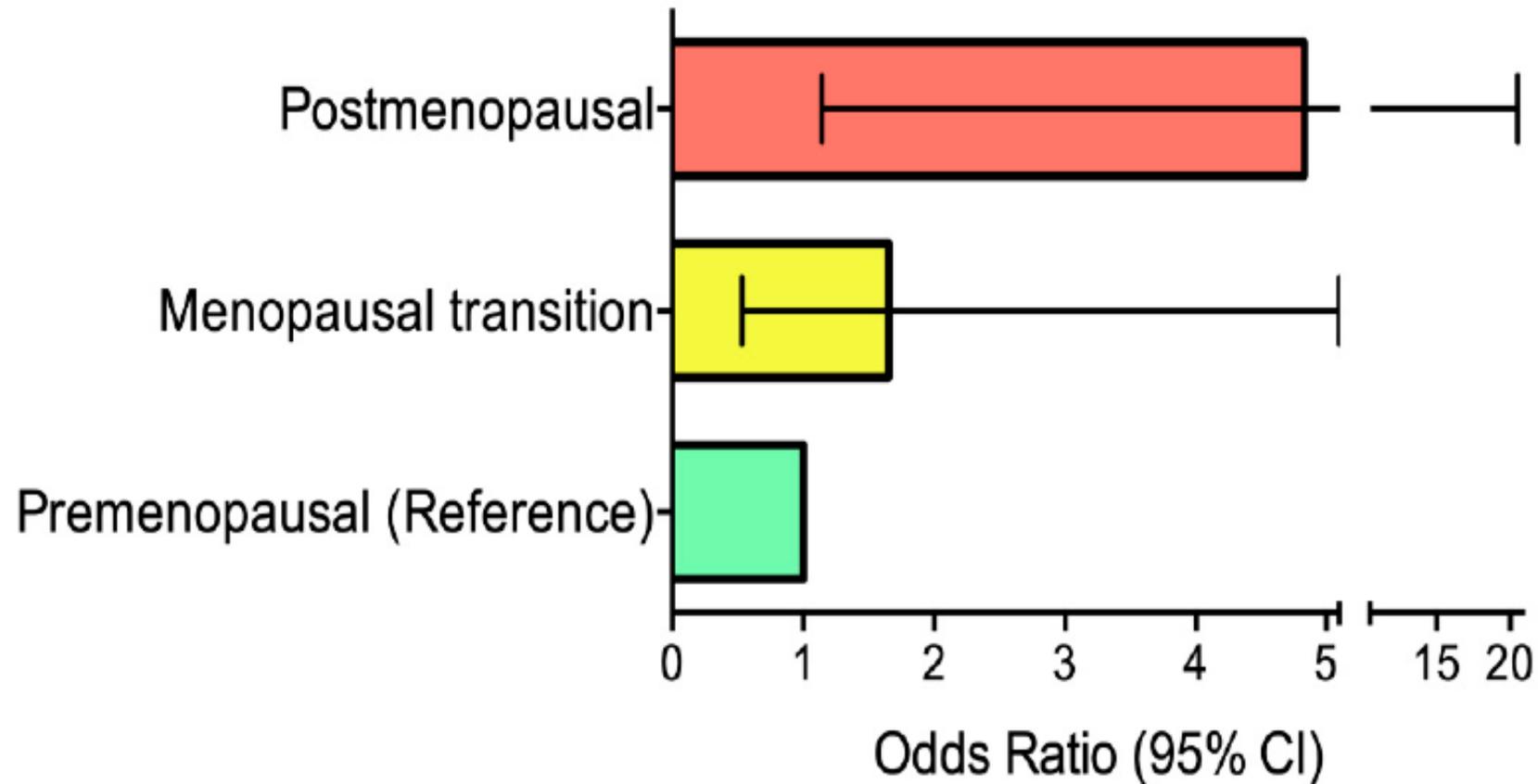
## Diseases Associated with Metabolic Syndrome

- Type 2 Diabetes
- Hypertension
- Non-alcoholic Fatty Liver Disease (NAFLD)
- Cardiovascular Events

## Drug Targets for Metabolic Syndrome

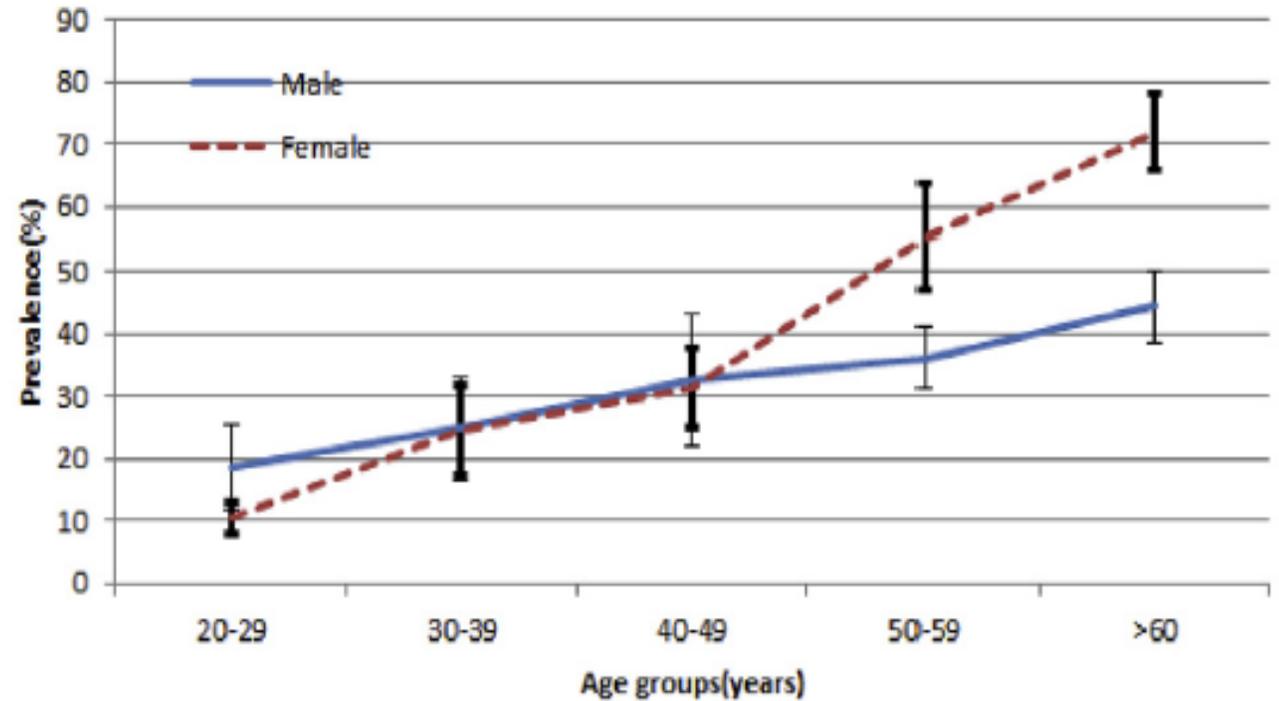
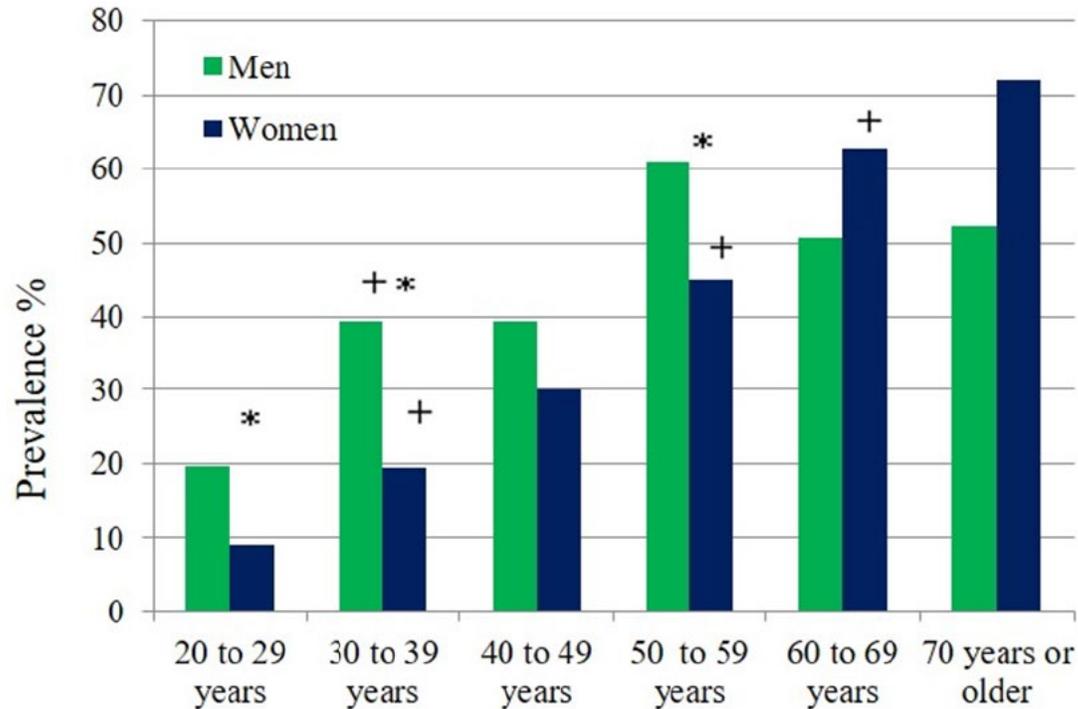
- Soluble Epoxide Hydrolase
- PPAR $\gamma$  / PPAR $\alpha$
- Farnesoid X Receptor
- Angiotensin Converting Enzyme
- Angiotensin Type 1 Receptor
- Dipeptidyl Peptidase 4
- Glucokinase

## Menopausa e Obesità Addominale

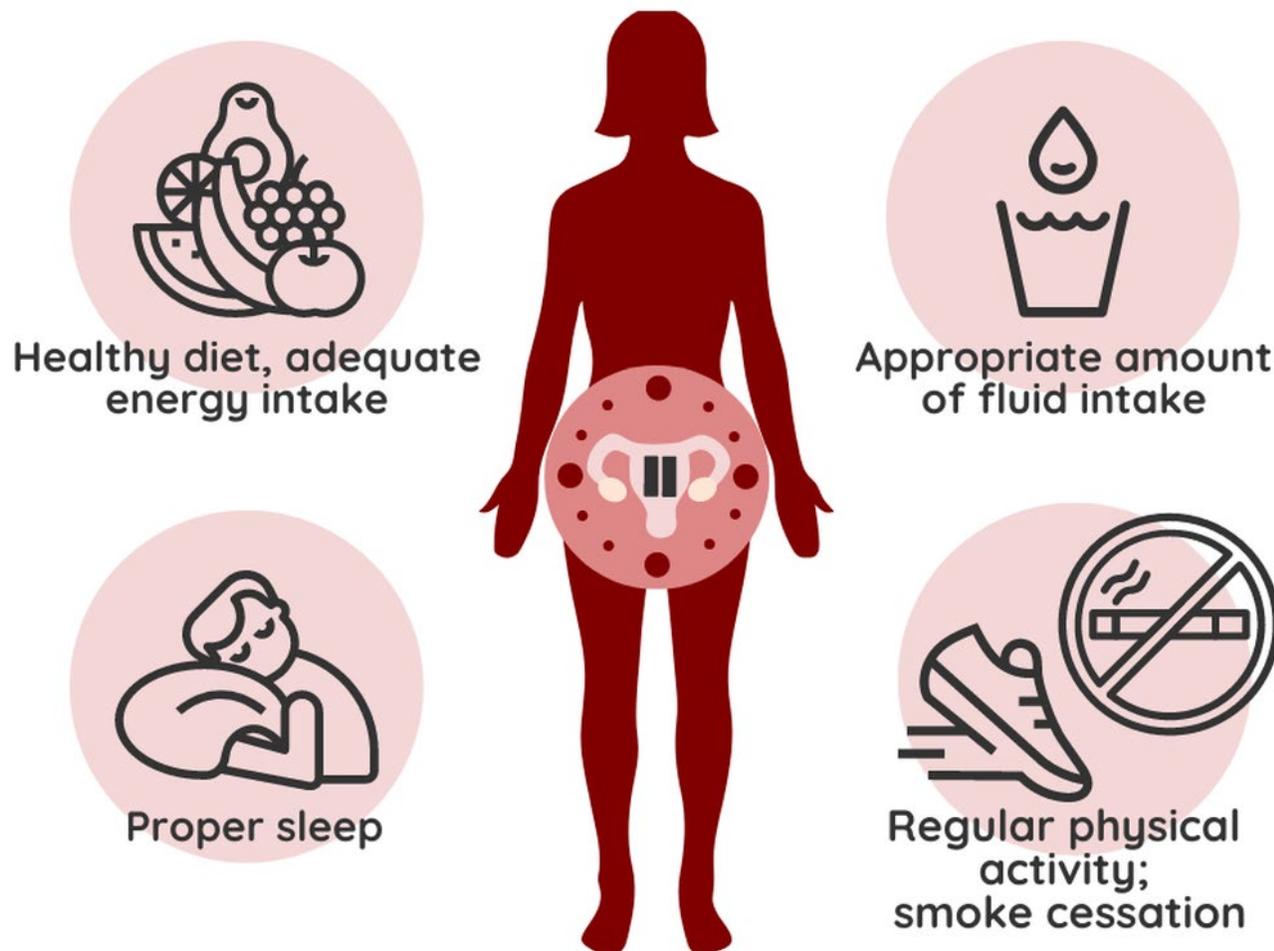


Odds ratio per obesità addominale, definita come una circonferenza della vita  $\geq 88$  cm, nelle donne in transizione menopausale e nelle donne in post-menopausa.

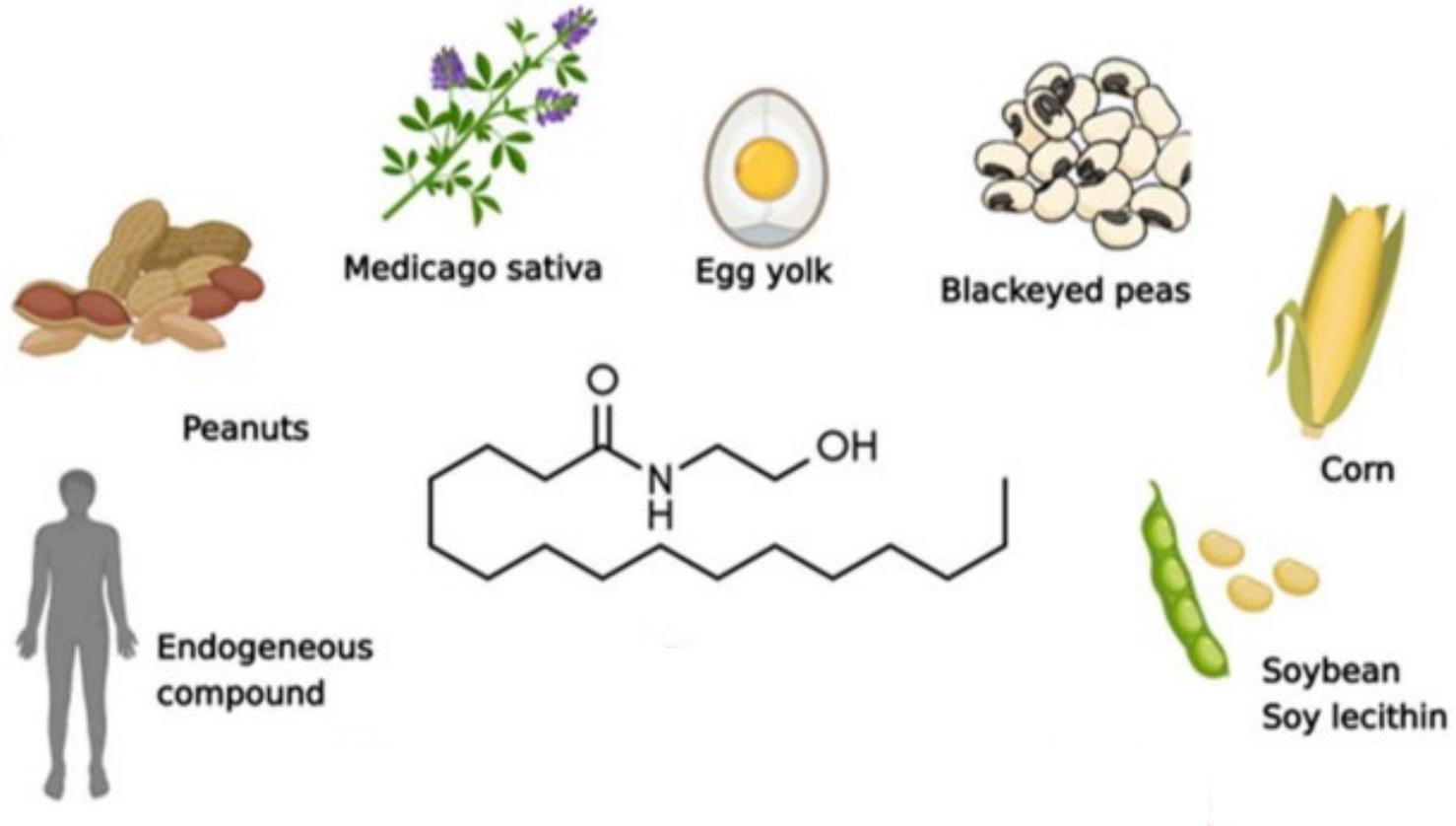
# Sindrome Metabolica e Menopausa



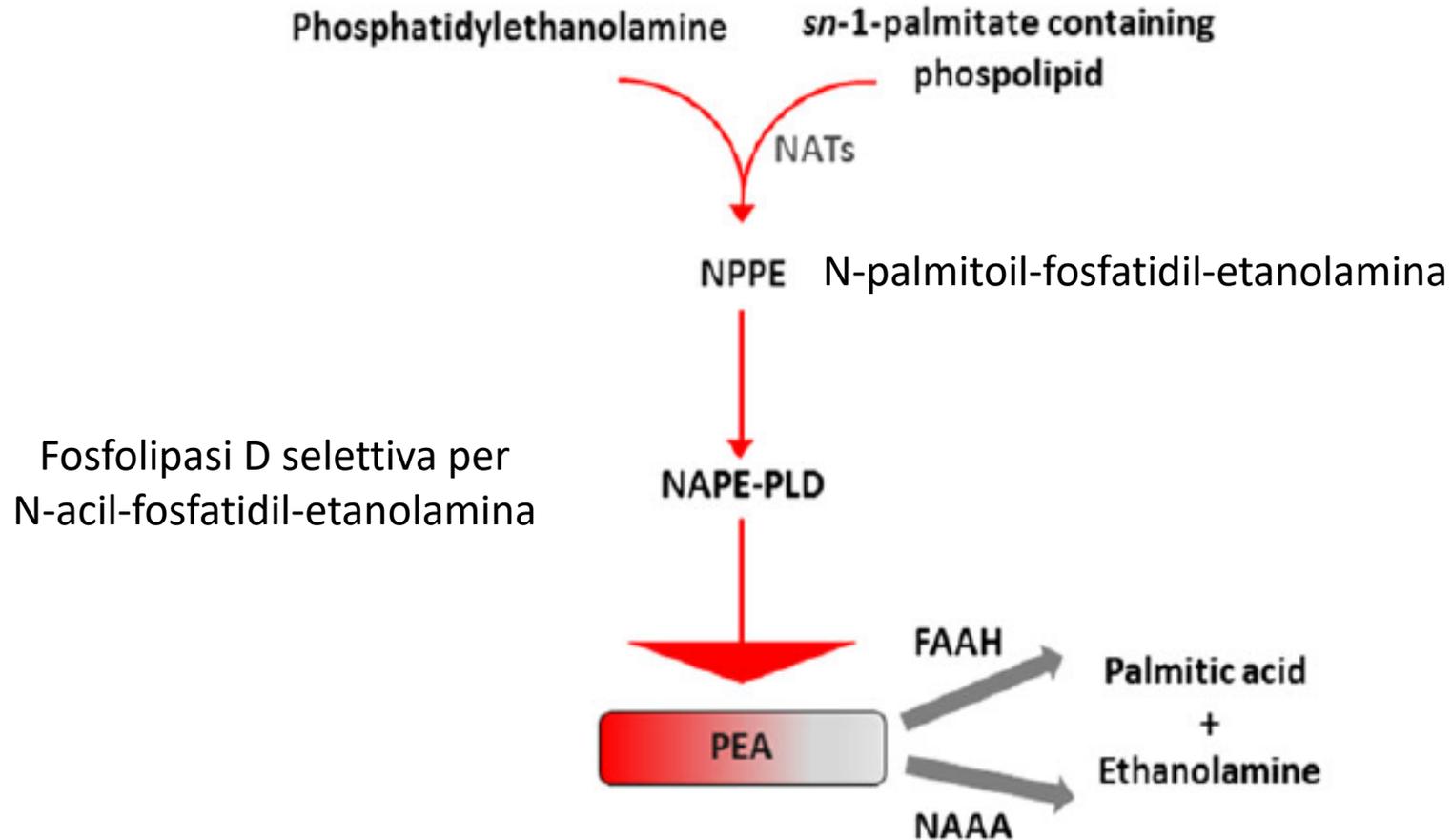
## Dietary and lifestyle factors in menopause



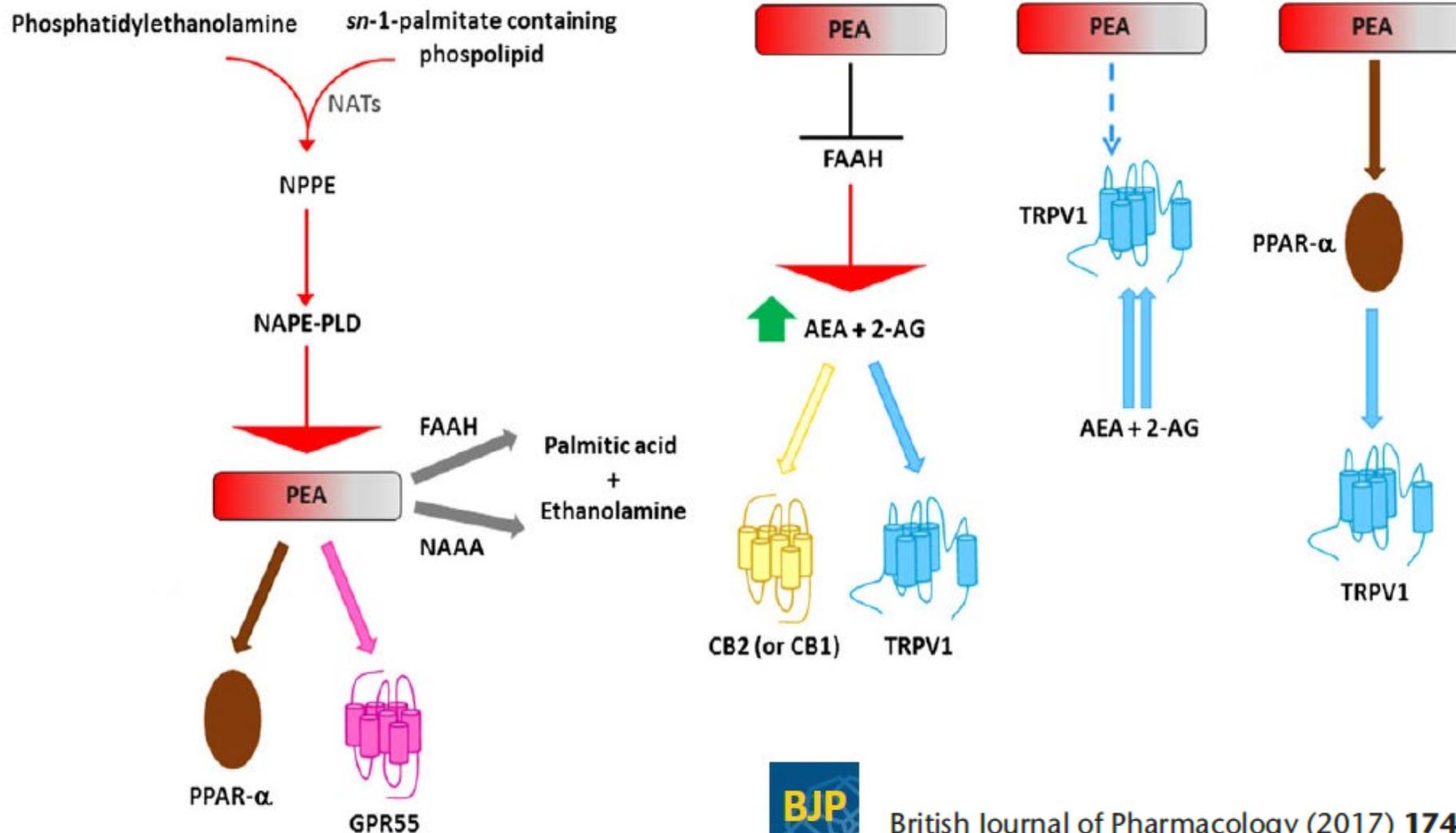
# Palmitoiletanolamide (PEA)



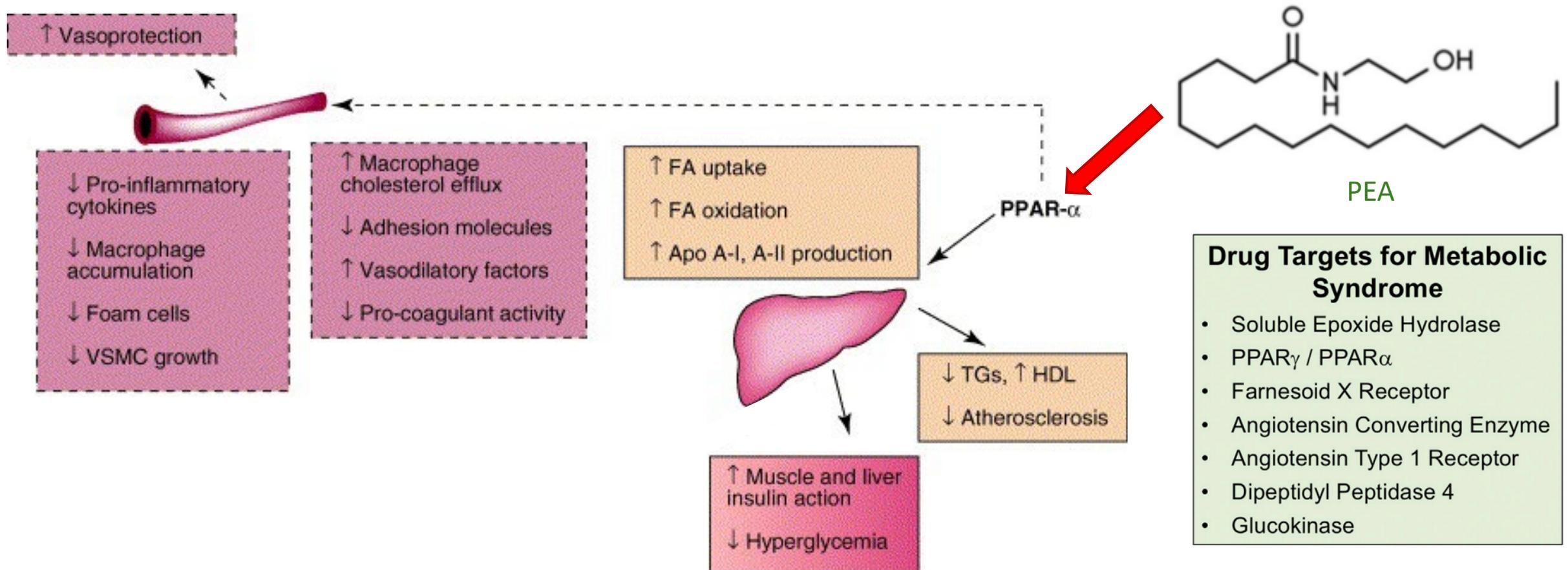
# Metabolismo della PEA



# Pathway metabolici e target molecolari della PEA

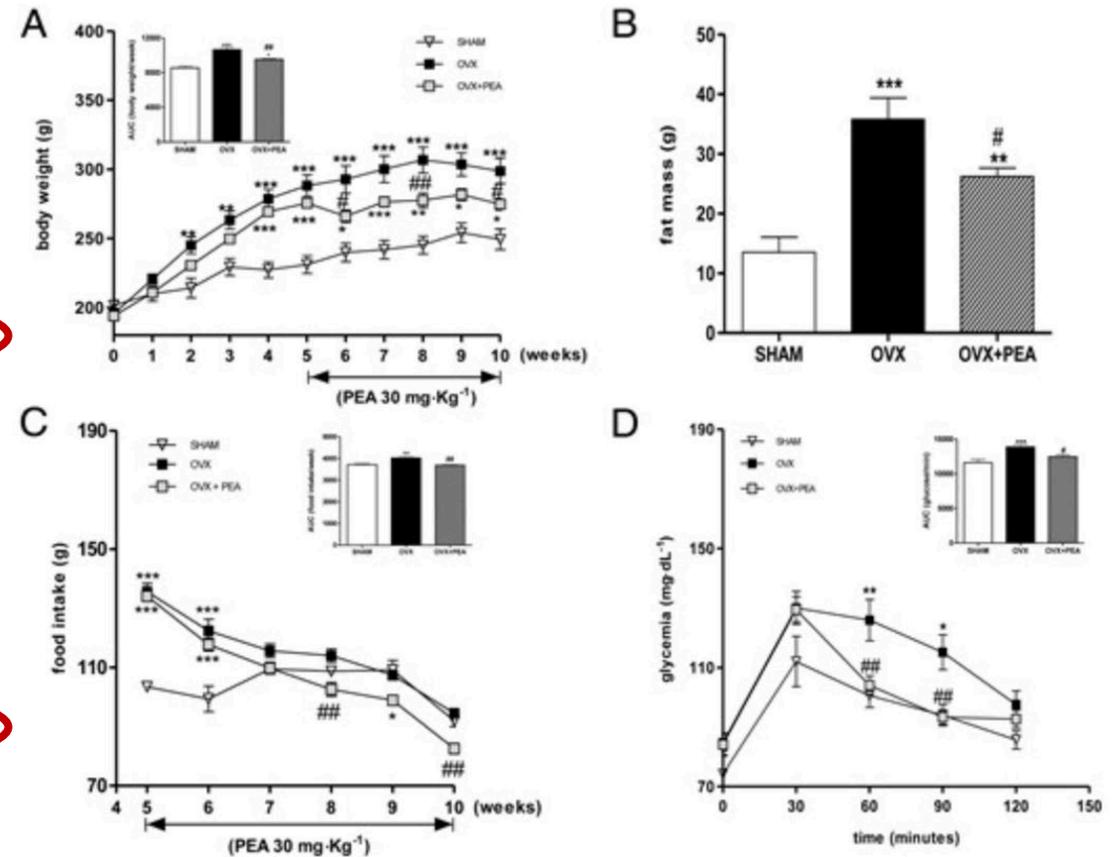


# Potenziali effetti metabolici della PEA attraverso PPAR $\alpha$

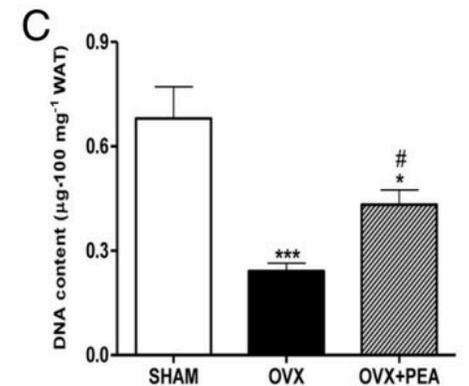
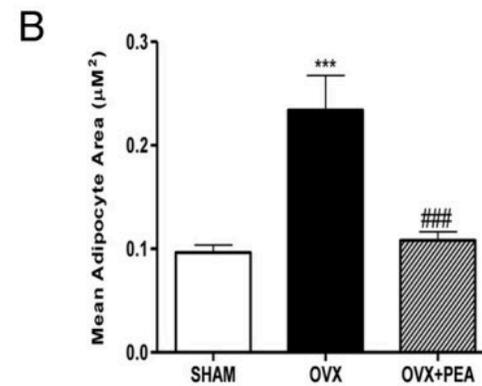
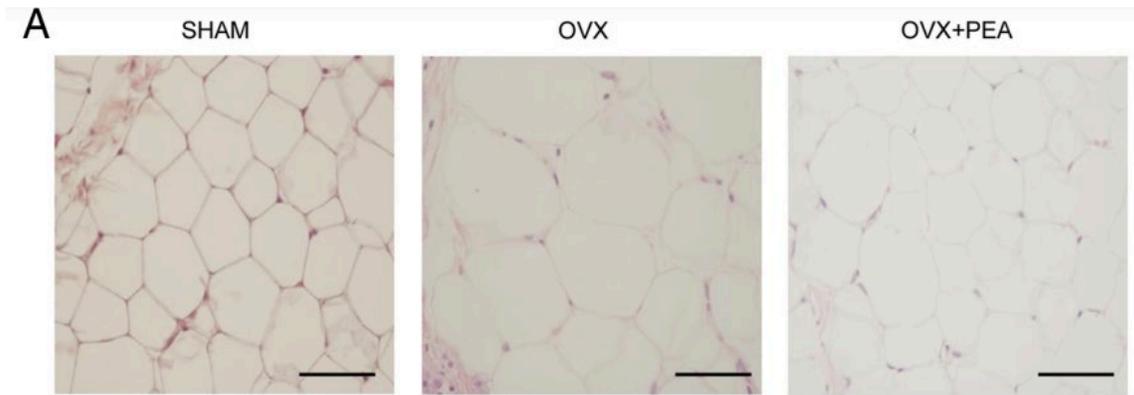
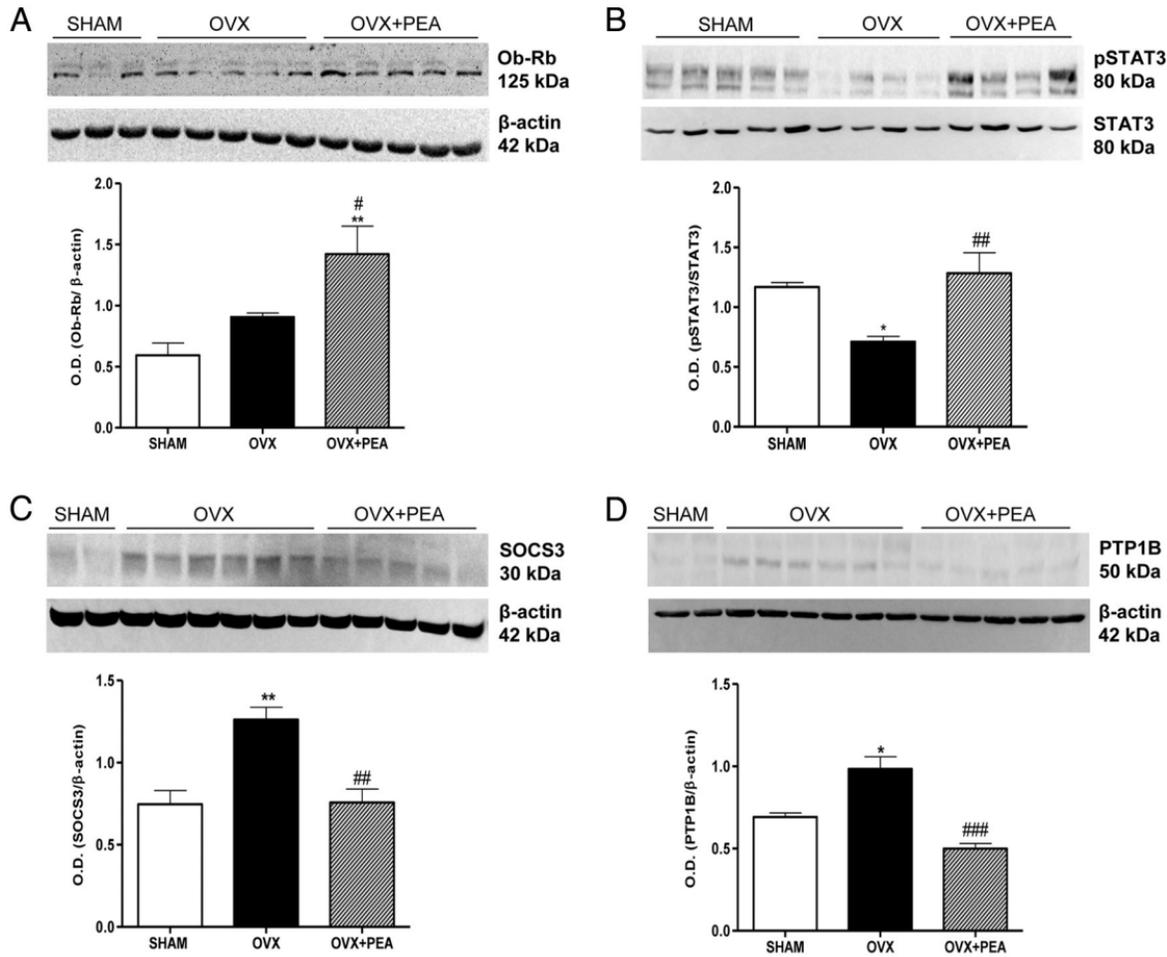


# Palmitoylethanolamide Prevents Metabolic Alterations and Restores Leptin Sensitivity in Ovariectomized Rats

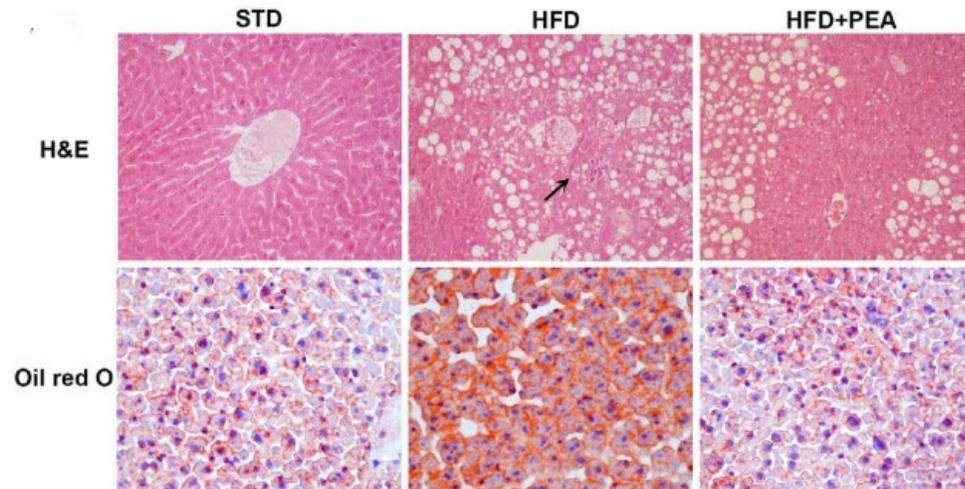
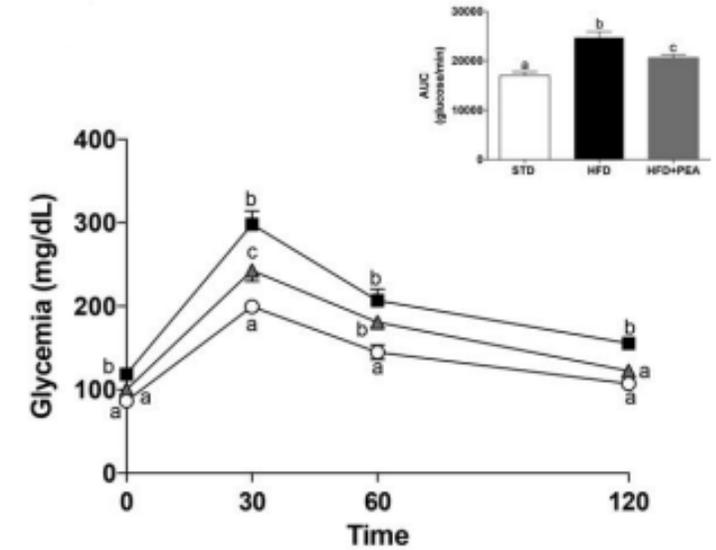
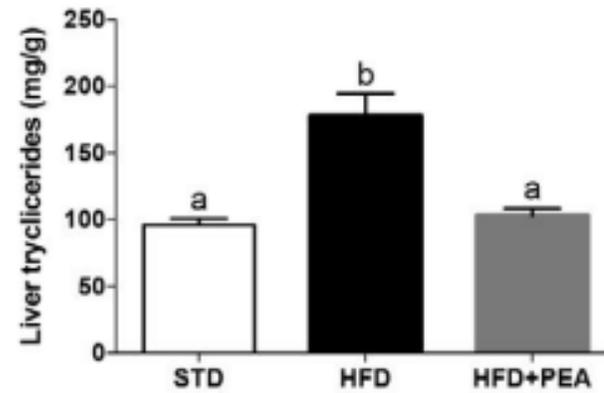
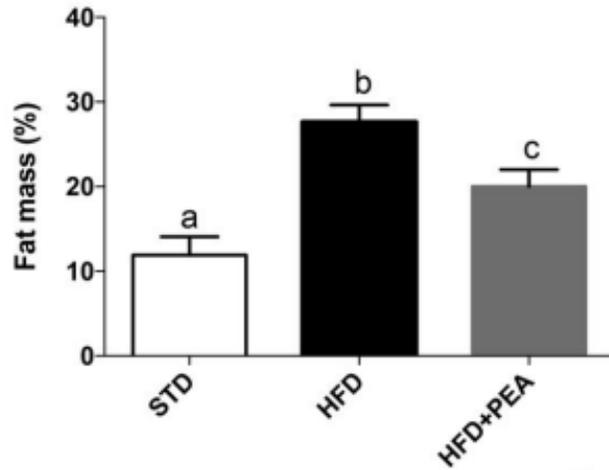
Serum Parameters	SHAM	OVX	OVX+PEA
Serum ALT (U/L)	38.17 ± 1.72	36.14 ± 2.76	37.43 ± 2.70
Serum AST (U/L)	166.7 ± 23.19	251.7 ± 14.68 <sup>a</sup>	237.4 ± 13.08 <sup>a</sup>
Total cholesterol (mg/dL)	46.40 ± 4.82	82.88 ± 4.81 <sup>b</sup>	65.25 ± 4.31 <sup>a,c</sup>
Serum TGL (mg/dL)	53.67 ± 5.28	52.75 ± 4.16	52.78 ± 2.60
Fasting glycemia (mg/dL)	89.56 ± 2.99	88.85 ± 2.75	88.08 ± 2.98
Fasting insulinemia (ng/mL)	0.16 ± 0.01	0.35 ± 0.11	0.31 ± 0.05
HOMA index	0.77 ± 0.11	2.08 ± 0.68	1.65 ± 0.28
Leptinemia (ng/mL)	1.07 ± 0.30	3.97 ± 0.76 <sup>a</sup>	2.01 ± 0.65 <sup>c</sup>



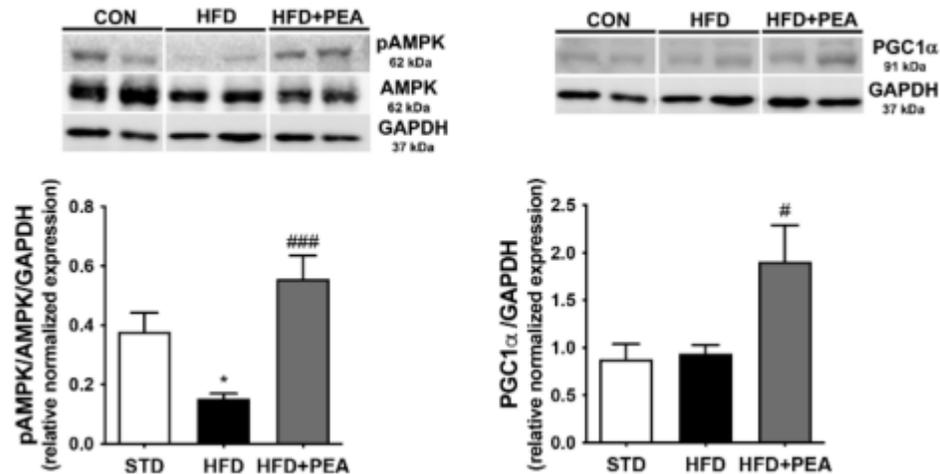
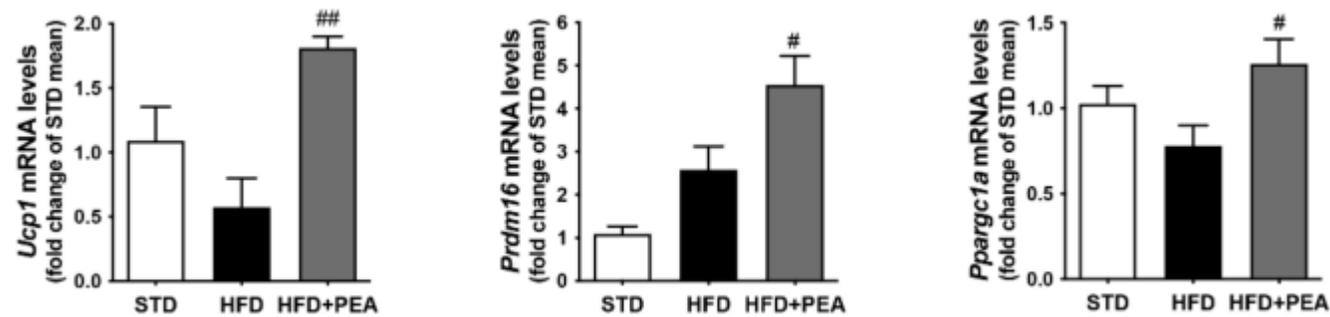
# Palmitoylethanolamide Prevents Metabolic Alterations and Restores Leptin Sensitivity in Ovariectomized Rats



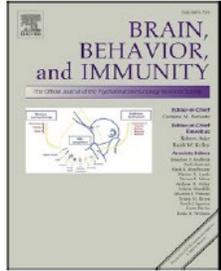
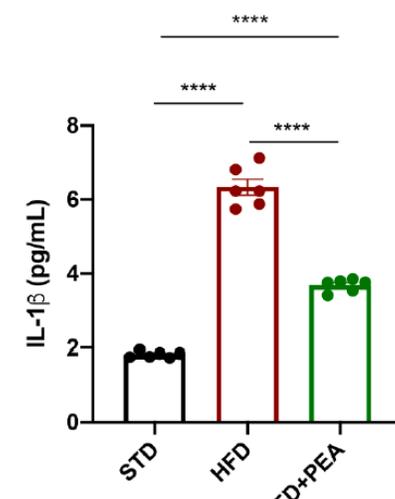
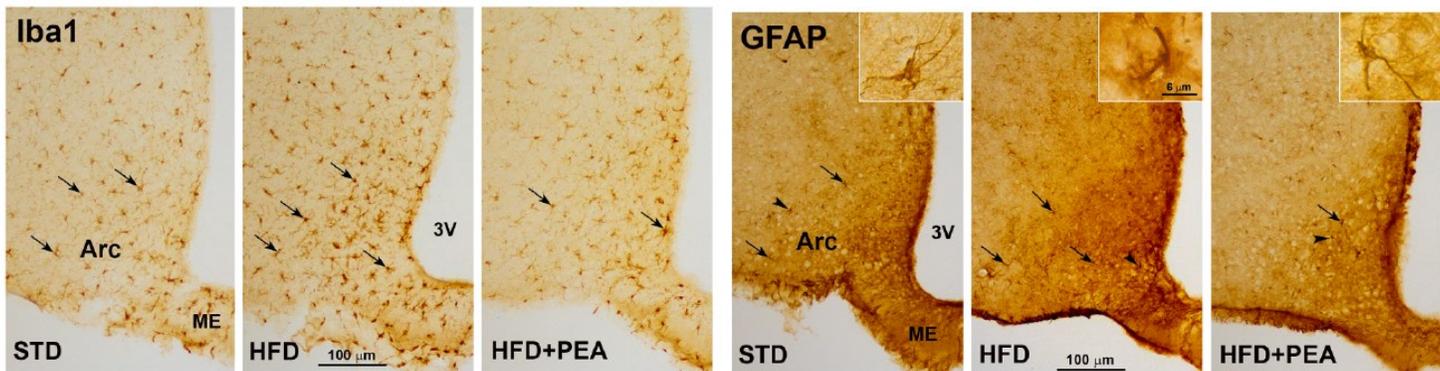
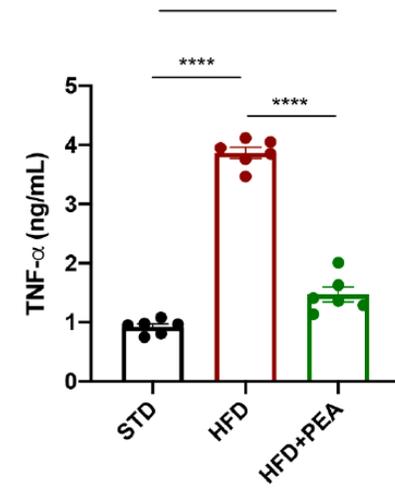
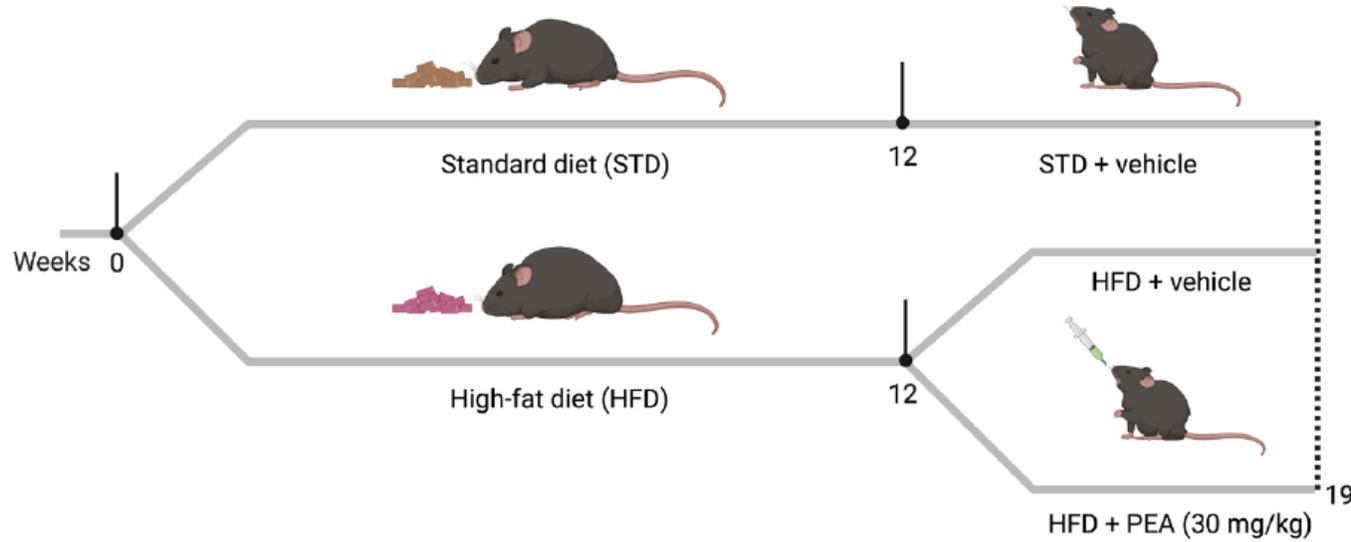
## Palmitoylethanolamide counteracts hepatic metabolic inflexibility modulating mitochondrial function and efficiency in diet-induced obese mice



# Palmitoylethanolamide Promotes White-to-Beige Conversion and Metabolic Reprogramming of Adipocytes: Contribution of PPAR- $\alpha$



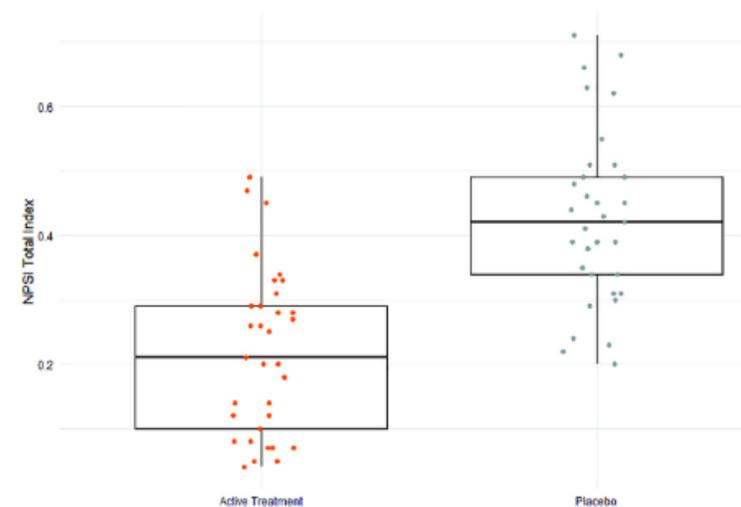
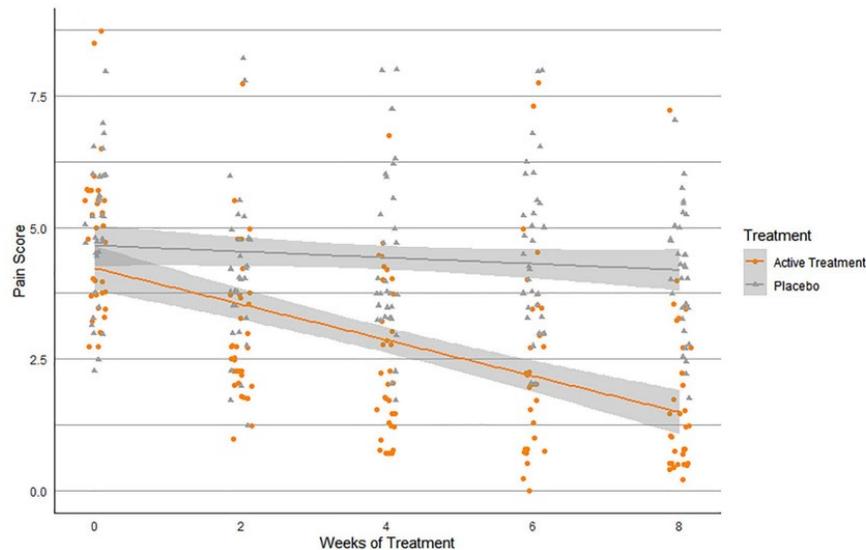
# Palmitoylethanolamide dampens neuroinflammation and anxiety-like behavior in obese mice



## A randomized controlled trial assessing the safety and efficacy of palmitoylethanolamide for treating diabetic-related peripheral neuropathic pain

Studio clinico controllato con placebo, quadruplo cieco e monocentrico, con 70 partecipanti che hanno ricevuto 600 mg di PEA o placebo al giorno per 8 settimane, con un tasso di completamento del 94%. Gli outcome primari erano il dolore neuropatico e tipi specifici di dolore (il BPI-DPN e l'NPSI). Gli outcome secondari includevano la qualità del sonno (MOS sleep scale), l'umore (DASS-21), e l'infiammazione.

		Baseline		Dopo 8 settimane			
C-reactive protein > 5.0 mg/L	Active	8.38 ± 1.89	5.0–12.0	0.18	6.17 ± 3.35	2.5–12.0	0.05
	Placebo	10.13 ± 4.60	5.0–21.0		9.43 ± 5.07	2.5–18.0	
Interleukin-6 (< 6 pg/mL)	Active	4.93 ± 1.79	1.0–9.0	0.44	4.13 ± 2.32	1.0–12.0	0.04 <sup>1</sup>
	Placebo	4.52 ± 2.27	1.0–12.0		5.44 ± 3.02	1.0–18.0	



# Limiti

La PEA ha una scarsa solubilità in acqua, il che limita la sua assorbimento e biodisponibilità. La micronizzazione della PEA ha migliorato la biodisponibilità rispetto alla PEA non micronizzata negli animali. Tuttavia, anche con la micronizzazione, la PEA rimane lipofila, portando all'aggregazione e a un minore assorbimento nello strato mucoso gastrointestinale idrofilo.

## Novel Approach to the Treatment of Neuropathic Pain Using a Combination with Palmitoylethanolamide and *Equisetum arvense* L. in an In Vitro Study

Sara Ruga <sup>1</sup>, Rebecca Galla <sup>1,2</sup>, Sara Ferrari <sup>1</sup>, Marco Invernizzi <sup>3,4</sup>  and Francesca Uberti <sup>1,\*</sup> 

Substance	Permeability value
<sup>a</sup> PEA-um 0.2μM	1.63x10 <sup>-6</sup>
<sup>b</sup> PEABO mesh 0.2μM	1.73x10 <sup>-6</sup>
<sup>c</sup> <i>Equisetum</i> A.L. 10% 50μg/ml	0.54x10 <sup>-6</sup>
<sup>d</sup> PEA 80mesh + <i>Equisetum</i> A.L.	2.13x10 <sup>-6</sup>

# Conclusioni

La Palmitoiletanolamide (PEA) si è dimostrata un potenziale intervento nella gestione dell'infiammazione e dei sintomi della menopausa, in particolare dei disturbi metabolici.

L'utilizzo della PEA, grazie alle sue proprietà di modulazione metabolica, potrebbe offrire un nuovo approccio non farmacologico per il trattamento della sindrome metabolica e il miglioramento della qualità della vita delle donne in menopausa.

Gli interventi mirati con la PEA potrebbero ridurre l'infiammazione e il dolore cronico e fornire supporto alla salute cardiovascolare.