



# Metabolic dysregulation in early pregnancy in association with offspring cardiometabolic risk in preschool children.

## The Mother Child "Rhea" Cohort in Crete, Greece.

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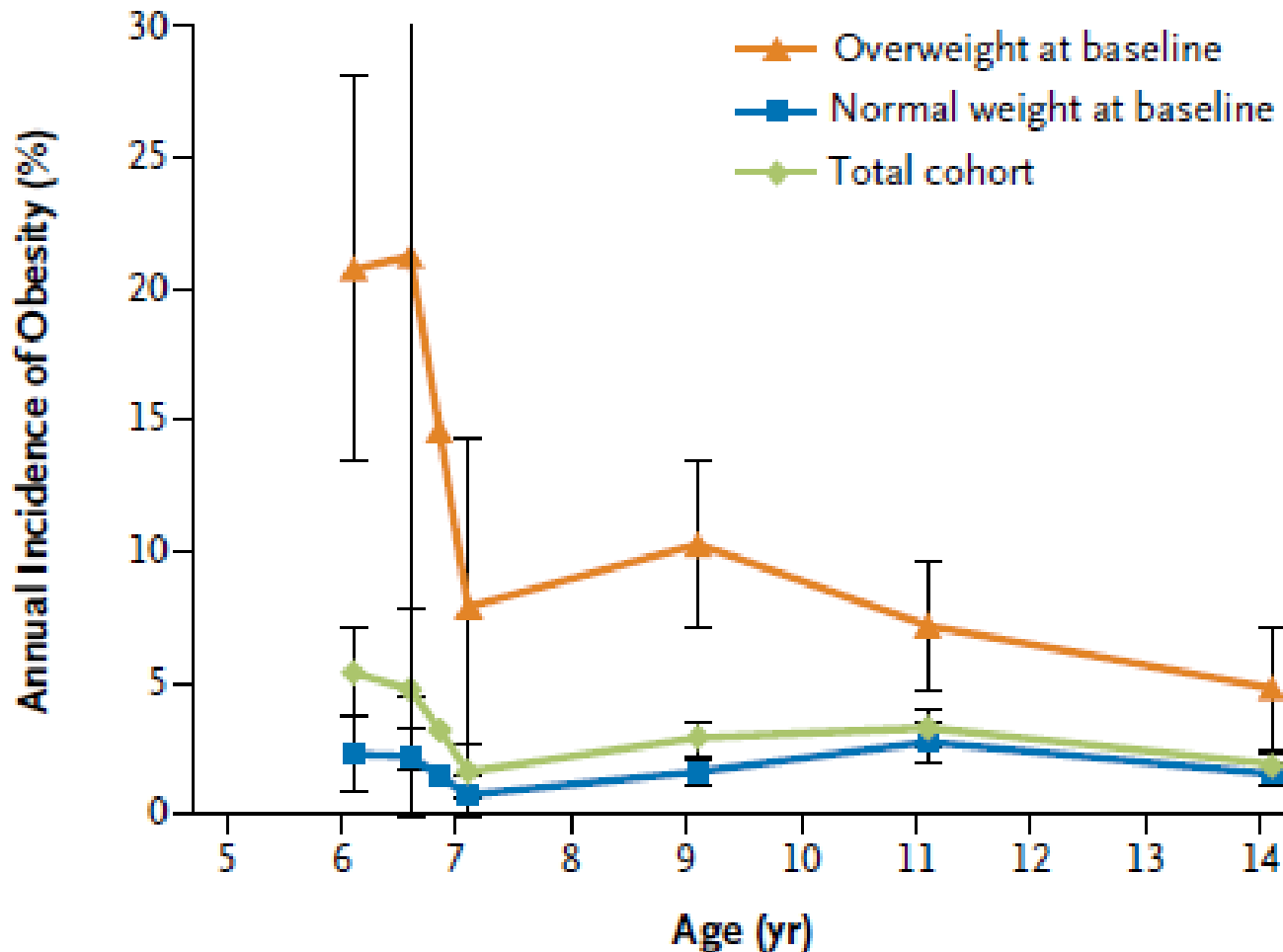
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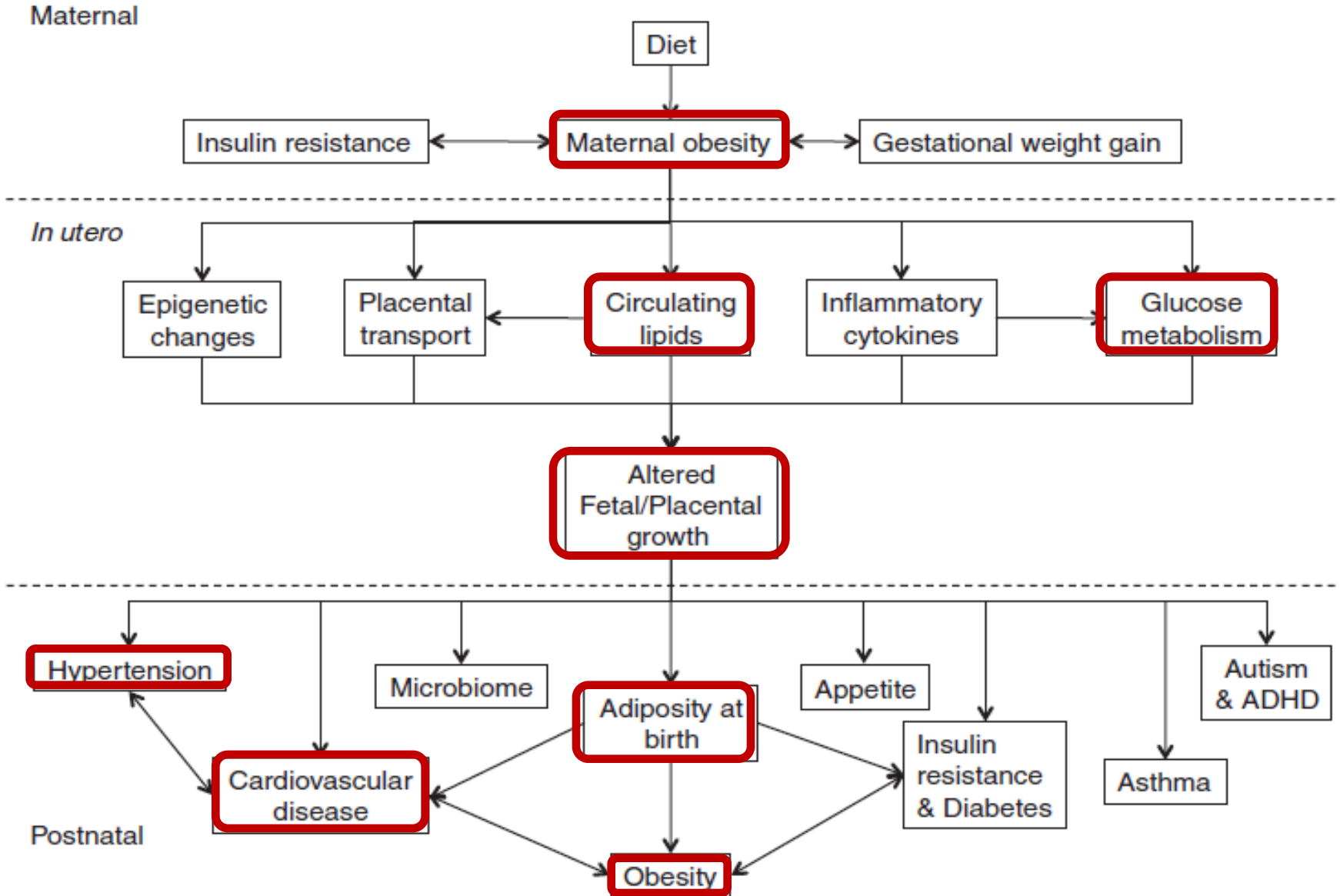


# Preschool age: a critical period in the development of obesity in adolescence and adulthood.

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# Developmental programming of childhood obesity



# Early intrauterine environment and cardiometabolic risk factors at preschool age.

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- **Maternal obesity pre-pregnancy has been linked with obesity at preschool age.**

**However its relation with other cardiometabolic risk factors at preschool age is not clear.**

*Patro et al Ann NutrMetab 2013*

- **Evidence for the relation of maternal lipid status in early pregnancy with cardiometabolic risk at preschool age are lacking so far.**

# **Aim of the study**

**To examine the association of pre-pregnancy maternal obesity and lipids' profile in early pregnancy with offspring obesity, blood pressure, and lipid levels at 4 years of age.**

# Rhea mother-child cohort study

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- **Setting: Heraklion, Crete, Greece**
- **Population: 1000 mother-child pairs**
- **Time period: 2007-2014**
- **Principal Investigators: Leda Chatzi , MD, PhD  
Manolis Kogevinas, MD, PhD**



# Study Protocol; pregnancy to 4 years

## Mother

## Child



Questionnaires



Biological samples



Questionnaires



Biological samples



Clinical assessment

Mother		Child	
Questionnaires		Biological samples	Questionnaires
		Biological samples	Clinical assessment
12 <sup>th</sup> –24 <sup>th</sup> w. pregnancy	Q 1 , FFQ, EPDS, STAI-T, EPQ, S. Capital, Q2	+ blood sampe + urine sample	
25 <sup>th</sup> –36 <sup>th</sup> w. pregnancy	Q3	+urine sample	
Delivery		+ blood sample	+ Cord blood
1 <sup>st</sup> month	EPDS		
9 <sup>th</sup> month	Q4 (parents) Asthma symptoms		
18 <sup>th</sup> month	Neurodevelopment Q5 (parents)		
4 <sup>th</sup> year			FFQ, Q6, AD/HD Physical activity Strengths & Difficulties (SDQ) Parenting Stress Index (PSI-SF)  + blood sampe + urine sample Anthropometric measurements (weight, height, waist & arm circumference, skinfolds) Blood pressure Neurodevelopment

# Study population

## The mother-child cohort in Crete (Rhea study)

922 mother-child pairs  
participating in 4 year follow up

### Exclusion criteria:

- Multiple pregnancies (n=50)
- Missing data on exposure (n=55) or confounding variables (n=186),
- Pregnancies with pre-eclampsia (n=4)
- Outliers of HDL (n=4)
- Children with very low birth weight (n=1)

618 mother-child pairs were  
available for the present analysis

348 pregnant women provided fasting  
blood samples for lipid measurements  
in early pregnancy



# Biological Samples and Measurements in Early Pregnancy

## ➤ Pre-pregnancy BMI (kg/m<sup>2</sup>) :

- no excess weight (BMI pre-pregnancy <25 kg/m<sup>2</sup>)
- overweight (BMI pre-pregnancy :25–29.9 kg/m<sup>2</sup>)
- obese (BMI pre-pregnancy ≥30kg/m<sup>2</sup>)

## ➤ Fasting lipid serum levels in early pregnancy

### Normal values according to AACE 2012 GUIDELINES

- Total cholesterol <200 mg/dl
- LDL cholesterol <130 mg/dl
- HDL cholesterol ≥ 50 mg/dL,
- Triglycerides <150mg/dl

# Outcomes at 4 years of age

## Obesity measures

### ➤ BMI

*Categorization according to International Obesity Task Force (IOTF) charts 2000*

### ➤ **Waist circumference (central obesity)**

Age- and gender-specific 90th percentiles based on national references

*Linardakis et al, Int J of Child Health and Human Dev, 2011*

### ➤ **Fat mass**

Expressed as the sum of 4 skinfolds (triceps, thigh, subscapular and suprailiac)

# Outcomes at 4 years of age

## Lipid profile

- Non fasting total cholesterol, LDL-C and triglyceride serum level
- Non fasting HDL-C serum level

## Blood pressure

- Systolic blood pressure
- Diastolic blood pressure

The 75th percentile of the study cohort distribution for serum lipid levels and blood pressure measurements and the 25<sup>th</sup> percentile for HDL-C serum level were used as a cut-off point to denote abnormal values in children.

# Potential confounders

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- maternal age at delivery
- maternal education
- mother's origin
- marital status
- physical activity before pregnancy
- parity
- type of delivery
- smoking during pregnancy
- gestational weight gain
- family history of hyperlipidemia
- gestational diabetes
- gestational hypertension and/or pre-eclampsia
- birth weight
- gestational age
- child's sex
- duration of breastfeeding
- day care attendance at 2 years
- Tv watching (hour/day) at 4 years
- child's energy intake at 4 years
- carbohydrates (gr/day); proteins (gr/day); fat (gr/day) at 4 years.

# Statistical analysis

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**Multivariable prognostic log-Poisson (with robust standard errors) and linear regression models after adjustment for confounders.**

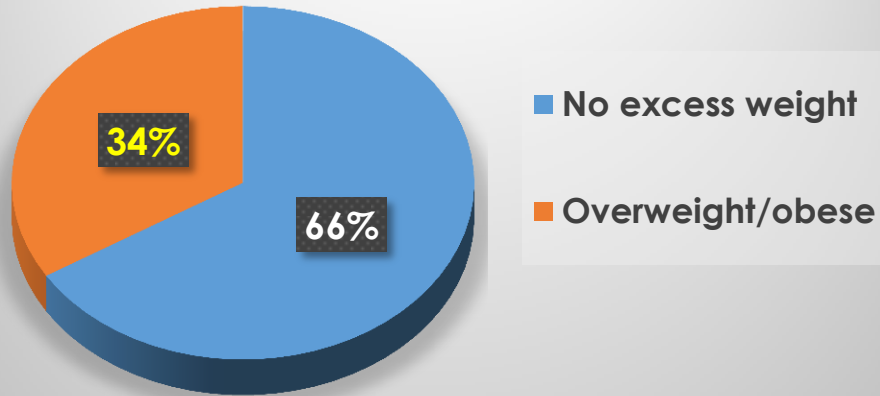
**Effect modification by child's sex, maternal smoking during pregnancy, and gestational weight gain were assessed through inclusion of the interaction terms in the models (statistically significant effect modification if  $p\text{-value} < 0.05$ ) and stratified analyses.**

# Demographic characteristics of the study population

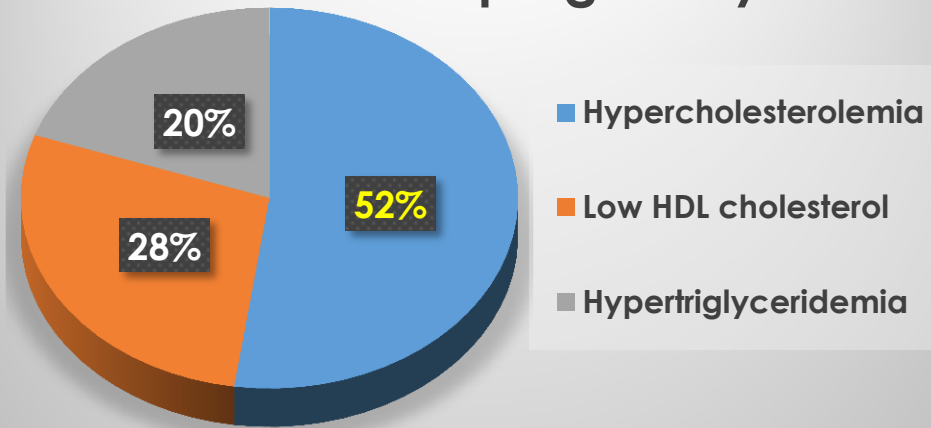
<b>Maternal Characteristics at initial visit</b>	<b>N (%) or Mean (SD)</b>
<b>Age at delivery (years), Mean <math>\pm</math> SD</b>	29.91 $\pm$ 4.8
<b>Greek origin, n(%)</b>	583 (94.3)
<b>Parity, n(%)</b>	
<b>Primiparous</b>	264 (42.7)
<b>Multiparous</b>	354 (57.3)
<b>Education, n (%)</b>	
<b>Low</b>	103 (16.7)
<b>Medium</b>	310 (50.2)
<b>High</b>	205 (33.1)
<b>Smoking during pregnancy, n (%)</b>	196 (31.7)
<b>Child Characteristics</b>	<b>N (%) or Mean (SD)</b>
<b>Sex, n(%)</b>	
<b>Male</b>	324 (52.4)
<b>Female</b>	294 (47.6)
<b>Gestational age (weeks), Mean <math>\pm</math> SD</b>	38.24 $\pm$ 1.47
<b>Birth weight (kg), Mean <math>\pm</math> SD</b>	3.2 $\pm$ 0.42
<b>Duration of breastfeeding (months),Mean <math>\pm</math> SD</b>	4.27 $\pm$ 4.42

# Maternal and child characteristics in early pregnancy

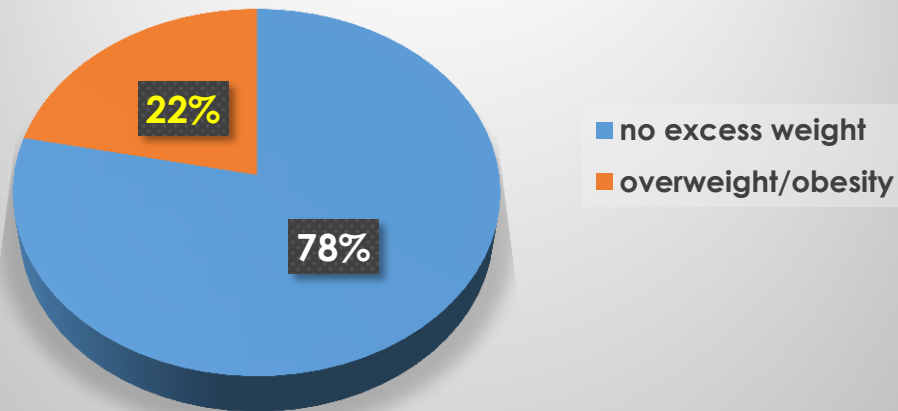
## Pre-pregnancy BMI



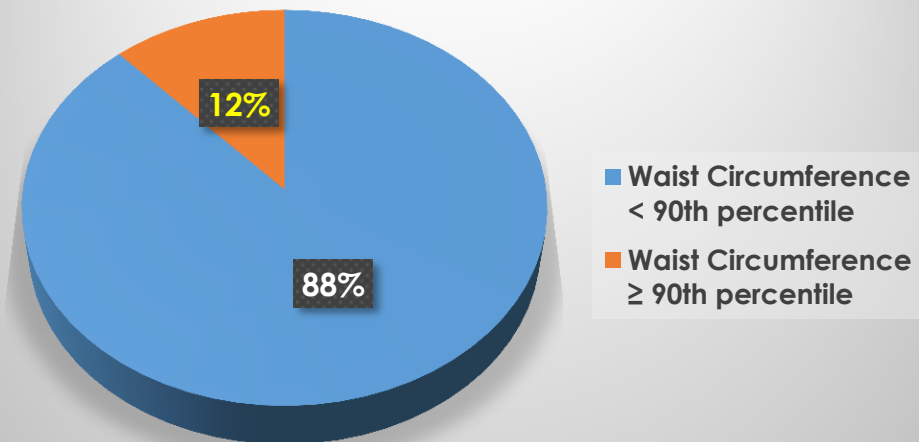
## Dyslipidemia in early pregnancy



## Prevalence of overweight/obesity at 4 years of age



## Central adiposity at 4 years of age



# Association of BMI pre-pregnancy and maternal lipid levels at 1<sup>st</sup> trimester of pregnancy with childhood obesity at 4 years of age.

	Overweight/ Obesity	Abdominal obesity (WC <sup>^</sup> ≥ 90 <sup>th</sup> percentile)	Sum of 4 Skinfolds (mm)
	n=134	n=72	n=601
	RR (95%CI)	RR (95%CI)	β-coeff. (95%CI)
<b>Pre-pregnancy BMI (≥25 kg/m<sup>2</sup>)</b>	<b>1.42 (1.02, 1.97)</b>	<b>1.75 (1.10, 2.82)</b>	<b>5.01 (2.15, 7.86)</b>
<b>Cholesterol (per increase in 40 mg/dL)<sup>a</sup></b>	<b>1.40 (1.02, 1.89)</b>	1.19 (0.71, 2.01)	<b>2.89 (1.00, 4.79)</b>
LDL-C(per increase in 15 mg/dL) <sup>a</sup>	1.09 (0.94, 1.28)	1.11 (0.86, 1.42)	0.89 (-0.15, 1.94)
HDL-C (per increase in 10 mg/dL) <sup>a</sup>	1.21 (0.99, 1.04)	1.13 (0.80, 1.60)	2.05 (0.80, 3.31)
Triglycerides (per increase in 25 mg/dL) <sup>a</sup>	1.07 (0.94, 1.22)	1.08 (0.86, 1.34)	0.70 (-0.12, 1.45)

All models are adjusted for maternal age, education, parity, smoking during pregnancy, weight gain during pregnancy, birth weight, and breastfeeding duration

<sup>a</sup>Also adjusted for prepregnancy BMI



## Association of BMI pre-pregnancy with childhood obesity at 4 years of age, according to gender.

Pre-pregnancy BMI ( $\geq 25 \text{ kg/m}^2$ ) n=209				
	All (n=618)	Boys (n=324)	Girls (n=294)	P for interaction
Overweight/Obesity, RR (95% CI)	1.43 (1.02, 1.98)	0.94 (0.58, 1.52)	<b>2.38 (1.47, 3.86)</b>	0.010
Abdominal obesity (WC $\geq 90$ th percentile), RR (95% CI)	1.74 (1.09, 2.79)	1.00 (0.53, 1.88)	<b>4.36 (1.93, 9.83)</b>	0.003
Sum of 4 skinfold (mm), $\beta$ -coeff. (95% CI)	5.28 (2.45, 8.10)	2.54 (-0.95, 6.03)	<b>8.36 (3.89, 12.84)</b>	0.025

All models are adjusted for maternal age, education, parity, smoking during pregnancy, weight gain during pregnancy, birth weight and breastfeeding duration

# Association of BMI pre-pregnancy and maternallipids at the 1<sup>st</sup> trimester of pregnancy with child blood pressure levels at 4 years of age.

	Systolic blood pressure(mmHg) $\geq$ 75 <sup>th</sup> percentile	Diastolic blood pressure(mmHg) $\geq$ 75 <sup>th</sup> percentile
	n=121	n=126
	RR (95%CI)	RR (95%CI)
<b>Prepregnancy BMI (<math>\geq</math>25kg/m<sup>2</sup>)<sup>1</sup></b>	<b>1.30 (1.00, 1.87)</b>	0.97 (0.67, 1.41)
Total Cholesterol (per increase in 40 mg/dL) <sup>a</sup>	0.79 (0.58, 1.06)	0.89 (0.69, 1.17)
LDL-C (per increase in 15 mg/dL) <sup>a</sup>	0.94(0.81,1.08)	0.96 (0.85, 1.10)
HDL-C(per increase in 10mg/dL) <sup>a</sup>	0.99 (0.82, 1.20)	1.02 (0.86, 1.12)
Triglycerides (per increase in 25 mg/dL) <sup>a</sup>	0.83 (0.72, 1.01)	0.83 (0.71, 0.97)

All models are adjusted for maternal age, maternal education, parity, smoking during pregnancy, weight gain during pregnancy, birth weight, and breastfeeding duration

<sup>a</sup> Also adjusted for child sex and pre-pregnancy BMI.

## Association of BMI pre-pregnancy and maternallipid levels at 1<sup>st</sup>trimester of pregnancy with offspring lipid profile at 4 years of age

	Cholesterol (mg/dl) ≥ 75 <sup>th</sup> percentile n=135	HDL (mg/dl) < 25 <sup>th</sup> percentile n=128	Triglycerides (mg/dl) ≥ 75 <sup>th</sup> percentile n=139
	RR (95%CI)	RR (95%CI)	RR (95%CI)
Pre-pregnancy BMI (≥25kg/m <sup>2</sup> )	1.20 (0.86, 1.66)	0.87 (0.61, 1.24)	0.80 (0.57, 1.12)
<b>Cholesterol (per increase in 40 mg/dL)<sup>a</sup></b>	<b>1.29 (1.00, 1.67)</b>	1.07 (0.82, 1.40)	1.23 (0.94, 1.59)
<b>LDL-C (per increase in 15 mg/dL)<sup>a</sup></b>	<b>1.16 (1.02, 1.33)</b>	1.07 (0.94, 1.23)	1.12 (0.98, 1.28)
<b>HDL-C (&lt; 50 mg/dl) <sup>a</sup></b>	<b>1.62 (1.00, 2.61)</b>	1.10 (0.66, 1.82)	0.94 (0.56, 1.57)
Triglycerides (per increase in 25 mg/dL) <sup>a</sup>	1.05 (0.94, 1.17)	0.95 (0.84, 1.08)	1.07 (0.96, 1.19)

All models are adjusted for maternal age, maternal education, parity, smoking during pregnancy, weight gain during pregnancy, birth weight, and breastfeeding duration

<sup>a</sup> Also adjusted for child sex and pre-pregnancy BMI.

# Strengths and limitations of the study

## Strengths

- Population based, prospective design
- Fasting serum lipid samples in early pregnancy
- Several factors were evaluated as potential confounders or effect modifiers

## Limitations

- Self reported BMI pre-pregnancy
- Non fasting serum lipid samples at 4 years of age.

# Conclusions

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- Maternal **pre gestational weight excess** was associated with increased risk of overweight/obesity, central adiposity, increased fat mass and increased levels of systolic blood pressure at 4 years of age.
  
- Maternal **total cholesterol lipid levels** in early pregnancy were associated with increased risk of overweight/obesity, increased fat mass and increased total cholesterol levels at 4 years of age.





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