



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

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

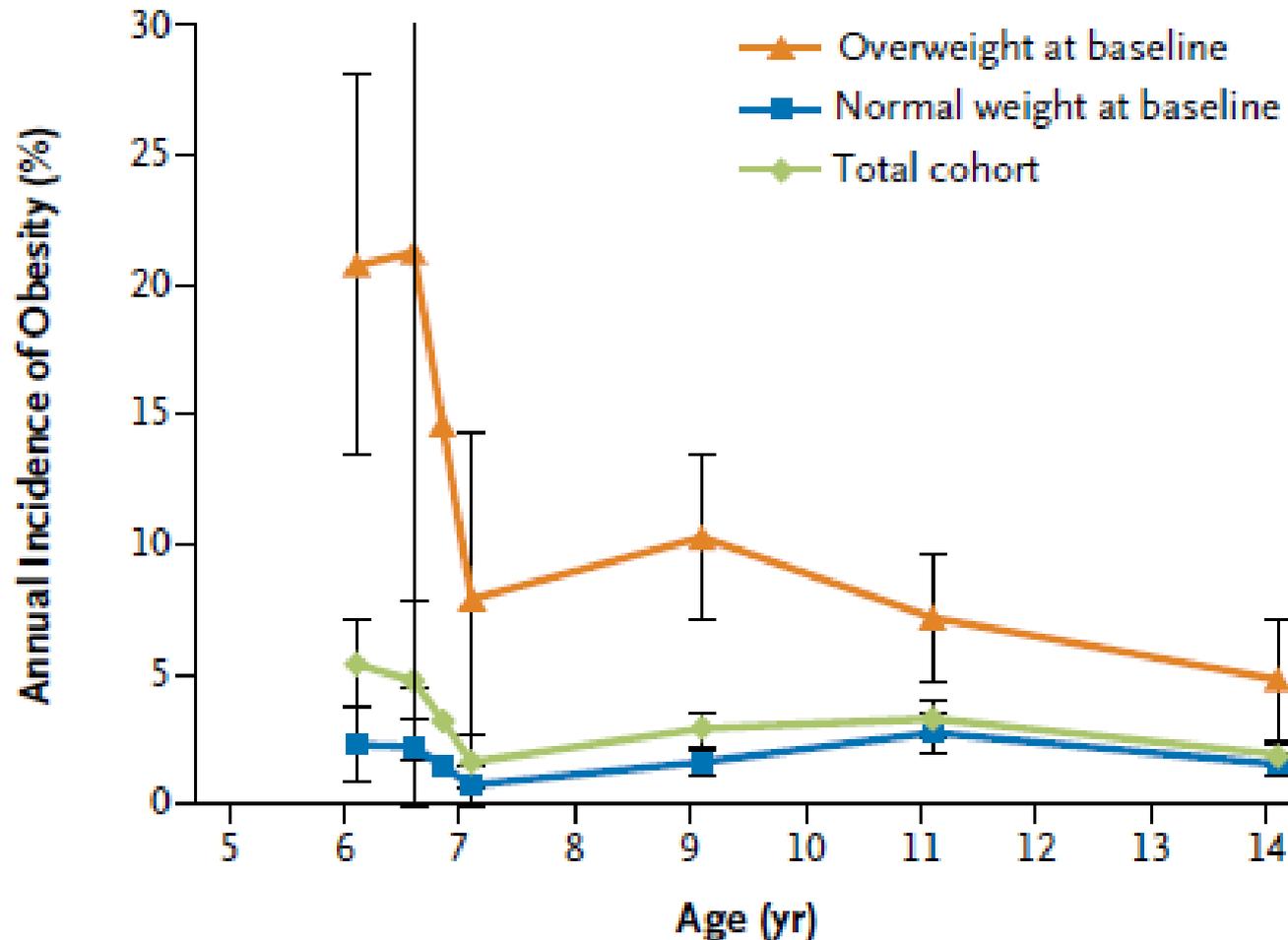
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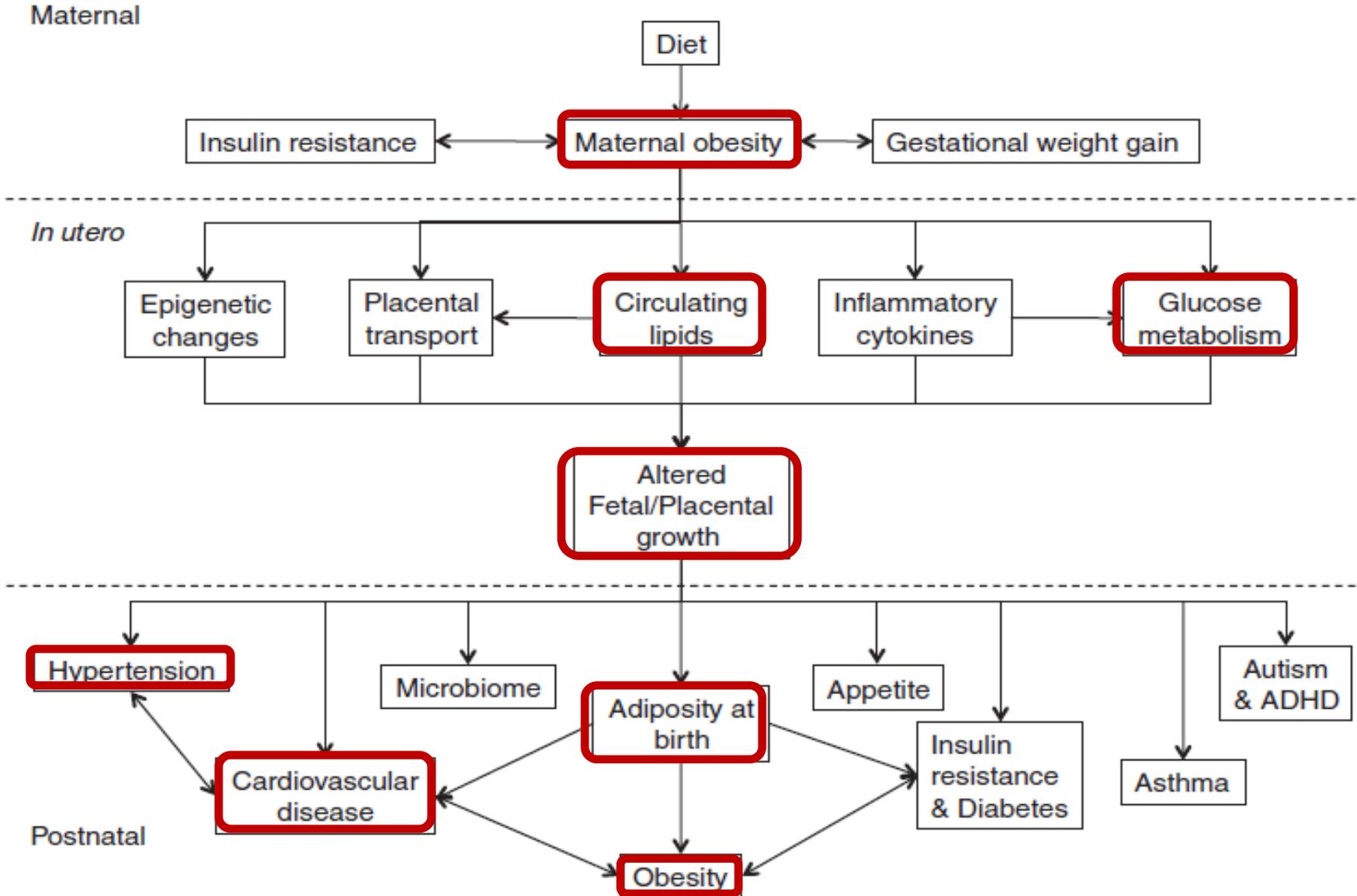
The "Program of prevention and early diagnosis of obesity and neurodevelopment disorders in preschool age children in the prefecture of Heraklion, Crete, Greece" (NSRF 2007-2013 project, MIS 349580), co-financed by the European Union-European Social Fund and the Hellenic Ministry of Health.



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



Developmental programming of childhood obesity



Early intrauterine environment and cardiometabolic risk factors at preschool age.

- **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

- **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 th –24 th w. pregnancy	Q 1 , FFQ, EPDS, STAI-T, EPQ, S. Capital, Q2	+ blood sampe + urine sample	
25 th –36 th w. pregnancy	Q3	+urine sample	
Delivery		+ blood sample	+ Cord blood
1 st month	EPDS		
9 th month	Q4 (parents) Asthma symptoms		
18 th month	Neurodevelopment Q5 (parents)		
4 th 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/m²) :

- no excess weight (BMI pre-pregnancy <25 kg/m²)
- overweight (BMI pre-pregnancy :25–29.9 kg/m²)
- obese (BMI pre-pregnancy ≥30kg/m²)

➤ 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 25th percentile for HDL-C serum level were used as a cut-off point to denote abnormal values in children.

Potential confounders

- 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

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

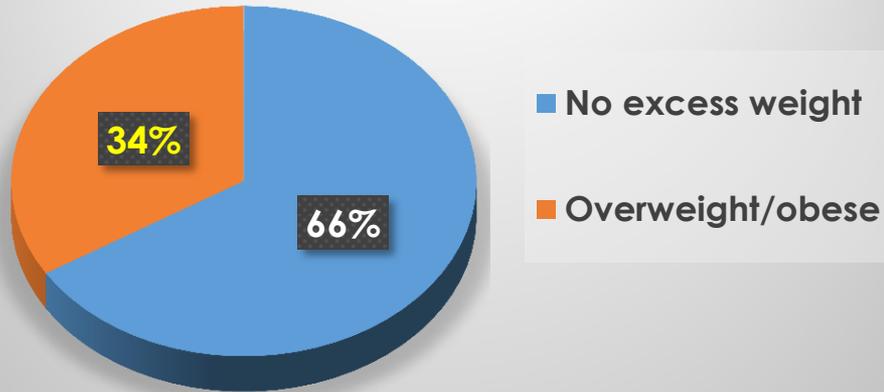
Effect modification by child's sex, maternal smoking during pregnancy, and gestational weight gain were assessed through inclusion of the interaction terms in the models (statistically significant effect modification if $p\text{-value} < 0.05$) and stratified analyses.

Demographic characteristics of the study population

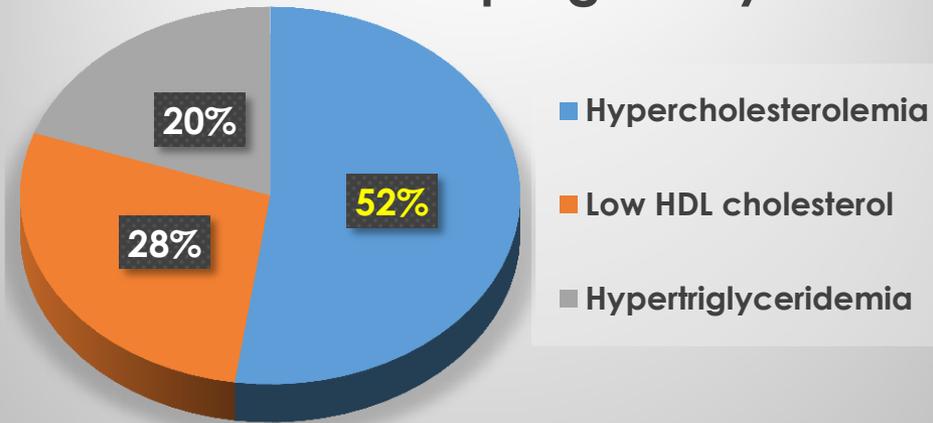
Maternal Characteristics at initial visit	N (%) or Mean (SD)
Age at delivery (years), Mean \pm SD	29.91 \pm 4.8
Greek origin, n(%)	583 (94.3)
Parity, n(%)	
Primiparous	264 (42.7)
Multiparous	354 (57.3)
Education, n (%)	
Low	103 (16.7)
Medium	310 (50.2)
High	205 (33.1)
Smoking during pregnancy, n (%)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

Maternal and child characteristics in early pregnancy

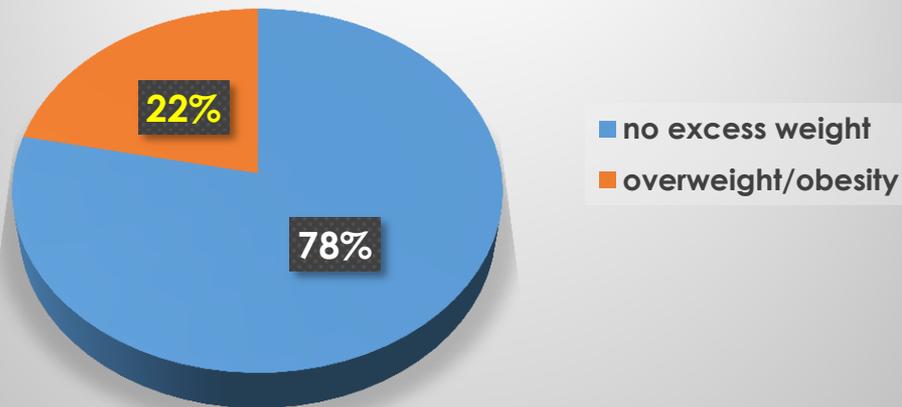
Pre-pregnancy BMI



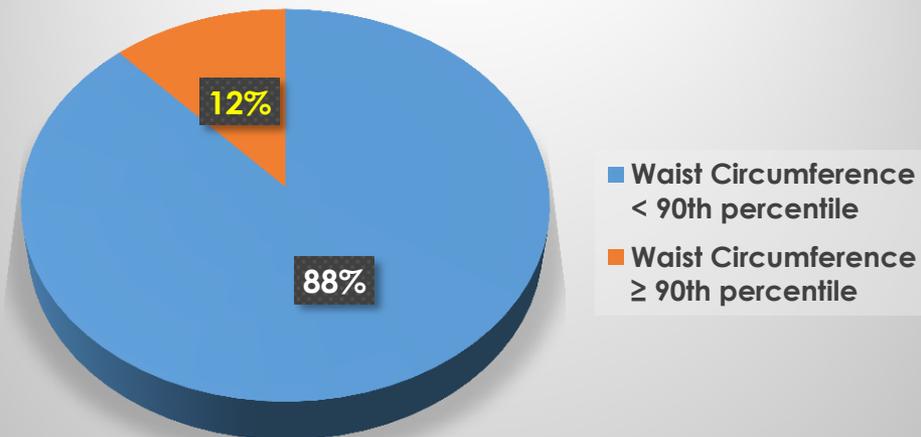
Dyslipidemia in early pregnancy



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 1st trimester of pregnancy with childhood obesity at 4 years of age.

	Overweight/ Obesity	Abdominal obesity (WC [^] ≥ 90 th percentile)	Sum of 4 Skinfolds (mm)
	n=134	n=72	n=601
	RR (95%CI)	RR (95%CI)	β-coeff. (95%CI)
Pre-pregnancy BMI (≥25 kg/m²)	1.42 (1.02, 1.97)	1.75 (1.10, 2.82)	5.01 (2.15, 7.86)
Cholesterol (per increase in 40 mg/dL)^a	1.40 (1.02, 1.89)	1.19 (0.71, 2.01)	2.89 (1.00, 4.79)
LDL-C(per increase in 15 mg/dL) ^a	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) ^a	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) ^a	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

^aAlso 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)	2.38 (1.47, 3.86)	0.010
Abdominal obesity (WC ≥ 90 th percentile), RR (95% CI)	1.74 (1.09, 2.79)	1.00 (0.53, 1.88)	4.36 (1.93, 9.83)	0.003
Sum of 4 skinfold (mm), β -coeff. (95% CI)	5.28 (2.45, 8.10)	2.54 (-0.95, 6.03)	8.36 (3.89, 12.84)	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 1st trimester of pregnancy with child blood pressure levels at 4 years of age.

	Systolic blood pressure(mmHg) ≥ 75 th percentile	Diastolic blood pressure(mmHg) ≥ 75 th percentile
	n=121	n=126
	RR (95%CI)	RR (95%CI)
Prepregnancy BMI (≥25kg/m²)¹	1.30 (1.00, 1.87)	0.97 (0.67, 1.41)
Total Cholesterol (per increase in 40 mg/dL) ^a	0.79 (0.58, 1.06)	0.89 (0.69, 1.17)
LDL-C (per increase in 15 mg/dL) ^a	0.94(0.81,1.08)	0.96 (0.85, 1.10)
HDL-C(per increase in 10mg/dL) ^a	0.99 (0.82, 1.20)	1.02 (0.86, 1.12)
Triglycerides (per increase in 25 mg/dL) ^a	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

^a Also adjusted for child sex and pre-pregnancy BMI.

Association of BMI pre-pregnancy and maternallipid levels at 1sttrimester of pregnancy with offspring lipid profile at 4 years of age

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

^a 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

- 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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