High maternal LDL-C in pregnancy and offspring CVD risk factors at 6-13 years

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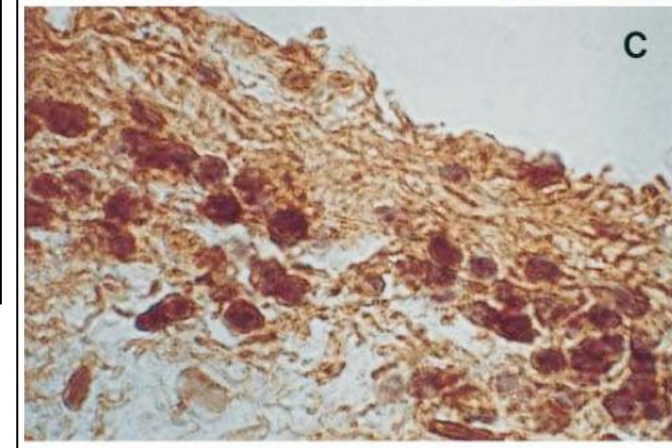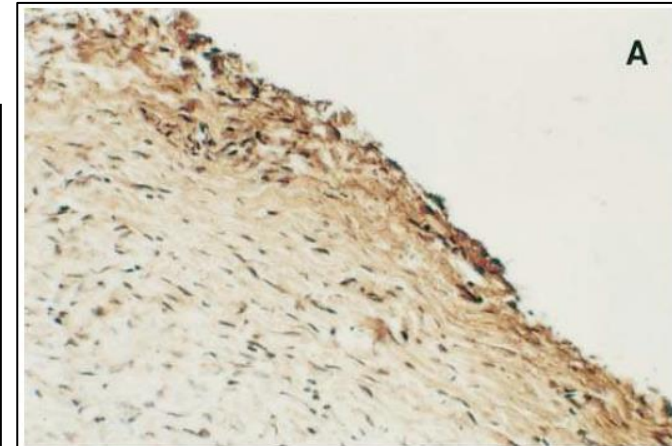
The Lipid Clinic,
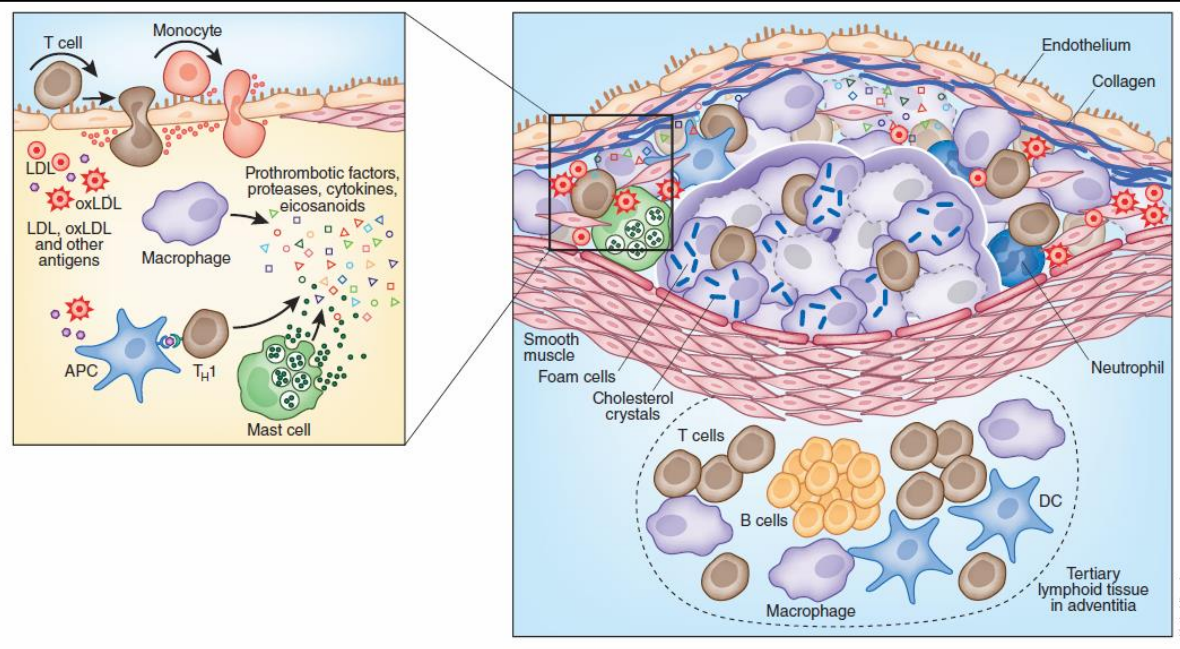Oslo University Hospital

High cholesterol

High cholesterol?
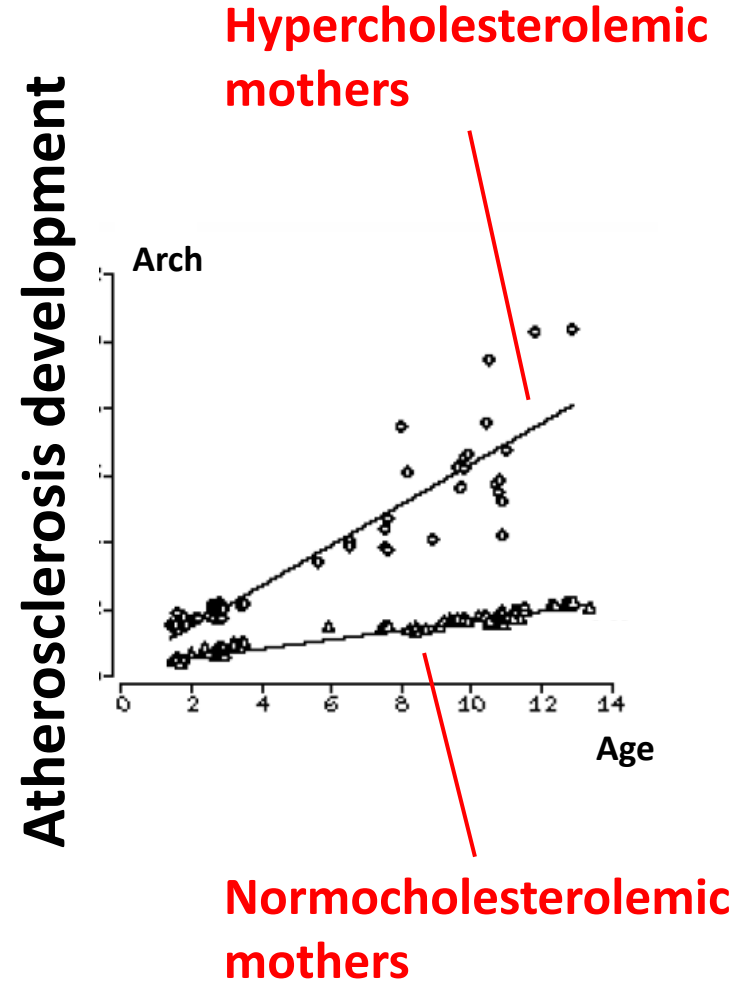**High triglyserides?**
Glucose disturbances?
High BP?
Markers of disease?

Most CVD is caused by atherosclerosis, a process which starts early in life

Hansson & Hermansson Nat Immunol 2011
Napoli C J Clin Invest 1997

Hypercholesterolemic women have children who develop atherosclerosis early in life

Napoli C J Clin Invest 1997
Napoli C Lancet 1999
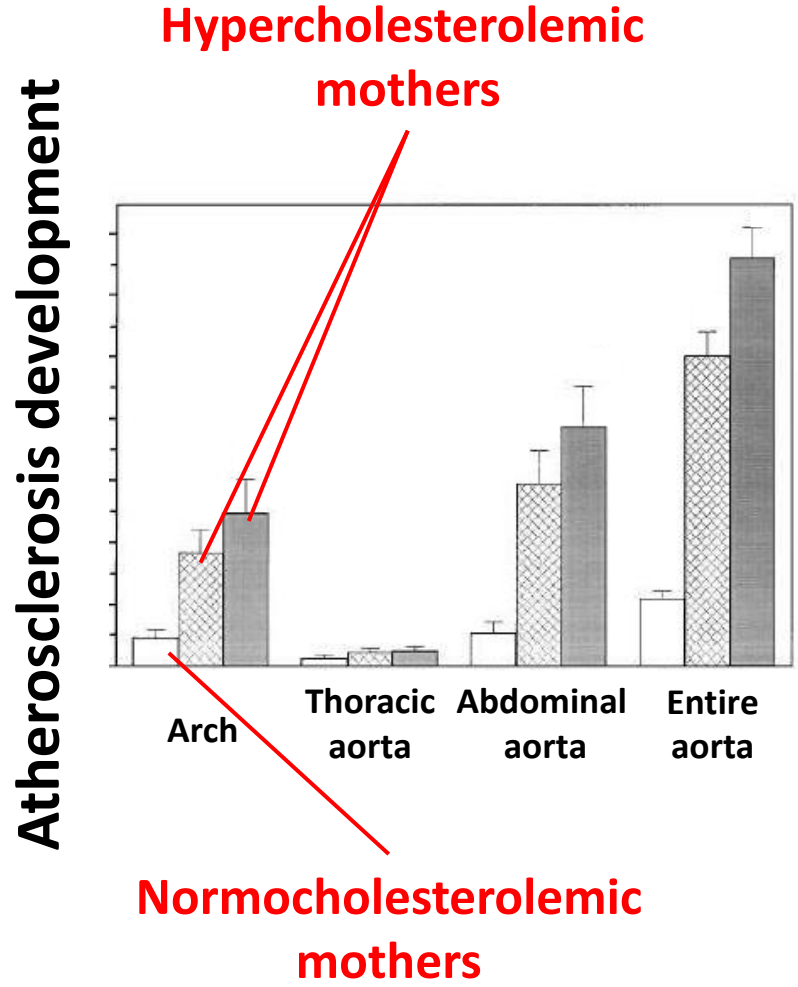
Visit 1: gw 14-16 → Visit 2: gw 22-24 → Visit 3: gw 30-32 → Visit 4: gw 36-38

n = 1031 healthy women

2001 - 2008

2015

Lipid profile

LDL-C ≥90th percentile

LDL-C ≤10th percentile

n = 100 invited

n = 100 invited

Approximately 30 % participation rate

We included women with 2.6 mM diff in LDL-C early in pregnancy

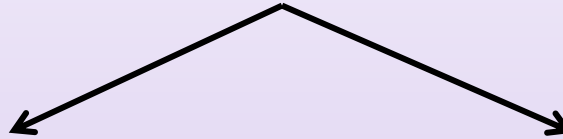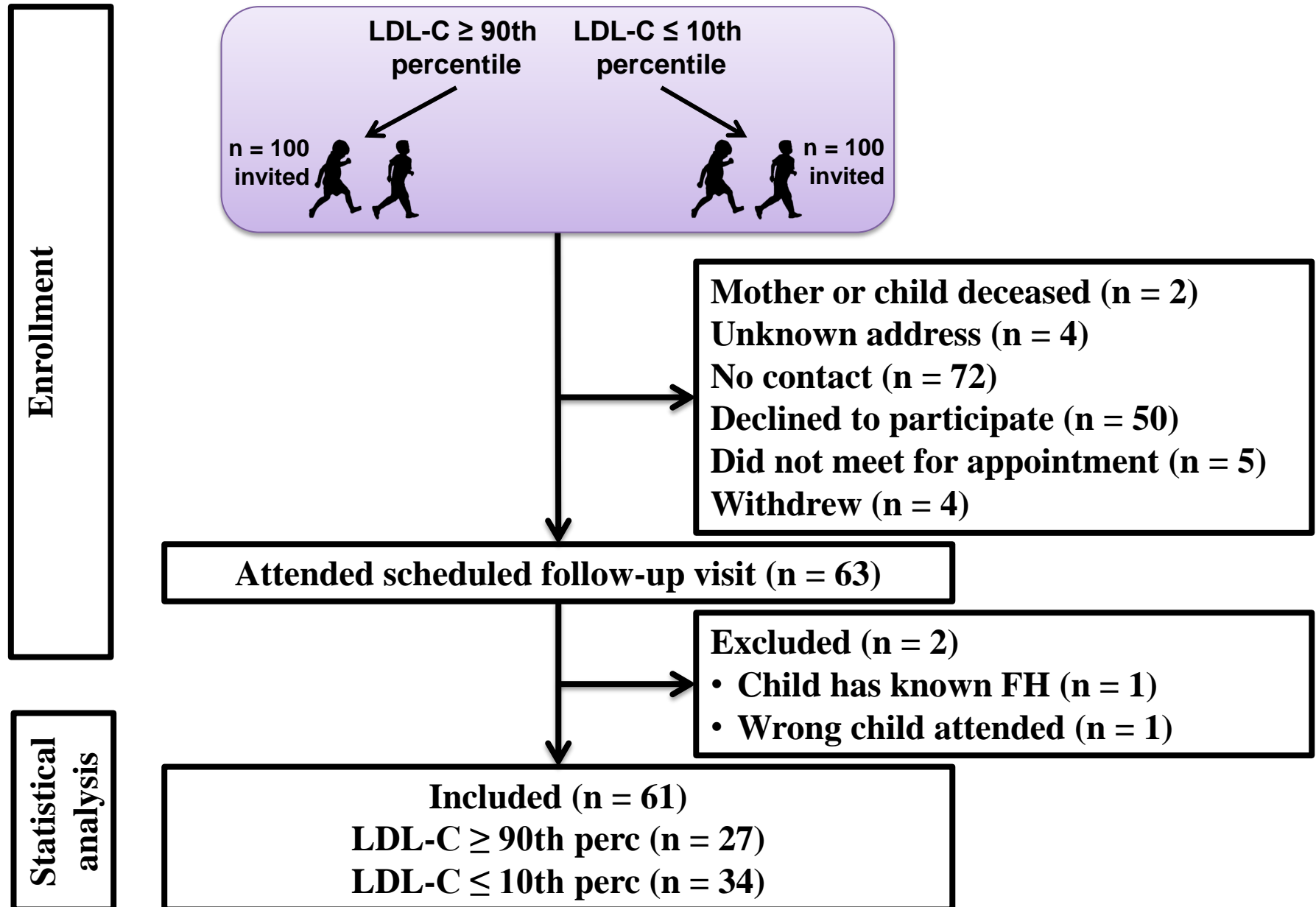|	High LDL-C in early pregnancy			Low LDL-C in early pregnancy			P	P	P
	Early-pregnancy	Late-pregnancy	Δ%	Early-pregnancy	Late-pregnancy	Δ%			
TC	6.3 (0.6)	7.6 (1.4)	20	3.8 (0.5)	5.6 (1.0)	49	*<0.001*	*<0.001*	*<0.001*
LDL-C	4.0 (0.3)	4.8 (1.3)	19	1.4 (0.2)	2.8 (0.8)	99	*<0.001*	*<0.001*	*<0.001*
HDL-C	1.6 (0.3)	1.4 (0.3)	-12	1.9 (0.4)	1.9 (0.5)	-4	*0.001*	*<0.001*	*0.075*
TG	1.7 (0.5)	3.3 (0.7)	104	0.9 (0.2)	2.0 (0.7)	129	*<0.001*	*<0.001*	0.12
Glucose	4.1 (0.5)	4.3 (0.4)	7	3.9 (0.3)	4.0 (0.5)	3	0.13	*0.011*	0.20
Insulin	28 (24 - 61)	57 (43 - 95)	76	23 (14 - 33)	34 (19 - 49)	60	*0.013*	*0.001*	0.28
HOMA2-IR	0.5 (0.4 - 1.1)	1.1 (0.8 - 1.7)	77	0.4 (0.2 - 0.6)	0.6 (0.3 - 0.9)	50	*0.011*	*<0.001*	0.31
CRP	5.2 (3.5 - 9.3)	3.9 (2.8 - 7.2)	-25	2.3 (1.5 - 4.1)	2.1 (1.3 - 4.0)	-18	*<0.001*	*0.002*	0.49

Other metabolic and clinical parameters were also different

	High LDL-C in early pregnancy			Low LDL-C in early pregnancy					
	Early-pregnancy	Late-pregnancy	Δ%	Early-pregnancy	Late-pregnancy	Δ%	P	P	P
Weight	76.4 (12.4)	86.6 (13.1)	14	66.1 (9.5)	75.9 (10.5)	15	*0.001*	*0.001*	0.21
Height	1.68 (0.05)			1.71 (0.06)			*0.064*		
BMI	27.2 (4.7)	30.8 (4.8)	14	22.7 (2.6)	26 (2.8)	15	*<0.001*	*<0.001*	0.22
SBP	113 (11)	117 (15)	3	110 (10)	109 (10)	0	0.18	*0.016*	0.17
DBP	70 (9)	75 (12)	8	65 (7)	71 (9)	10	*0.022*	0.14	0.65
MAP	84 (9)	89 (12)	6	80 (7)	84 (9)	5	*0.039*	*0.06*	0.81

At birth, gestational length was different, but body composition was similar

	High LDL-C in early pregnancy	Low LDL-C in early pregnancy	P
Gestational length, weeks	40.0 (1.3)	40.7 (1.0)	*0.018*
Birthweight (bw), g	3698 (558)	3699 (369)	0.99
Length, cm	50.9 (2.0)	51.3 (1.4)	0.40
Birth size			
SGA, n (%)	1 (4)	1 (3)	0.73
AGA, n (%)	20 (74)	28 (82)	
LGA, n (%)	6 (22)	5 (15)	
Head circumference, cm	35.1 (2.1)	35.0 (1.2)	0.87
Placental weight (pw), g	737 228	713 132	0.63
Placental efficiency (bw/pw)	5.2 (1.1)	5.3 (0.9)	0.81

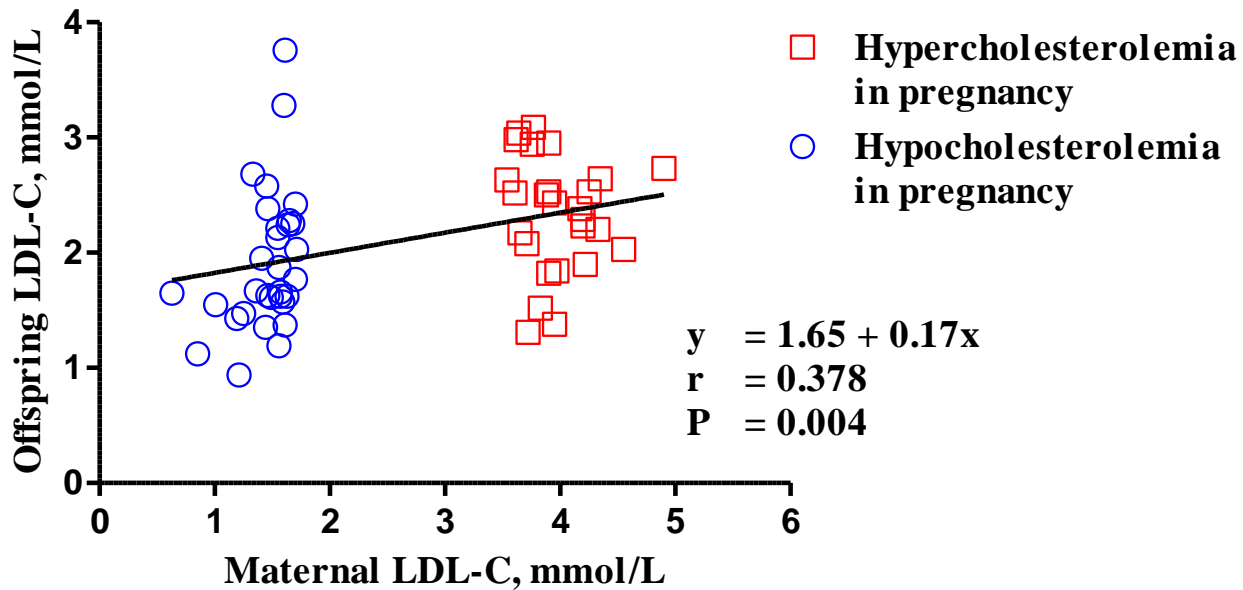# By chance, age and height were different in children at 6-13 years

	High LDL-C in early pregnancy	Low LDL-C in early pregnancy	P
Age, years	9.4 (1.6)	10.4 (2.1)	*0.044*
Gender			
Girls, n (%)	13 (48)	17 (50)	0.89
Boys, n (%)	14 (52)	17 (50)	
Clinical measurements:			
Weight	34.1 (9.0)	39.0 (14.4)	0.13
Height	1.39 (0.1)	1.46 (0.1)	*0.042*
BMI	17.5 (2.5)	17.8 (3.1)	0.67
SBP	106 (7)	107 (7)	0.58
DBP	61 (4)	62 (5)	0.36
MAP	76 (4)	77 (5)	0.37
Heart rate	77 (10)	76 (10)	0.68
Total body fat	27 (7)	25 (6)	0.37
Visceral fat	20 (11)	18 (8)	0.38
Hip fat	31 (8)	29 (8)	0.38

LDL-C was 0.4 mM higher in children of hypercholesterolemic women

	High LDL-C in early pregnancy	Low LDL-C in early pregnancy	P
Biochemical measurements:			
TC	4.2 (0.5)	3.9 (0.7)	0.11
LDL-C	2.3 (0.5)	1.9 (0.6)	*0.007*
HDL-C	1.5 (0.2)	1.6 (0.3)	0.14
TG	0.9 (0.4)	0.9 (0.5)	0.98
Glucose	5.3 (0.5)	5.1 (0.6)	0.38
C peptide	881 (435)	825 (322)	0.58
Creatinin	42 (6)	44 (7)	0.21
ALAT	17 (16 - 21)	18 (15 - 19)	0.87
CRP	0.6 (0.6 - 0.8)	0.6 (0.6 - 0.6)	0.50
Estradiol	0.04 (0.4 - 0.4)	0.04 (0.04 - 0.10)	0.13
Testosterone	0.4 (0.4 - 0.4)	0.4 (0.4 - 0.5)	0.30
FSH	1.4 (0.9 - 2.7)	1.7 (1.0 - 4.9)	0.13

LDL-C association slightly attenuated after adjusting for HDL-C

	B	SE	P
Univariable regression			
Maternal LDL-C	0.17	0.06	***0.004***
Maternal HDL-C	-0.58	0.18	***0.002***
Maternal triglycerides	0.25	0.15	*0.091*
Maternal BMI	0.03	0.02	*0.068*
Maternal education	-0.20	0.29	0.49
Age of child	0.00	0.04	0.98
Puberty	-0.04	0.19	0.81
Sex of child	-0.05	0.16	0.77
Multivariable regression models			
Model 1	0.12	0.06	*0.056*
Model 2	0.21	0.09	***0.016***
Model 3	0.16	0.07	***0.026***
Model 4	0.18	0.06	***0.003***
Model 5	0.17	0.10	*0.084*

Christensen et al. J Clin Lipidol (in press)

$$y = 1.65 + 0.17x$$
$$r = 0.378$$
$$P = 0.004$$

Christensen et al. J Clin Lipidol (in press)
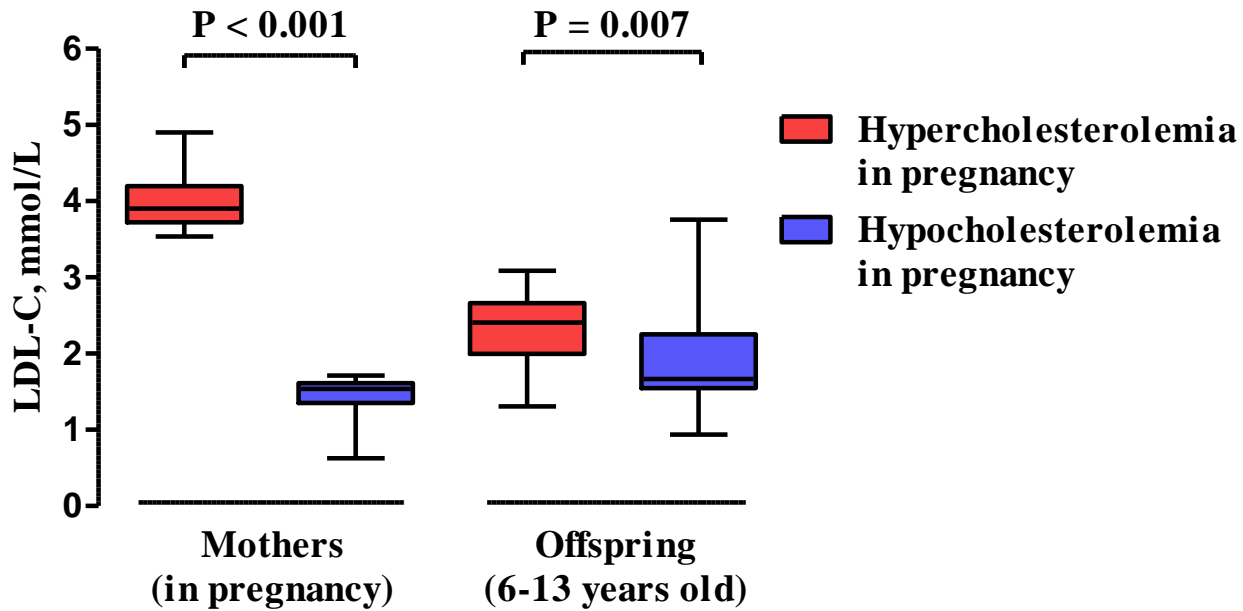
A 0.4 mM difference in LDL-C in children is important because it might track into adulthood

Table II. Age- and sex-specific Spearman correlation co-efficients for 27-year tracking of cardiovascular risk factors

Age in 1980	BMI n	BMI r	SBP n	SBP r	DBP n	DBP r	TC n	TC r	LDL-C n	LDL-C r	HDL-C n	HDL-C r	TG n	TG r
Female subjects														
3 years	155	0.29	-	-	-	-	162	0.39	160	0.34	160	0.45	162	0.08[†]
6 years	193	0.43	195	0.35	194	0.25*	201	0.40	200	0.44	201	0.41	201	0.34
9 years	183	0.53	182	0.35	182	0.26*	190	0.52	189	0.50	190	0.41	190	0.36
12 years	223	0.45	213	0.36	213	0.09[†]	232	0.57	231	0.63	232	0.42	232	0.28
15 years	212	0.37	201	0.36	201	0.19*	214	0.56	211	0.61	214	0.58	214	0.35
18 years	188	0.51	168	0.33	168	0.28*	184	0.53	184	0.57	184	0.48	184	0.38
All	1179	0.43	1124	0.32	958	0.21	1183	0.50	1175	0.52	1181	0.46	1183	0.30
Male subjects														
3 years	153	0.36	-	-	-	-	154	0.56	151	0.53	154	0.45	154	0.22*
6 years	142	0.35	139	0.33	139	0.23*	142	0.56	137	0.61	141	0.50	142	0.36
9 years	172	0.54	169	0.39	167	0.29*	173	0.57	168	0.58	172	0.59	173	0.13[†]
12 years	171	0.59	159	0.23*	158	0.11[†]	166	0.49	159	0.59	165	0.56	166	0.34
15 years	182	0.33	155	0.28*	155	0.27*	170	0.50	168	0.55	167	0.48	170	0.32
18 years	155	0.58	137	0.27*	136	0.35	148	0.43	143	0.48	147	0.49	148	0.24*
All	975	0.46	909	0.27	755	0.25	953	0.52	919	0.56	946	0.51	953	0.27

Non-FH subjects have different trajectories of cholesterol burden
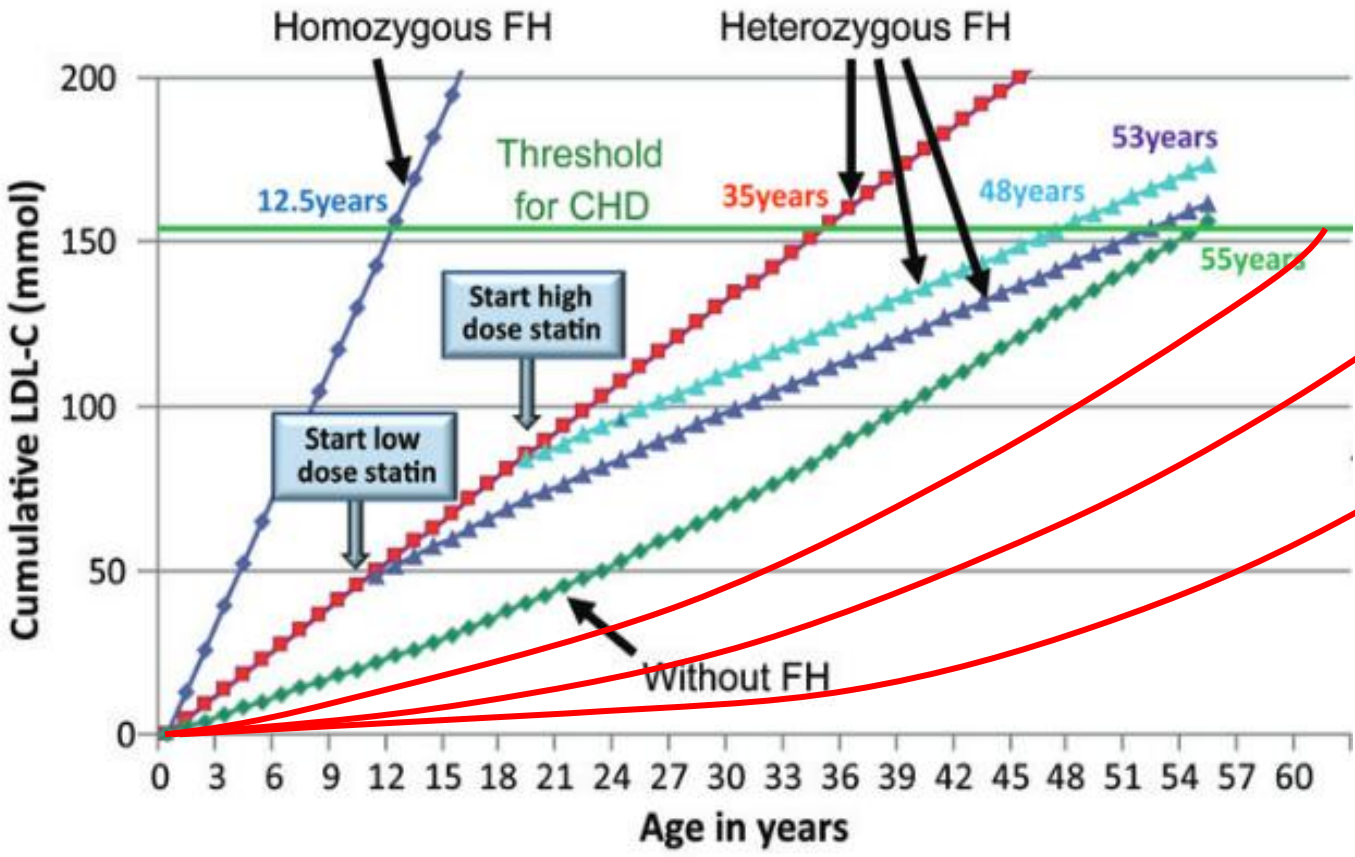
Sequence Variations in *PCSK9*, Low LDL, and Protection against Coronary Heart Disease
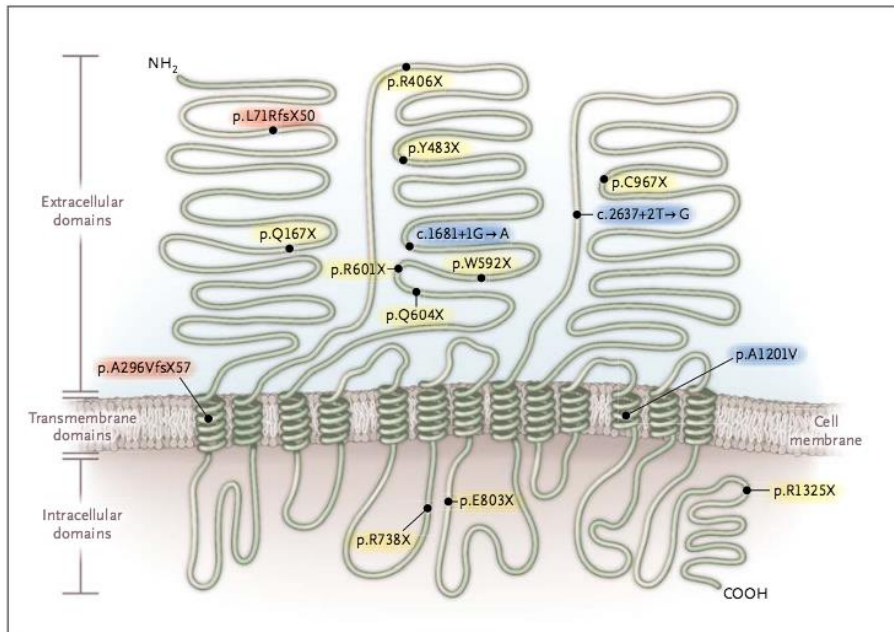
Jonathan C. Cohen, Ph.D., Eric Boerwinkle, Ph.D., Thomas H. Mosley, Jr., Ph.D., and Helen H. Hobbs, M.D.
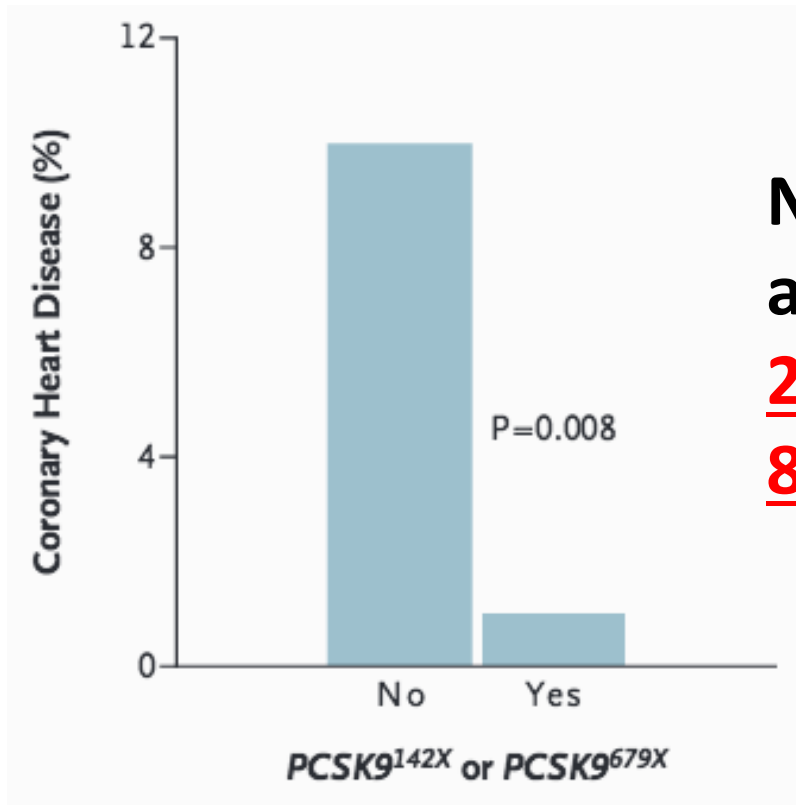
Nonsense mutations were associated with 28 % reduction in LDL-C and 88 % reduction in the risk of CHD

Inactivating Mutations in *NPC1L1* and Protection from Coronary Heart Disease

The Myocardial Infarction Genetics Consortium Investigators

Inactivating mutations were associated with

0.31 mmol/L lower LDL-C and
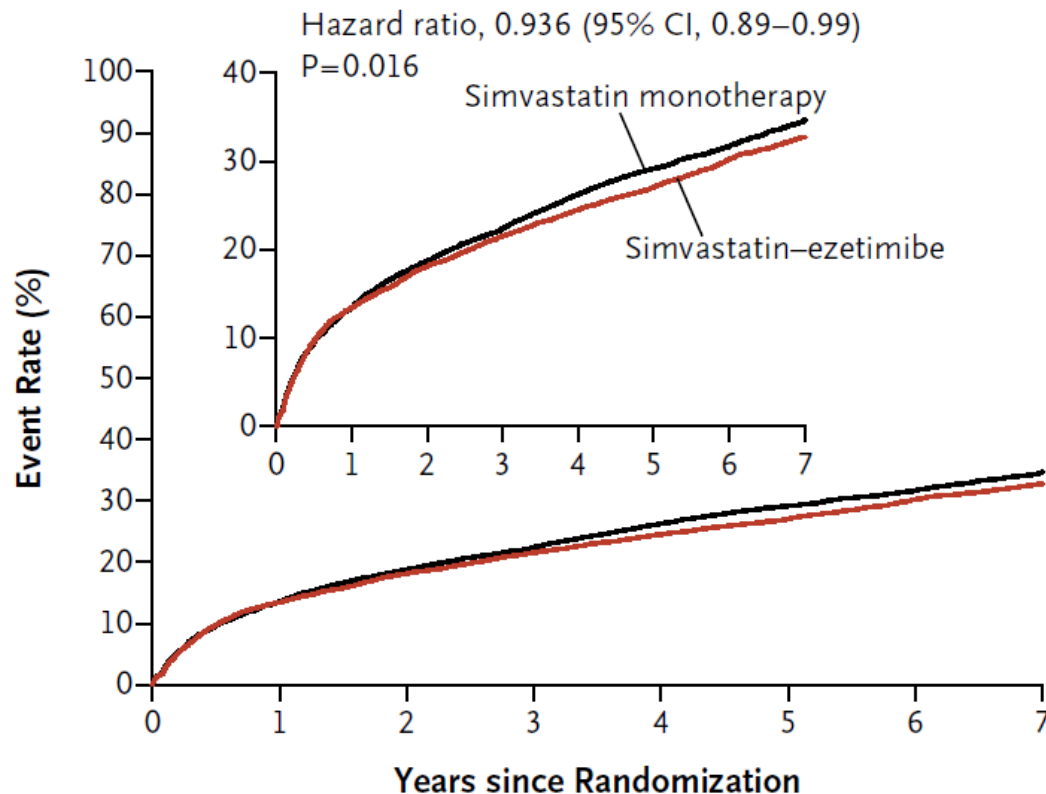
53 % lower risk of CHD

Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes

Statin + ezetimibe vs statin = 0.4 mmol/L lower LDL-C

Median 6 years follow-up

6.4 % reduced CVD risk

Cannon CP NEJM 2015

Hypercholesterolemia can often be prevented and treated by dietary changes

Effects of a healthy Nordic diet on cardiovascular risk factors in hypercholesterolaemic subjects: a randomized controlled trial (NORDIET)

Characteristics	Control diet	Nordic diet	P^b
Plasma triglycerides (mmol L^{-1})	-0.03 ± 0.40 (-2)	0.11 ± 0.58 (7)	0.46
Plasma cholesterol (mmol L^{-1})	0.23 ± 0.55 (4)	-0.98 ± 0.75 (-16)	<0.0001
Plasma LDL-C (mmol L^{-1})	0.10 ± 0.53 (2)	-0.83 ± 0.67 (-21)	<0.001
Plasma HDL-C (mmol L^{-1})	0.11 ± 0.19 (7)	-0.08 ± 0.23 (-5)	0.001
LDL/HDL ratio	-0.11 ± -0.35 (-4)	-0.42 ± -0.57 (-14)	0.003
Plasma apolipoprotein A1 (g L^{-1})	0.11 ± 0.14 (7)	-0.11 ± 0.20 (-7)	<0.001
Plasma Apo B (g L^{-1})	0.16 ± 0.12 (14)	-0.09 ± 0.15 (-8)	<0.001
Apo B/A1 ratio	0.05 ± 0.10 (7)	-0.01 ± 0.13 (-1)	0.02

20 % decrease from baseline

Adamsson JIM 2011

From 6-11 months, children are advised to consume <10 E % from saturated fatty acids

Nordic Nutrition Recommendations 2012
Integrating nutrition and physical activity

10 Fat and fatty acids

Age	6–11 mo.	12–23 mo.	Adults and children from 2 years of age
Cis-MUFA	10–25 E%	10–20 E%	10–20 E%*
Cis-PUFA	5–10 E%	5–10 E%	5–10 E%*
- n-3	≥1 E%	≥1 E%	≥1 E%
SFA	<10 E%	<10 E%	<10 E%
TFA	As low as possible	As low as possible	As low as possible
Total fat	30–45 E%	30–40 E%	25–40 E%

Acknowledgements

In summary, maternal LDL-C associates with offspring LDL-C at 6-13 years of age

High LDL-C may track into adulthood and accelerate atherosclerosis

Young, fertile women with high LDL-C may be important for lifelong CVD prevention

Questions?

Extra slides

⇧ LDL-C
in pregnancy

No differences
in newborn size or
body composition

⇧ LDL-C
in children
aged 6-13 years

*Tracking of
⇧ LDL-C
into adulthood*

*⇧ Early-life
cholesterol
exposure*

*⇧ Cholesterol
burden*

⇧ Atherosclerosis

⇧ Risk of CVD
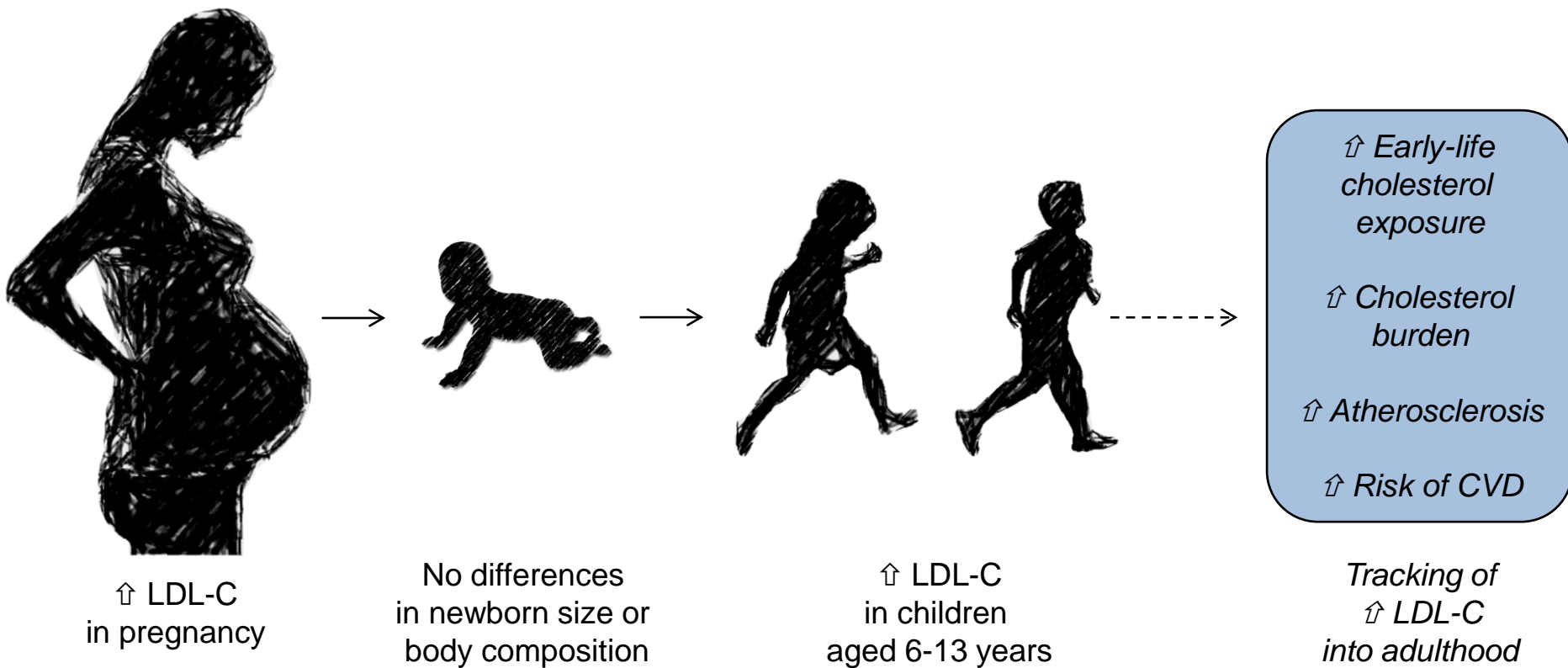
Shared genes, lifestyle and diet in mother and offspring
Effects of exposure to high LDL cholesterol and associated factors

Maternal, but not paternal, pre-pregnancy LDL-C associates with offspring LDL-C at 26 y

Odds ratios (ORs) for elevated adult offspring LDL-C levels (solid line) and 95% CIs (dashed lines) across a range of maternal (A) and paternal (B) prepregnancy LDL-C levels (to convert LDL-C to millimoles per liter, multiply by 0.0259). An OR of 1 indicates no increase in risk.

B = 0.38 (SE = 0.06) mg/dL
P < 0.001

Mendelsson MM JAMA Cardiol 2016

Diet affect LDL-C in children similarly as in adults, with no adverse effects

Substitution of whole cows' milk with defatted milk for 4 months reduced serum total cholesterol, HDL-cholesterol and total apoB in a sample of Mexican school-age children (6–16 years of age)

Villalpando S Br J Nutr 2015

Effect of low-saturated fat, low-cholesterol dietary intervention on fatty acid compositions in serum lipid fractions in 5-year-old children. The STRIP project

Salo P Eur J Clin Nutr 1999

There were no differences in socio-economic status

	High LDL-C in early pregnancy	Low LDL-C in early pregnancy	P
Age, years	31.7 (3.3)	31.9 (3.2)	0.75
Parity			
0, n (%)	11 (41)	15 (45)	0.91
1, n (%)	13 (48)	14 (42)	
2, n (%)	3 (11)	4 (12)	
Highest completed education			
University/college, n (%)	23 (85)	33 (97)	0.16
High school, n (%)	4 (15)	1 (3)	
Smoking status			
Never smoker, n (%)	20 (74)	28 (82)	0.39
Former smoker, n (%)	7 (26)	5 (15)	
Current smoker, n (%)	0 (0)	1 (3)	

Still 0.4 mM difference in LDL-C after adjusting for puberty

	High LDL-C in early pregnancy	Low LDL-C in early pregnancy	P
Age, years	9.1 (1.4)	9.6 (1.9)	0.38
Gender			
Girls, n (%)	10 (46)	8 (36)	0.54
Boys, n (%)	12 (55)	14 (64)	
Clinical measurements:			
Weight	33 (8)	34.3 (8.6)	0.59
Height	1.37 (0.1)	1.41 (0.1)	0.36
BMI	17.3 (2.4)	17.1 (1.9)	0.75
SBP	107 (8)	108 (5)	0.84
DBP	61 (4)	62 (4)	0.49
MAP	77 (3)	77 (4)	0.53
Heart rate	78 (9)	77 (10)	0.61
Total body fat	27 (7)	25 (6)	0.27
Visceral fat	20 (11)	17 (8)	0.28
Hip fat	31 (8)	28 (8)	0.20

Still 0.4 mM difference in LDL-C after adjusting for puberty

	High LDL-C in early pregnancy	Low LDL-C in early pregnancy	P
Biochemical measurements:			
TC	4.2 (0.5)	4 (0.8)	0.39
LDL-C	2.3 (0.5)	1.9 (0.7)	***0.035***
HDL-C	1.5 (0.2)	1.6 (0.4)	0.16
TG	0.9 (0.4)	0.9 (0.5)	0.63
Glucose	5.3 (0.6)	5.1 (0.6)	0.25
C peptide	878 (462)	760 (257)	0.30
Creatinin	42 (6)	43 (6)	0.54
ALAT	17 (16 - 21)	18 (16 - 18)	0.82
CRP	0.6 (0.6 - 1.0)	0.6 (0.6 - 0.6)	0.72
Estradiol	0.04 (0.04 - 0.04)	0.04	0.33
Testosterone	0.4 (0.4 - 0.4)	0.4 (0.4 - 0.4)	0.21
FSH	1.1 (0.7 - 2.2)	1.4 (0.6 - 1.9)	0.99

Maternal diet in pregnancy may have contributed to the observed association

	High LDL-C in early pregnancy	Low LDL-C in early pregnancy	P
Dietary data:			
Energy intake, kJ/d	8733 (2342)	8687 (2052)	0.94
Protein intake, E %	15.6 (2.1)	15.4 (1.9)	0.70
Carbohydrate intake, E %	50.6 (4.7)	52.5 (5.4)	0.15
Sugar intake, E %	8.4 (4.1)	6.6 (3.8)	*0.078*
Fiber intake, E %	2.2 (0.4)	2.5 (0.6)	***0.010***
Fiber intake, g/10 MJ	27 (5.5)	31.4 (7)	***0.010***
Fat intake, E %	33.7 (4.7)	31.7 (5.7)	0.17
SFA intake, E %	13.2 (1.6)	11.9 (2)	***0.045***
MUFA intake, E %	11.1 (1.8)	10.2 (1.8)	***0.049***
PUFA intake, E %	6.8 (2.3)	6.9 (2.3)	0.83

Christensen et al. J Clin Lipidol (in press)

No differences in dietary intake in offspring at 6-13 years of age

Dietary data:	High LDL-C in early pregnancy	Low LDL-C in early pregnancy	P
	n = 9 (32 %)	n = 16 (47 %)	
Energy intake, kJ/d	5750 (1067)	6480 (1074)	0.12
Energy intake, kcal/d	1373 (255)	1548 (256)	0.12
Protein intake, E %	15.7 (2)	16.7 (2)	0.26
Fat intake, E %	30.0 (6.1)	31.0 (4)	0.62
SFA intake, E %	11.8 (2)	13.1 (2)	0.19
TFA intake, E %	0.3 (0)	0.4 (0)	0.25
MUFA intake, E %	10.3 (3)	10.3 (2)	0.99
PUFA intake, E %	5.1 (1)	4.6 (1)	0.30
PS ratio	0.44 (0.1)	0.37 (0.1)	0.13
Carbohydrate intake, E %	52.5 (7)	50.3 (5)	0.33
Starch, E %	23.3 (4)	23.3 (5)	0.98
Fiber intake, E %	1.8 (1)	2.0 (1)	0.46
Mono and disaccharides, E %	25.7 (6)	24.0 (5)	0.43
Sugar intake, E %	13.3 (7)	9.7 (2)	*0.072*

No differences in plasma total fatty acid composition in offspring at 6-13 years

		High LDL-C in early pregnancy	Low LDL-C in early pregnancy	P
Saturated fatty acids:				
C12:0	Lauric acid	0.19 (0.17)	0.21 (0.15)	0.57
C14:0	Myristic acid	1.18 (0.41)	1.30 (0.53)	0.37
C15:0	Pentadecanoic acid	0.25 (0.04)	0.26 (0.05)	0.55
C16:0	Palmitic acid	21.8 (1.1)	22.0 (1.4)	0.45
C18:0	Stearic acid	7.5 (0.6)	7.7 (0.5)	0.14
C20:0	Eicosanoic acid	0.28 (0.05)	0.28 (0.04)	0.62
C22:0	Docosanoic acid	0.81 (0.12)	0.76 (0.15)	0.19
C24:0	Tetracosanoic acid	0.70 (0.12)	0.67 (0.15)	0.40
Monounsaturated fatty acids:				
C16:1c9	Palmitoleic acid	1.81 (0.53)	1.90 (0.51)	0.50
C18:1c9	Oleic acid	20.4 (2.9)	19.9 (2.5)	0.48
C18:1c11	Vaccenic acid	1.36 (0.16)	1.37 (0.16)	0.78
C20:1n9	Eicosenoic acid	0.18 (0.05)	0.18 (0.05)	0.99

No differences in plasma total fatty acid composition in offspring at 6-13 years

		High LDL-C in early pregnancy	Low LDL-C in early pregnancy	P
Omega-6 polyunsaturated fatty acids:				
C18:2n6	Linoleic acid	26.3 (2.7)	25.8 (2.8)	0.45
C18:3n6	γ-Linoleic acid	0.39 (0.20)	0.39 (0.19)	0.98
C20:2n6	Eicosadienoic acid	0.23 (0.03)	0.24 (0.05)	0.37
C20:3n6	DH-γ-Linoleic acid	1.55 (0.35)	1.54 (0.30)	0.94
C20:4n6	Arachidonic acid	6.2 (1.2)	6.1 (1.0)	0.75
Omega-3 polyunsaturated fatty acids:				
C18:3n3	α-Linolenic acid	0.61 (0.18)	0.69 (0.21)	0.14
C20:5n3	EPA	1.02 (0.52)	1.18 (0.93)	0.44
C22:5n3	DPA	0.60 (0.11)	0.64 (0.11)	0.20
C22:6n3	DHA	2.38 (0.75)	2.52 (1.14)	0.59
Desaturase activity indices:				
SCD-16	(C16:1c9/C16:0)	0.08 (0.02)	0.09 (0.02)	0.58
SCD-18	(C18:1c9/C18:0)	2.77 (0.53)	2.62 (0.41)	0.25
D6D	(C18:3n6/C18:2n6)	0.02 (0.01)	0.02 (0.01)	0.86
D5D	(C20:4n6/C20:3n6)	4.21 (1.16)	4.16 (1.15)	0.87