First trimester fetal growth restriction and cardiovascular risk factors in school age children: population based cohort study

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Figure S1. Participants Flow Chart in the Generation R Study, Rotterdam, the Netherlands

N = 8,880

Mothers enrolled during pregnancy

N = 4,685

Excluded due to no first-trimester crown to rump length measurement available

N = 4,195

Mothers with singleton pregnancy with first-trimester fetal crown to rump length

N = 1,431

Excluded due to unknown first day of last menstrual period or irregular cycle or pregnancy leading to miscarriage, stillbirth, or unknown birth outcomes.

N = 1,619

Mothers with a known gestational age based on last menstrual period and singleton life born children

N = 435

Excluded due to no participation in follow up studies

Childhood outcomes at age of 6 years:

N= 1,184

Adiposity outcomes:

Body mass index: n = 1181

Body fat distribution: n = 1152

Cardiovascular outcomes:

Systolic blood pressure: n = 1125

Diastolic blood pressure: n = 1125

Metabolic outcomes:

Cholesterol: n = 794

Triglycerides: n = 789

Insulin and C-peptide: n = 785
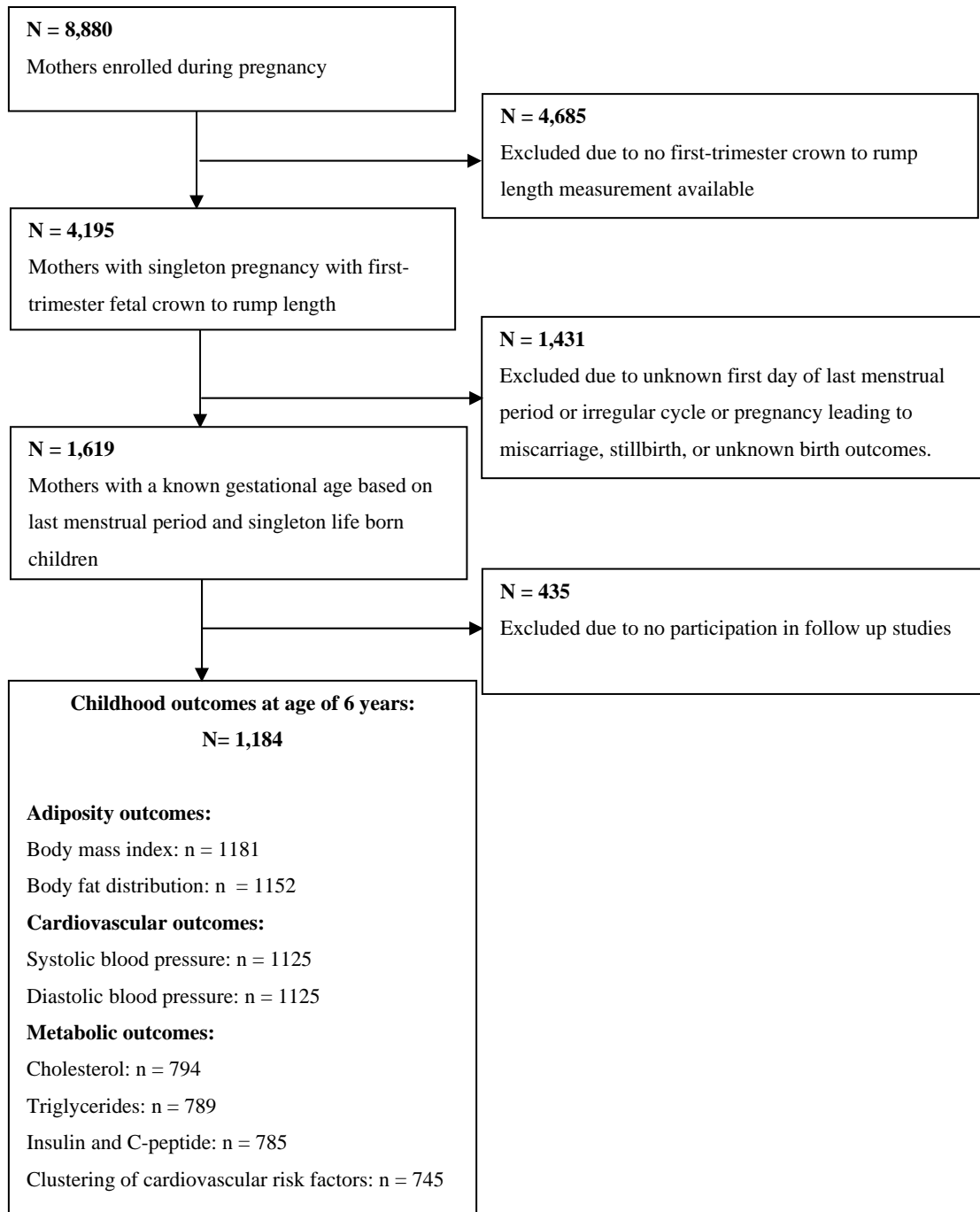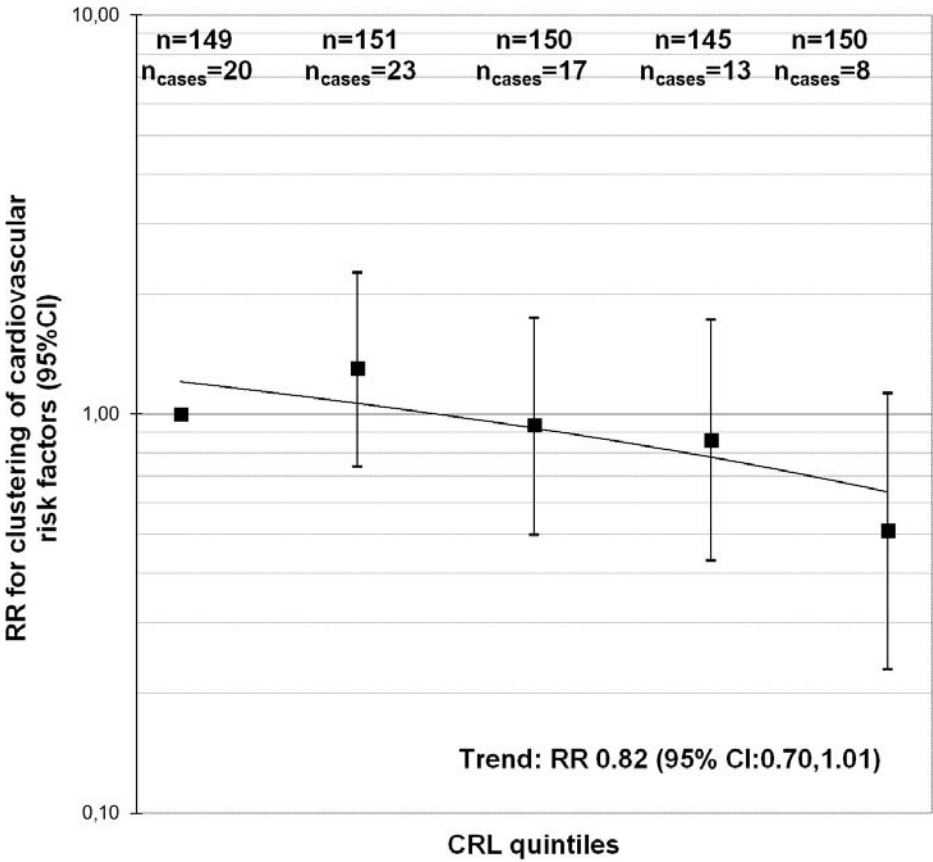
Clustering of cardiovascular risk factors: n = 745

Figure S2. First-Trimester Fetal Growth and Clustering of Cardiovascular Risk Factors Adjusted for Gestational Age and Weight at Birth (N = 745)[1]

[1]Values are risk ratios (95% confidence interval) from generalized linear models that reflect the risk of childhood clustering of cardiovascular risk factors for first-trimester fetal crown to rump length SDS categories, as compared to the reference group (lowest quintile). Model is adjusted for child sex and age at measurement, maternal duration of last menstrual cycle, age, educational level, ethnicity, parity, pre-pregnancy body mass index, diastolic blood pressure, smoking during pregnancy, folic acid supplement use, breastfeeding duration and gestational age and weight at birth (fetal pathway model).

Table S1. Associations of Covariates with Childhood Body Fat Outcomes (N = 1, 184) [1]

	Body mass index (kg/m^2)	Total fat mass (%)	Android/Gynoid fat mass ratio (%)
Duration of menstrual cycle, days	0.03 (-0.04, 0.10)	-0.08 (-0.30, 0.14)	0.03 (-0.23, 0.28)
Child sex			
Boys	*Reference*	*Reference*	*Reference*
Girls	-0.22 (-0.42, 0.03)*	4.19 (3.64, 4.75)*	0.39 (-0.30, 1.09)
Childhood age at outcome	0.63(0.41, 0.85)*	1.43 (0.66, 2.20)*	1.41 (0.51, 2.31)*
Maternal age, yr	-0.03 (-0.05, -0.01)*	-0.16 (-0.22, -0.09)*	-0.13 9-0.21, -0.05)*
Education			
Primary	0.91 (0.45, 1.37)*	3.04 (1.69, 4.40)*	1.44 (-0.21, 3.09)
Secondary	0.37 (0.17, 0.57)*	1.95 (1.33, 2.57)*	1.48 (0.75, 2.21)**
Higher	*Reference*	*Reference*	*Reference*
Ethnicity			
Dutch or European	*Reference*	*Reference*	*Reference*
Non – European	0.40 (0.19, 0.62)*	1.44 (0.77, 2.11)*	0.90 (0.12, 1.68)*
Parity			
Nulliparous	*Reference*	*Reference*	*Reference*
Multiparous	0.02 (-0.17, 0.22)	-0.79 (-0.141, -0.18)*	-0.45 (-1.17, 0.26)
Prepregnancy body mass index, kg/m^2	0.13 (0.10, 0.15)*	0.33 (0.25, 0.41)*	0.27 (0.18, 0.36)*
Diastolic blood pressure, mmHg	0.01 (0, 0.02)*	0.04 (0.01, 0.08)*	0.02 (-0.02, 0.06)
Smoking			
Yes	0.34 (0.09, 0.58)*	1.16 (0.26, 2.06)*	1.85 (0.91, 2.79)*
No	*Reference*	*Reference*	*Reference*
Folic acid supplement use			
Yes	*Reference*	*Reference*	*Reference*
No	0.36 (0.15, 0.57)*	1.48 (0.84, 2.11)*	1.30 (0.56, 2.05)*
Breastfeeding duration, month)	-0.02 (-0.05, 0.01)	-0.09 (-0.18, 0)	-0.08 (-0.18, 0.03)
Childhood height at outcome	-	0.13 (0.07, 0.18)*	0.11 (0.05, 0.18)*
Gestational age at birth, wks	-0.03 (-0.09, 0.03)	-0.12 (-0.30, 0.05)	-0.33 (-0.53, -0.13)*
Birth weight, SD	0.25 (0.15, 0.35)*	-0.17 (-0.47, 0.13)	-0.14 (-0.49, 0.21)
Childhood body mass index, kg/m^2	-	1.98 (1.84, 2.12)*	2.10 (1.93, 2.27)*

[1]Values are regression coefficients (95% Confidence Interval) from univariate regression models and reflect differences in childhood body fat distribution measures per unit change of each covariate and for different categories of each covariate as compared to the reference group. *P-value<0.05.

Table S2. Associations of Covariates with Childhood Blood Pressure (N = 1,125)[1]

	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)
Duration of menstrual cycle, days	-0.01 (-0.35, 0.34)	0.10 (-0.19, 0.39)
Child sex		
Boys	*Reference*	*Reference*
Girls	0.12 (-0.83, 1.07)	0.35 (-0.45, 12.14)
Childhood age at outcome measurement, yr	3.05 (1.89, 4.21)*	
Maternal age, yr	-0.14 (-0.24, -0.03)*	-0.12 (-0.21, -0.03)*
Education		
Primary	2.65 (0.43, 4.87)*	3.25 (1.43, 5.07)*
Secondary	1.25 (0.26, 2.24)*	1.32 (0.49, 2.15)*
Higher	*Reference*	*Reference*
Ethnicity		
Dutch or European	*Reference*	*Reference*
Non – European	1.68 (0.62, 2.73)*	1.51 (0.63, 2.40)*
Parity		
Nulliparous	*Reference*	*Reference*
Multiparous	-0.69 (-1.66, 0.29)	-0.88 (-1.70, -0.06)*
Prepregnancy body mass index, kg/m^2	0.25 (0.12, 0.38)*	0.12 (0.01, 0.23)*
Diastolic blood pressure, mmHg	0.10 (0.05, 0.15)*	0.07 (0.02, 0.11)*
Smoking		
Yes	0.75 (-0.39, 1.88)	0.67 (-0.30, 1.65)
No	*Reference*	*Reference*
Folic acid supplement use		
Yes	*Reference*	*Reference*
No	1.61 (0.51, 2.71)*	0.56 (-0.35, 1.47)
Breastfeeding duration, month)	-0.07 (-0.20, 0.06)	-0.09 (-0.20, 0.03)
Childhood height at outcome measurement, cm	-	-
Gestational age at birth, wks	-0.23 (-0.51, 0.04)	-0.03 (-0.26, 0.20)
Birth weight, SD	-0.35 (-0.82, 0.12)	-0.32 (-0.72, 0.08)
Childhood body mass index, kg/m^2	1.25 (0.98, 1.52)*	1.40 (0.42, 2.39)*

[1]Values are regression coefficients (95% Confidence Interval) from univariate regression models and reflect differences in childhood blood pressure per unit change of each covariate and for different categories of each covariate as compared to the reference group. *P-value<0.05.

Table S3. Associations of Covariates with Childhood Metabolic Outcomes (N = 789)[1]

	Total cholesterol (mmol/l)	Triglycerides (mmol/l)	Insulin (pmol/l)
Duration of menstrual cycle, days	0.01 (-0.03, 0.04)	0.01 (-0.02, 0.03)	0.02 (-0.02, 0.06)
Child sex			
Boys	*Reference*	*Reference*	*Reference*
Girls	0.12 (0.03, 0.21)*	0.08 (0.02, 0.15)*	0.04 (-0.07, 0.15)
Childhood age at outcome measurement, yr	-0.01 (-0.12, 0.09)	-0.02 (-0.10, 0.05)	0.08 (-0.05, 0.21)
Maternal age, yr	0 (-0.01, 0.01)	0 (-0.01, 0.01)	-0.01 (-0.02, 0.01)
Education			
Primary	0 (-0.23, 0.23)	-0.04 (-0.13, 0.21)	0.09 (-0.21, 0.39)
Secondary	0.05 (-0.04, 0.15)	0.01 (-0.06, 0.08)	0 (-0.12, 0.12)
Higher	*Reference*	*Reference*	*Reference*
Ethnicity			
Dutch or European	*Reference*	*Reference*	*Reference*
Non – European	0.12 (0.01, 0.22)*	0 (-0.07, 0.08)	-0.09 (-0.22, 0.04)
Parity			
Nulliparous	*Reference*	*Reference*	*Reference*
Multiparous	-0.02 (-0.11, 0.08)	-0.01 (-0.08, 0.05)	0.05 (-0.06, 0.16)
Prepregnancy body mass index, kg/m^2	0 (-0.01, 0.01)	-0.01 (-0.02, 0)*	0 (-0.01, 0.02)
Diastolic blood pressure, mmHg	0 (-0.01, 0)	0 (-0.01, 0)	0 (-0.01, 0.01)
Smoking			
Yes	-0.03 (-0.17, 0.10)	-0.04 (-0.12, 0.05)	0.11 (-0.03, 0.25)
No	*Reference*	*Reference*	*Reference*
Folic acid supplement use			
Yes	*Reference*	*Reference*	*Reference*
No	0.04 (-0.06, 0.14)	0.04 (-0.03, 0.11)	-0.04 (-0.16, 0.08)
Breastfeeding duration, month)	-0.01 (-0.02, 0)	0 (-0.01, 0.01)	-0.01 (-0.02, 0.01)
Childhood height at outcome measurement, cm	-	-	-
Gestational age at birth, wks	0.01 (-0.2, 0.04)	0 (-0.03, 0.02)	0.01 (-0.03, 0.05)
Birth weight, SD	0 (-0.05, 0.05)	-0.04 (-0.07, 0)	-0.02 (-0.06, 0.02)
Childhood body mass index, kg/m^2	0.03 (0, 0.06)*	0.02 (0, 0.04)	0.08 (0.05, 0.12)**

[1]Values are regression coefficients (95% Confidence Interval) from univariate regression models and reflect differences in childhood blood levels per unit change of each covariate and for different categories of each covariate as compared to the reference group. *P-value<0.05.

Table S4. Fetal and Childhood Growth Characteristics (N = 1,184)[1]

Fetal growth	
First trimester	
Gestational age, median (90% range), wks	12.4 (11.0, 13.9)
First trimester fetal crown to rump length, mean (SD), mm	61 (11)
Second trimester	
Gestational age, median (90% range), wks[2]	20.4 (19.1, 22.2)
Femur length, mean (SD), mm	33 (3)
Estimated fetal weight, mean (SD), g	372 (74)
Third trimester	
Gestational age, median (90% range), wks[2]	30.3 (29.1, 32.1)
Femur length, mean (SD), mm	58 (3)
Estimated fetal weight, mean (SD), g	1630 (241)
Birth	
Gestational age, median (90% range), wks[2]	40.1 (37.0, 42.0)
Male sex, No (%)	575 (48.6)
Birth weight, mean (SD), g	3456 (551)
Childhood growth	
6 months	
Age at follow up, median (90% range), mo	6.2 (5.5, 7.3)
Height, mean (SD), cm	67.7 (2.5)
Weight, mean (SD), kg	7.8 (0.9)
12 months	
Age at follow up, median (90% range), mo	11.1 (10.2, 12.3)
Height, mean (SD), cm	74.4 (2.6)
Weight, mean (SD), kg	9.6 (1.1)
24 months	
Age at follow up, median (90% range), mo	25.0 (23.5, 27.3)
Height, mean (SD), cm	88.3 (3.4)
Weight, mean (SD), kg	12.9 (1.5)
36 months	
Age at follow up, median (90% range), mo	37.1 (35.5, 39.9)
Height, mean (SD), cm	97.3 (3.6)
Weight, mean (SD), kg	15.2 (1.8)
48 months	
Age at follow up, median (90% range), mo	46.0 (44.8, 47.9)
Height, mean (SD), cm	103.2 (4.1)
Weight, mean (SD), kg	16.9 (2.2)
72 months	

Age at follow up, median (90% range), mo	73.2 (68.9, 81.4)
Height, mean (SD), cm	119.0 (5.5)
Weight, mean (SD), kg	22.8 (3.7)

[1]Values represent means (SD), median (90% range) or number of subjects (valid %)

Table S5. Non-Response Analysis for First-Trimester Crown to Rump Length Measurement in Full Cohort (N = 8,880)[1]

	First trimester CRL measurement N = 4,195	No first trimester CRL measurement N = 4,685	p-value[4]
Maternal characteristics			
Age, median (90% range), yr	30.5 (21.1, 37.2)	29.9 (19.8, 38.4)	<0.01
Height, mean (SD), cm	167.8 (7.3)	167.1 (7.5)	<0.01
Pre-pregnancy weight, mean (SD), kg	66.4 (12.6)	66.2 (13.0)	0.64
Pre-pregnancy body mass index, mean (SD), kg/m^2	23.5 (4.2)	23.8 (4.5)	0.02
Gestational age at intake, median (90% range), wks[2]	12.5 (9.9, 14.9)	16.8 (12.6, 24.6)	<0.01
Systolic blood pressure, mean (SD), mmHg	116.2 (12.3)	114.7 (12.3)	<0.01
Diastolic blood pressure, mean (SD), mmHg	68.8 (9.6)	67.4 (9.5)	<0.01
Parity, nulliparous, No. (%)[3]	1743 (42.0)	2152 (46.7)	<0.01
Education, No. (%)[3]			
Primary or secondary school	2080 (53.3)	2604 (62.6)	<0.01
Higher education	1826 (46.7)	1553 (37.4)	
Race / Ethnicity, No. (%)[3]			
Dutch, other European	2563 (64.7)	2153 (50.8)	<0.01
Non-European	1397 (35.3)	2089 (49.2)	
Smoking habits, No. (%)[3]			
None	2715 (74.7)	2983 (76.1)	0.49
Yes	920 (25.3)	935 (23.9)	
Folic acid supplement use, No. (%)[3]			
No use	683 (21.4)	1245 (37.0)	<0.01
First 10 weeks use	1007 (31.5)	1033 (30.7)	
Preconception use	1504 (47.1)	1088 (32.3)	
Fetal characteristics			
Second trimester estimated fetal weight, mean (SD),	369 (78)	396 (110)	<0.01
Third trimester estimated fetal weight, mean (SD), g	1607 (245)	1623 (285)	<0.01
Birth characteristics			
Males, No. (%)[3]	2072 (50.4)	2295 (50.6)	0.81
Gestational age, median (90% range), wks[2]	40.1 (36.9, 42.0)	40.0 (36.4, 42.1)	<0.01
Birth weight, mean (SD), g	3421 (566)	3398 (562)	0.08

[1] Values are means (standard deviation) or percentages. [2]Median (90% range) [3]Values are observed numbers and valid percentages. [4]Differences in subject characteristics between the groups were evaluated using one-way ANOVA tests for continuous variables and chi-square tests for proportions.

Table S6. Non-Response Analysis for First-Trimester Crown to Rump Length With and Without Information About Last Menstrual Period and Singleton Live-born Child (N = 4,195)[1]

	Known last menstrual period and singleton live-born child	Unknown last menstrual period and singleton live-born child	p-value[4]
Maternal characteristics			
Age, median (90% range), yr	31.4 (21.9, 37.9)	29.8 (20.6, 37.0)	<0.01
Height, mean (SD), cm	168.7 (7.0)	167.2 (7.5)	<0.01
Pre-pregnancy weight, mean (SD), kg	66.9 (11.8)	66.2 (13.1)	0.22
Pre-pregnancy body mass index, mean (SD), kg/m^{2}	23.4 (3.8)	23.6 (4.5)	0.07
Gestational age at intake, median (90% range), wks[2]	12.4 (10.6, 13.9)	12.5 (9.6,15.1)	0.01
Systolic blood pressure, mean (SD), mmHg	116.8 (12.5)	115.8 (12.2)	<0.01
Diastolic blood pressure, mean (SD), mmHg	69.1 (9.4)	68.7 (9.8)	0.16
Parity, nulliparous, No. (%)[3]	956 (59.4)	1451 (57.1)	0.15
Education, No. (%)[3]			
Primary or secondary school	703 (45.4)	1377 (58.4)	<0.01
Higher education	845 (54.6)	981 (41.6)	
Race / Ethnicity, No. (%)[3]			
Dutch, other European	1106 (70.7)	1457 (60.8)	<0.01
Non-European	458 (29.3)	939 (39.2)	
Smoking habits, No. (%)[3]			
None	1110 (76.8)	1605 (73.3)	0.13
Yes	336 (23.2)	584 (26.7)	
Folic acid supplement use, No. (%)[3]			
No use	192 (14.7)	491 (26.0)	<0.01
First 10 weeks use	415 (31.8)	592 (31.3)	
Preconception use	696 (53.4)	808 (42.7)	
Fetal characteristics			
Second trimester estimated fetal weight, mean (SD),	371 (74)	368 (81)	0.33
Third trimester estimated fetal weight, mean (SD), g	1622 (240)	1598(247)	<0.01
Birth characteristics			
Males, No. (%)[3]	802 (49.5)	1270 (50.9)	0.39
Gestational age, median (90% range), wks[2]	39.9 (37.1, 42.0)	39.8 (36.7, 42.0)	0.04
Birth weight, mean (SD), g	3453 (565)	3402 (564)	<0.01

[1] Values are means (standard deviation) or percentages. [2] Median (90% range) [3] Values are observed numbers and valid percentages. [4] Differences in subject characteristics between the groups were evaluated using one-way ANOVA tests for continuous variables and chi-square tests for proportions.

Table S7. Non-Response Analysis for Loss to Follow-Up at the Age of 6 Years (N = 1,619)[1]

	Follow-up at 6 years N = 1,184	Loss to follow-up at 6 years N = 435	p-value[4]
Maternal characteristics			
Age, median (90% range), yr	31.3 (22.7, 38.1)	29.7 (5.0)	<0.01
Height, mean (SD), cm	168.8 (7.0)	168.5 (7.1)	0.43
Pre-pregnancy weight, mean (SD), kg	66.9 (11.8)	66.0 (11.9)	0.22
Pre-pregnancy body mass index, mean (SD), kg/m^2	23.4 (3.9)	23.2 (3.7)	0.29
Gestational age at intake, median (90% range), wks[2]	12.4 (10.5, 13.9)	12.4 (10.9, 13.9)	0.84
Systolic blood pressure, mean (SD), mmHg	116.7 (12.4)	116.8 (12.8)	0.87
Diastolic blood pressure, mean (SD), mmHg	69.1 (9.4)	69.1 (9.6)	0.93
Parity, nulliparous, No. (%)[3]	717 (60.8)	237 (55.2)	0.04
Education, No. (%)[3]			
Primary or secondary school	507 (43.9)	198 (49.5)	0.02
Higher education	648 (56.1)	202 (50.5)	
Race / Ethnicity, No. (%)[3]			
Dutch, other European	855 (72.8)	258 (63.1)	<0.01
Non-European	320 (27.2)	151 (36.9)	
Smoking habits, No. (%)[3]			
None	820 (77.4)	290 (75.1)	0.38
Yes	240 (22.6)	96 (24.9)	
Folic acid supplement use, No. (%)[3]			
No use	119 (12.5)	73 (20.6)	<0.01
First 10 weeks use	294 (31.0)	121 (34.2)	
Preconception use	536 (56.5)	160 (45.2)	
Fetal characteristics			
First trimester crown to rump length, mean (SD), mm	61 (11)	61 (11)	0.44
Second trimester estimated fetal weight, mean (SD), g	372 (74)	368 (73)	0.34
Third trimester estimated fetal weight, mean (SD), g	1630 (241)	1599 (238)	0.02
Birth and infant characteristics			
Males, No. (%)[3]	575 (48.6)	226 (52.1)	0.21
Gestational age, median (90% range), wks[2]	40.1 (37.0, 42.0)	40.3 (37.1, 42.1)	0.89
Birth weight, mean (SD), g	3456 (551)	3444 (602)	0.70
Ever breastfeeding, No (%|)			
No	80 (7.6)	36 (12.6)	0.01
Yes	966 (92.4)	250 (87.4)	
Breastfeeding duration, mean (SD), mo	5.3 (3.8)	4.6 (3.8)	0.02

[1] Values are means (standard deviation) or percentages. [2]Median (90% range) [3]Values are observed numbers and valid percentages. [4]Differences in subject characteristics between the groups were evaluated using one-way ANOVA tests for continuous variables and chi-square tests for proportions.

Table S8. Fetal and Childhood Length and Weight Growth in Children with Clustering of Cardiovascular Risk Factors Adjusted for Confounders (N = 745)[1]

	SDS - difference (95% Confidence Interval) in Growth Characteristics in Children with Clustering of Cardiovascular Risk Factors	
	Length (SDS)	**Weight (SDS)**
Gestational age		
20 weeks	-0.11 (-0.32, 0.10)	-0.15 (-0.36, 0.06)
30 weeks	-0.10 (-0.31, 0.12)	**-0.24 (-0.44, -0.03)**
40 weeks	-0.09 (-0.39, 0.22)	**-0.32 (-0.59, -0.05)**
Childhood age		
6 months	0.02 (-0.18, 0.23)	0.24 (-0.04, 0.51)
12 months	0.07 (-0.14, 0.27)	**0.31 (0.03, 0.58)**
24 months	0.16 (-0.04, 0.36)	**0.45 (0.18, 0.72)**
36 months	**0.26 (0.05, 0.45)**	**0.59 (0.32, 0.86)**
48 months	**0.35 (0.15, 0.55)**	**0.73 (0.45, 1.00)**
72 months	**0.54 (0.32, 0.75)**	**1.09 (0.71, 1.31)**

[1]Values are based on repeated linear regression models. Regression coefficients (95% confidence interval) reflect the difference in length and weight standard deviation score for children with clustering of cardiovascular risk factors, as compared to children without this clustering. Models are adjusted for duration of last menstrual cycle, child sex and age at outcome measurements, maternal age, educational level, ethnicity, parity, pre-pregnancy body mass index, diastolic blood pressure, smoking during pregnancy and folic acid supplement use, breastfeeding duration. Length and weight growth characteristics used in the models: Fetal period: first trimester: crown to rump length as both length and weight measure (starting point); second and third trimester: femur length and estimated fetal weight; At birth: birth length and birth weight; During childhood: length and weight. Clustering of cardiovascular and metabolic risk factors, was defined as having 3 or more following components: android fat mass % =>75th percentile; systolic or diastolic blood pressure =>75th percentile; HDL-cholesterol <=25th percentile or triglycerides => 75th percentile; and insulin level =>75th percentile [22].