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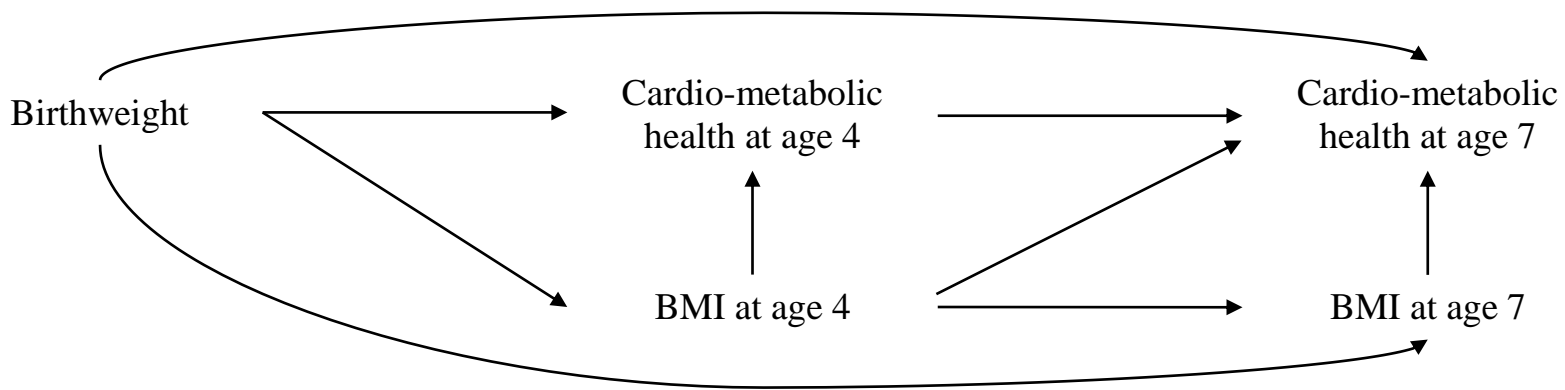
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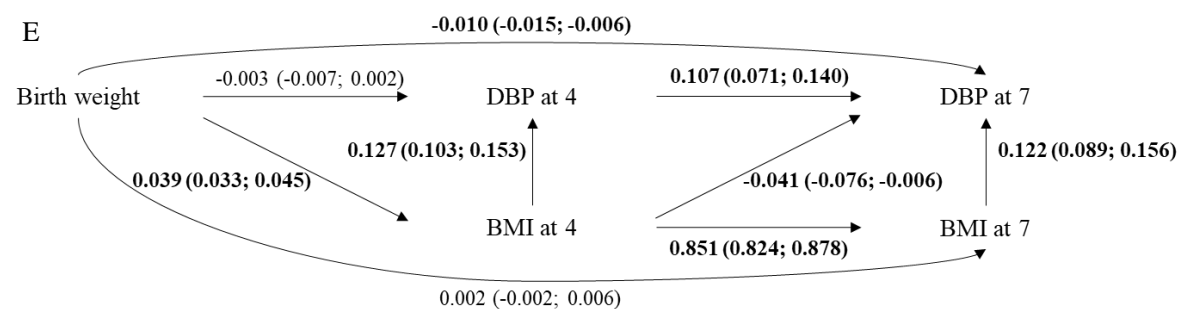
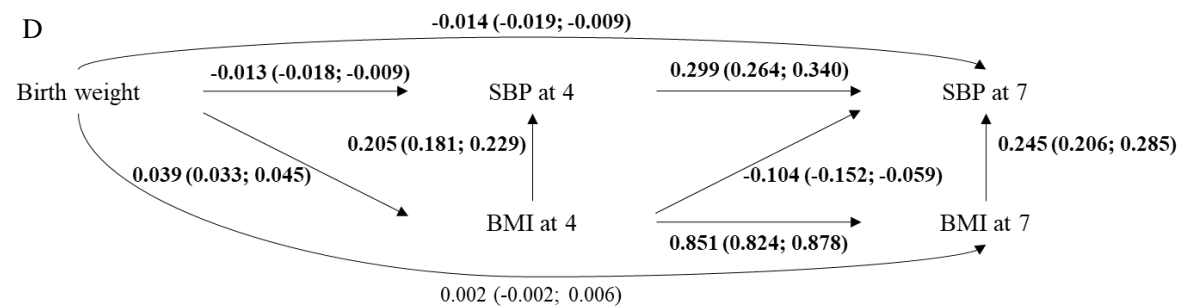
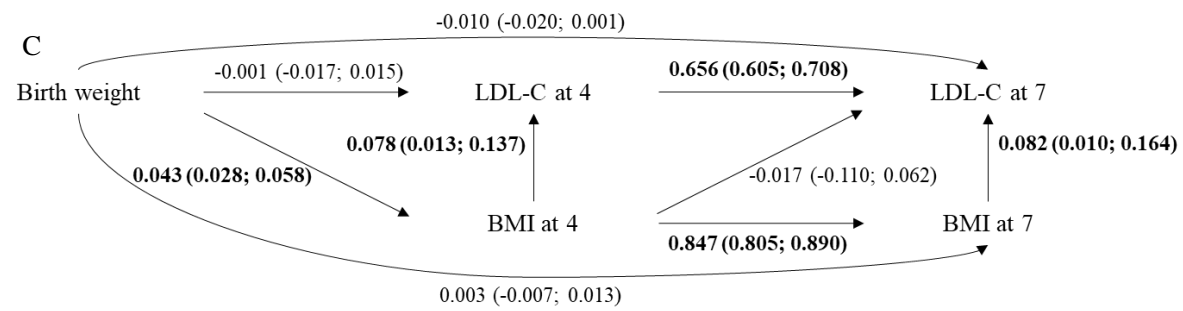
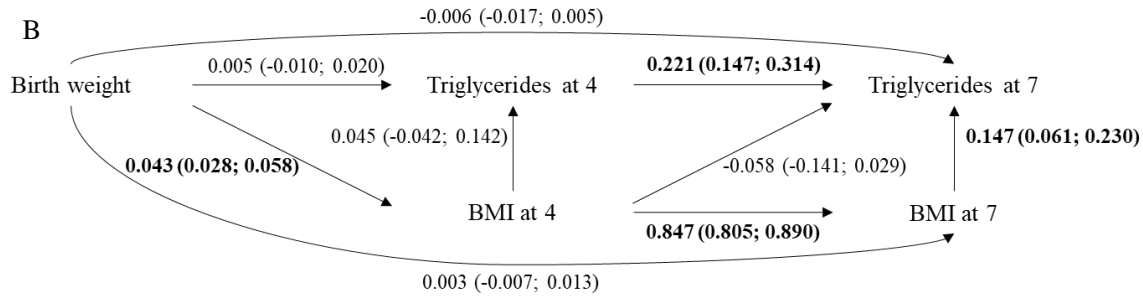
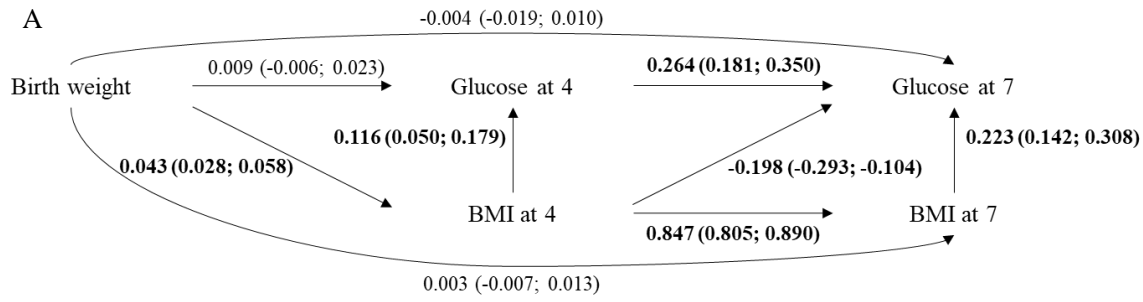
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**Fig. 1** Hypothesized mechanism linking birthweight with cardio-metabolic health at ages 4 and 7: an overall effect with direct and indirect (BMI-mediated) paths.



**Fig. 2** Path analysis of the associations of birthweight with cardio-metabolic traits z-scores at ages 4 and 7 (A – Glucose; B – Triglycerides; C - LDL-cholesterol; D – Systolic blood pressure; E – Diastolic blood pressure)

Supplementary table 1. Comparison between eligible children included and not included regarding maternal, pregnancy, delivery and newborn characteristics.

	Not included n=3470	Included <sup>a</sup> n=4881	p
<b>Maternal characteristics</b>			
Education (years), mean (SD)	9.5 (4.0)	11.1 (4.3)	<0.001
Age at delivery (years), mean (SD)	27.8 (5.9)	29.8 (5.3)	<0.001
Pre-pregnancy BMI (kg/m <sup>2</sup> ), mean (SD)	23.8 (4.4)	23.90 (4.2)	0.363
<b>Pregnancy and delivery characteristics</b>			
Tobacco smoke during 3 <sup>rd</sup> trimester, n (%)	624 (18.3)	602 (12.5)	<0.001
Caesarean delivery, n (%)	1111 (32.6)	1788 (37.2)	<0.001
<b>Newborn characteristics</b>			
Gestational age (weeks), mean (SD)	38.6 (1.8)	38.7 (1.7)	0.118
Sex, n (%)			
	Male	1779 (51.3)	2487 (51.0)
	Female	1691 (48.7)	2394 (49.0)
Birthweight (g), mean (SD)	3178 (509)	3191 (487)	0.223

Abbreviations: BMI, body mass index; SD, standard deviation.

<sup>a</sup> Considered included if participant was included in the blood pressure analysis (n=4877) and/or in the glucose, LDL-cholesterol and triglycerides analysis (n=1031).

Supplementary table 2. Distribution of relevant characteristics by birth weight category.

	n	Birth Weight			p
		< 2500g	2500g - 4000g	≥ 4000g	
<b>Body mass index (z-score), mean (SD)</b>	4881				
4 years of age		0.21 (1.15)	0.62 (1.07)	1.00 (1.02)	<0.001
7 years of age		0.38 (1.28)	0.73 (1.18)	1.09 (1.14)	<0.001
<b>Cardiometabolic traits (z-score), mean (SD)</b>					
<b>Glucose</b>	1031				
4 years of age		-0.02 (1.24)	-0.04 (0.97)	0.36 (0.72)	0.070
7 years of age		-0.05 (1.24)	0.02 (0.94)	0.10 (0.98)	0.786
<b>LDL-cholesterol</b>	1031				
4 years of age		0.11 (1.11)	-0.03 (0.99)	-0.05 (1.04)	0.627
7 years of age		0.21 (0.97)	-0.07 (0.98)	-0.22 (0.81)	0.102
<b>Triglycerides</b>	1031				
4 years of age		0.00 (0.84)	0.00 (1.04)	-0.16 (0.83)	0.664
7 years of age		-0.02 (0.70)	-0.07 (0.90)	-0.19 (0.60)	0.682
<b>Systolic blood pressure</b>	4877				
4 years of age		0.42 (0.70)	0.42 (0.74)	0.25 (0.67)	0.025
7 years of age		0.79 (0.81)	0.69 (0.81)	0.59 (0.71)	0.023
<b>Diastolic blood pressure</b>	4877				
4 years of age		0.34 (0.71)	0.45 (0.70)	0.47 (0.69)	0.039
7 years of age		1.10 (0.69)	1.03 (0.68)	0.93 (0.62)	0.019
<b>Maternal characteristics</b>					
Education (years), mean (SD)	4855	10.7 (4.4)	11.1 (4.3)	10.9 (4.2)	0.219
Age at delivery (years), mean (SD)	4881	29.4 (5.5)	29.8 (5.3)	30.5 (4.8)	0.079
Pre-pregnancy BMI (kg/m <sup>2</sup> ), mean (SD)	4487	23.1 (4.0)	23.9 (4.2)	25.4 (5.0)	<0.001
Primipara, n (%)	4881	232 (69.5)	2565 (58.7)	79 (44.1)	<0.001
<b>Pregnancy and delivery characteristics</b>					
Gestational diabetes, n (%)	4854	28 (8.5)	269 (6.2)	18 (10.1)	0.036
Gestational hypertension, n (%)	4854	15 (4.5)	93 (2.1)	3 (1.7)	0.016
Pre-eclampsia / Eclampsia, n (%)	4854	33 (10.0)	30 (0.7)	0 (0.0)	<0.001

Tobacco smoke during 3 <sup>rd</sup> trimester	4814	58 (17.7)	534 (12.4)	10 (5.6)	<0.001
Gestational weight gain, mean (SD)	4569	11.5 (5.7)	13.6 (5.7)	15.5 (5.9)	<0.001
Caesarean delivery	4811	159 (48.8)	1527 (35.4)	102 (58.0)	<0.001
<b>Newborn characteristics</b>					
Gestational age (weeks), mean (SD)	4877	35.3 (3.0)	38.9 (1.2)	39.6 (1.0)	<0.001
Sex, n (%)	4881				
Male		164 (49.1)	2206 (50.5)	117 (65.4)	
Female		170 (50.9)	2162 (49.5)	62 (34.6)	<0.001

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Table 1. Characteristics of the study sample at 4 and 7 years follow-up.

	n	4 years follow-up	7 years follow-up
Body mass index (kg/m <sup>2</sup> ), mean (SD)	4881	16.3 (1.8)	17.0 (2.5)
Glucose (mg/dL), mean (SD)	1031	78.7 (8.1)	83.2 (7.1)
LDL-cholesterol (mg/dL), mean (SD)	1031	103.2 (24.0)	98.9 (22.8)
Triglycerides (mg/dL), median (IQR)	1031	61.0 (30.0)	58.0 (32.0)
Systolic blood pressure (mmHg), mean (SD)	4877	98.1 (8.3)	105.0 (9.0)
Diastolic blood pressure (mmHg), mean (SD)	4877	57.7 (8.1)	69.7 (7.8)

1 Abbreviations: BMI, body mass index; SD, standard deviation.



1 Table 2. Unadjusted Pearson correlations coefficients of birthweight and BMI and cardio-metabolic traits z-scores in childhood.

	Birthweight	BMI 4y	Glucose 4y	TG 4y	LDL-C 4y	SBP 4y	DBP 4y	BMI 7y	Glucose 7y	TG 7y	LDL-C 7y	SBP 7y	DBP 7y
Birthweight	1	0.184**	0.057	0.012	0.003	-0.041*	0.053**	0.149**	0.003	0.001	-0.041	-0.062**	-0.072**
BMI 4y	-	1	0.128**	0.054	0.070*	0.293**	0.208**	<b>0.801**</b>	0.026	0.110**	0.089**	0.194**	0.107**
Glucose 4y	-	-	1	0.099**	-0.051	0.061*	0.046	0.098**	<b>0.248**</b>	-0.002	-0.008	0.024	0.017
TG 4y	-	-	-	1	0.018	0.031	0.043	0.003	-0.071*	<b>0.235**</b>	0.093**	0.019	0.036
LDL-C 4y	-	-	-	-	1	0.030	0.017	0.009	-0.027	0.052	<b>0.667**</b>	-0.010	0.039
SBP 4y	-	-	-	-	-	1	0.357**	0.249**	0.033	-0.001	0.009	<b>0.310**</b>	0.187**
DBP 4y	-	-	-	-	-	-	1	0.185**	0.027	-0.025	0.031	0.146**	<b>0.143**</b>
BMI 7y	-	-	-	-	-	-	-	1	0.114**	0.122**	0.062*	0.286**	0.167**
Glucose 7y	-	-	-	-	-	-	-	-	1	0.061	0.065*	0.120**	0.132**
TG 7y	-	-	-	-	-	-	-	-	-	1	0.023	0.074*	0.095**
LDL-C 7y	-	-	-	-	-	-	-	-	-	-	1	0.062*	-0.008
SBP 7y	-	-	-	-	-	-	-	-	-	-	-	1	0.541**
DBP 7y	-	-	-	-	-	-	-	-	-	-	-	-	1

Abbreviations: BMI, body mass index; birthweight, birthweight; DBP, diastolic blood pressure; LDL-C, low density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides.

\*p<0.05

\*\*p<0.01

Table 3. Estimated total, direct, and indirect (BMI-mediated) effect of birthweight (per 100g increase) on cardio-metabolic traits at 4 and 7 years of age.

	<b>Total</b> β (95% CI)	<b>Direct</b> β (95% CI)	<b>Indirect (BMI-mediated)</b> β (95% CI)
Model 1. Cardio-metabolic traits at age 4			
<b>Glucose z-score</b>	0.014 (-0.001; 0.029)	0.009 (-0.006; 0.023)	0.005 (0.002; 0.009)*
<b>Triglycerides z-score</b>	0.007 (-0.007; 0.020)	0.005 (-0.010; 0.020)	0.002 (-0.002; 0.006)
<b>LDL-cholesterol z-score</b>	0.002 (-0.015; 0.018)	-0.001 (-0.017; 0.015)	0.003 (0.001; 0.007)*
<b>Systolic blood pressure z-score</b>	-0.005 (-0.010; -0.001)*	-0.013 (-0.018; -0.009)*	0.008 (0.007; 0.010)*
<b>Diastolic blood pressure z-score</b>	0.002 (-0.002; 0.007)	-0.003 (-0.007; 0.002)	0.005 (0.004; 0.006)*
Model 2. Cardio-metabolic traits at age 7			
<b>Glucose z-score</b>	-0.001 (-0.014; 0.014)	-0.004 (-0.019; 0.010)	0.002 (-0.002; 0.005)
<b>Triglycerides z-score</b>	-0.001 (-0.013; 0.010)	-0.006 (-0.017; 0.005)	0.004 (0.001; 0.007)*
<b>LDL-cholesterol z-score</b>	-0.006 (-0.021; 0.008)	-0.010 (-0.020; 0.001)	0.005 (0.002; 0.008)*
<b>Systolic blood pressure z-score</b>	-0.011 (-0.017; -0.006)*	-0.014 (-0.019; -0.009)*	0.007 (0.005; 0.009)*
<b>Diastolic blood pressure z-score</b>	-0.008 (-0.012; -0.004)*	-0.010 (-0.015; -0.006)*	0.003 (0.002; 0.005)*

Abbreviations: LDL, low density lipoprotein; β, regression coefficient; CI, confidence interval.

Models adjusted for maternal pre-pregnancy BMI and tobacco smoke during 3<sup>rd</sup> pregnancy trimester.

\*p<0.05