

Supplementary information

Fetal tobacco and cannabis exposure, body fat and cardio-metabolic health in childhood

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Table S1. Descriptive statistics according to tobacco use

	No n =3334	First trimester only n = 357	Continued smoking in pregnancy n = 570
Maternal characteristic			
Age, years, mean (SD)	31.1 (4.7)	30.9 (4.6)	29.9 (5.6)**
Ethnicity			
Dutch (%)	57.6	61.3*	51.2**
Non-Dutch Non-Western (%)	30.4	24.1	38.1
Non-Dutch Western (%)	12.0	14.6	10.7
Educational level			
None/Primary (%)	7.1	3.6*	13.5**
Secondary (%)	38.9	44.8	59.8
Higher (%)	54.0	51.5	26.7
Pre-pregnancy BMI, kg/m ² , median (95% range)	22.7 (18.2-34.7)	22.2 (18.0-31.3)	22.9 (18.0-35.9)
Psychopathology score, median (95% range)	0.14 (0-1.15)	0.17 (0-1.67)*	0.25 (0-1.32)**
Maternal alcohol use			
Never drank in pregnancy (%)	46.6	21.3**	42.8
Drank until pregnancy was known (%)	12.8	25.5	13.2
Continued drinking (%)	40.6	53.2	44.0
Paternal characteristics			
Age, years, mean (SD)	33.8 (5.7)	30.8 (6.3)**	31.8 (5.8)**
Ethnicity			
Dutch (%)	59.8	66.7**	48.6**
Non-Dutch Non-Western (%)	30.9	20.7	40.0
Non-Dutch Western (%)	9.3	12.6	11.4
Cannabis use, yes (%)	4.5	10.7**	14.4**
Tobacco use, yes (%)	34.3	63.2**	72.8**
Alcohol use, yes (%)	77.6	89.6**	76.0
BMI, kg/m ² , mean (SD)	25.1 (19.7-32.7)	24.7 (19.9-32.4)*	25.5 (19.5-33.2)*
Child characteristics			
Female sex, yes (%)	51.2	54.3	48.2
Age, years, median (95% range)	9.7 (9.4-10.6)	9.7 (9.4-10.6)	9.7 (9.4-11.0)*
BMI, kg/m ² , median (95% range)	16.9 (14-24.6)	16.7 (14.1-23.5)	17.5 (14.2-26.7)**
Body composition			
Total fat mass, kg, median (95% range)	8.4 (4.5-21.6)	8.3 (4.4-20)	9.3 (4.8-24.9)**
Android/gynoid ratio, median (95% range)	0.24 (0.15-0.48)	0.24 (0.15-0.48)	0.27 (0.16-0.52)**
Fat-free mass, kg, median (95% range)	25.3 (19.0-33.6)	25.4 (19.6-34.0)	25.2 (19.2-35.6)
Blood pressure, mmHg			
Systolic, mean (SD)	103.0 (8.0)	102.4 (7.3)	104.3 (8.4)**
Diastolic, mean (SD)	58.5 (6.4)	58.2 (6.2)	59.3 (6.8)**
Lipid concentrations			
Total-cholesterol, mmol/L, mean (SD)	4.3 (0.7)	4.3 (0.7)	4.3 (0.6)
HDL-cholesterol, mmol/L, mean (SD)	1.48 (0.34)	1.50 (0.34)	1.44 (0.35)
Triglycerides, mmol/L, median (95% range)	0.98 (0.42-2.49)	1.01 (0.43-2.94)	1.03 (0.45-3.04)**
Insulin, pmol/L, median (95% range)	174.0 (35-623.7)	163.5 (38.8-541.4)	179.6 (39.2-744.3)
Glucose, mmol/L, mean (SD)	5.2 (0.9)	5.2 (0.9)	5.2 (0.9)
Overweight, yes (%)	17.5	16.9	26.0**
Cardio-metabolic clustering risk, yes (%)	9.1	7.6	13.0**

Note: Groups are categorized on maternal only tobacco use during pregnancy, maternal cannabis users were excluded. Values are presented as means (SD), medians (95% range), or percentages. There were no missing data on these variables as they were imputed using multiple imputation methods, to except parental cannabis and tobacco use, and childhood cardio-metabolic profile. p-values are resultant from t-Test or Man Whitney-U test for continuous variables and chi-squared for categorical variables between each group with non-exposure group (reference). p-value < 0.05 (*), p-value < 0.01 (**).

Abbreviations: SD: standard deviation, BMI: body mass index, HDL-cholesterol: high-density lipoprotein cholesterol.

Table S2. Descriptive statistics according to cannabis and tobacco use

	No n =3982	Maternal cannabis use during pregnancy n = 118	Maternal cannabis use before pregnancy n = 122	Maternal continued tobacco use in pregnancy n = 570
Maternal characteristic				
Age, years, mean (SD)	31.0 (4.7)	27.8 (5.9)**	29.5 (5.7)**	29.9 (5.6)**
Ethnicity				
Dutch (%)	57.5	58.5	64.8*	51.2**
Non-Dutch Non-Western (%)	30.4	32.2	19.7	38.1
Non-Dutch Western (%)	12.1	9.3	15.6	10.7
Educational level				
None/Primary (%)	7.1	11.0**	8.2*	13.5**
Secondary (%)	39.6	64.4	51.6	59.8
Higher (%)	53.3	24.6	40.2	26.7
Pre-pregnancy BMI, kg/m ² , median (95% range)	22.6 (18.1-34.6)	21.7 (16.9-36.2)**	22.0 (18.1-35.1)**	22.9 (18.0-35.9)
Psychopathology score, median (95% range)	0.14 (0-1.18)	0.27 (0-1.68)**	0.22 (0-0.96)**	0.25 (0-1.67)**
Maternal alcohol use				
Never drank in pregnancy (%)	44.3	30.5*	32.0**	42.8
Until pregnancy was known (%)	14.0	17.8	9.8	13.2
Continued drinking (%)	41.7	51.7	58.2	44.0
Maternal tobacco use				
Never smoked in pregnancy (%)	90.3	12.8**	53.7**	-
Until pregnancy was known (%)	9.7	15.4	18.2	-
Continued smoking (%)	-	71.8	28.1	100
Paternal characteristics				
Age, years, mean (SD)	33.8 (5.7)	30.8 (6.3)**	31.8 (5.8)**	32.1 (6.3)**
Ethnicity				
Dutch (%)	59.9	44.9**	54.9	48.6**
Non-Dutch Non-Western (%)	30.5	44.1	30.3	40.0
Non-Dutch Western (%)	9.6	11.0	14.8	11.4
Cannabis use, yes (%)	5.1	81.1**	64.0**	14.4**
Tobacco use, yes (%)	36.9	82.5**	63.9**	72.8**
Alcohol use, yes (%)	78.8	90.7**	91.8**	76.0
BMI, kg/m ² , mean (SD)	25.1 (19.7-32.7)	24 (18.6-33.8)**	24 (19.4-31.6)**	25.5 (19.5-33.2)*
Child characteristics				
Female sex, yes (%)	51.1	42.4	49.2	48.2
Age, years, median (95% range)	9.7 (9.3-10.7)	9.8 (9.4-11.5)	9.7 (9.4-10.4)	9.7 (9.4-11)
BMI, kg/m ² , median (95% range)	16.9 (14-24.5)	17.6 (14.3-24.1)**	17.0 (14.1-24.7)	17.5 (14.2-26.7)**
Body composition				
Total fat mass, kg, median (range)	8.5 (4.5-21.6)	9.1 (5-22.5)	8.3 (4.6-20.1)	9.3 (4.8-24.9)**
Android/gynoid ratio, median (range)	0.24 (0.15-0.48)	0.26 (0.17-0.51)*	0.24 (0.15-0.46)	0.27 (0.16-0.52)**
Fat free-mass, kg, median (range)	25.3 (19-33.6)	26.2 (20.7-33.9)*	24.9 (20.1-34.1)	25.2 (19.2-35.6)
Blood pressure, mmHg				
Systolic, mean (SD)	103 (7.9)	104.5 (8.0)*	102.7 (7.5)	104.3 (8.4)**
Diastolic, mean (SD)	58.5 (6.4)	58.8 (6.9)	58.7 (6.5)	59.3 (6.8)**
Lipid concentrations, mmol/L				
Total-cholesterol, mean (SD)	4.3 (0.7)	4.3 (0.8)	4.2 (0.7)	4.3 (0.6)
HDL-cholesterol, mean (SD)	1.48 (0.34)	1.44 (0.35)	1.52 (0.34)	1.44 (0.35)*
Triglycerides, median (95% range)	0.97 (0.42-2.55)	0.97 (0.4-2.8)	0.89 (0.37-1.76)	1.03 (0.45-3.04)**
Insulin, pmol/L, median (95% range)	175.5 (34.9-618.4)	183.8 (30.1-509.5)	180.9 (42.8-672.3)	179.6 (39.2-744.3)
Glucose, mmol/L, mean (SD)	5.2 (0.9)	5.2 (0.9)	5.2 (1.0)	5.2 (0.9)
Overweight, yes (%)	17.6	22.0	18.0	26.0**
Cardio-metabolic clustering, yes (%)	9.0	12.7	4.9	13.0**

Note: Groups are categorized on maternal cannabis and tobacco use during pregnancy in non-overlapping groups. Values are presented as means (SD), medians (95% range), or percentages. There were no missing data on these variables as they were imputed using multiple imputation methods, to except parental cannabis and tobacco use, and childhood cardio-metabolic profile. p-values are resultant from t-Test or Man Whitney-U test for continuous variables and chi-squared for categorical variables between each group with non-exposure group (reference). p-value < 0.05 (*), p-value < 0.01 (**).
Abbreviations: SD: standard deviation, BMI: body mass index, HDL-cholesterol: high-density lipoprotein cholesterol.

Table S3. Non-response analysis

	Follow up at 10 years n = 4792	No follow up at 10 years n = 3324	p-value*
Maternal characteristic			
Age, years, mean (SD)	30.8 (4.9)	28.2 (5.4)	<0.01
Missing (%)	-	0.06	
Ethnicity			<0.01
Dutch (%)	56.7	35.0	
Non-Dutch Non-Western (%)	30.5	49.0	
Non-Dutch Western (%)	11.9	10.4	
Missing (%)	0.9	5.6	
Educational level			<0.01
None/Primary (%)	7.3	15.9	
Secondary (%)	41.3	48.1	
Higher (%)	48.3	26.9	
Missing (%)	3.2	9.1	
Pre-pregnancy BMI, kg/m ² , median (95% range)	22.6 (18.1-34.5)	22.7 (17.7-35.5)	0.06
Missing (%)	14.0	17.9	
Psychopathology score, median (95% range)	0.15 (0-1.27)	0.21 (0-1.73)	<0.01
Missing (%)	15.9	4.0	
Maternal alcohol use			<0.01
Never drank (%)	39.3	52.6	
Drank until pregnancy was known (%)	12.7	11.0	
Continued drinking (%)	39.2	24.4	
Missing (%)	8.8	12.0	
Maternal tobacco use			<0.01
None (%)	71.2	62.2	
Smoked until pregnancy was known (%)	8.3	7.5	
Continued in pregnancy (%)	14.4	21.6	
Missing (%)	6.1	8.7	
Maternal cannabis use			<0.01
None (%)	93.6	90.7	
Before pregnancy (%)	2.5	3.2	
During pregnancy (%)	2.5	3.9	
Missing (%)	1.4	2.1	
Paternal characteristics			
Age, years, mean(SD)	33.5 (5.7)	31.7 (6.4)	<0.01
Missing(%)	10.2	23.6	
Ethnicity			<0.01
Dutch (%)	57.0	32.6	
Non-Dutch Non-Western (%)	29.0	42.8	
Non-Dutch Western (%)	9.5	7.3	
Missing (%)	4.5	17.2	
Paternal tobacco use			<0.01
No exposure (%)	53.0	45.1	
Exposure (%)	39.7	43.7	
Missing (%)	7.3	11.2	
Paternal cannabis use			<0.01
No exposure (%)	82.0	75.6	
Exposure (%)	8.7	10.8	
Missing (%)	9.3	13.6	
Paternal alcohol use			<0.01
No exposure (%)	19.0	30.1	
Exposure (%)	73.3	57.9	
Missing (%)	7.7	12.1	
BMI, kg/m ² , median (95% range)	24.9 (19.6-32.8)	25.1 (19.2-34.0)	0.28

Missing (%)	20.9	36.5	
Child characteristics			
Female sex (%)	50.5	47.9	0.02
Missing (%)	-	0.1	
Age, years, median (95% range)	9.7 (9.4-10.7)	9.8 (9.5-12.6)	<0.01
Missing (%)	-	96.0	

Note: Values are means and standard deviation (SD), medians (90% range), or percentages.

*Differences in subjects' characteristics between the groups were evaluated using T-test for the normally distributed continuous variables, Man Whitney-U test for the not-normally distributed continuous variables, and chi-square tests for proportions.

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

Figure S1. Directed acyclic graph of the study

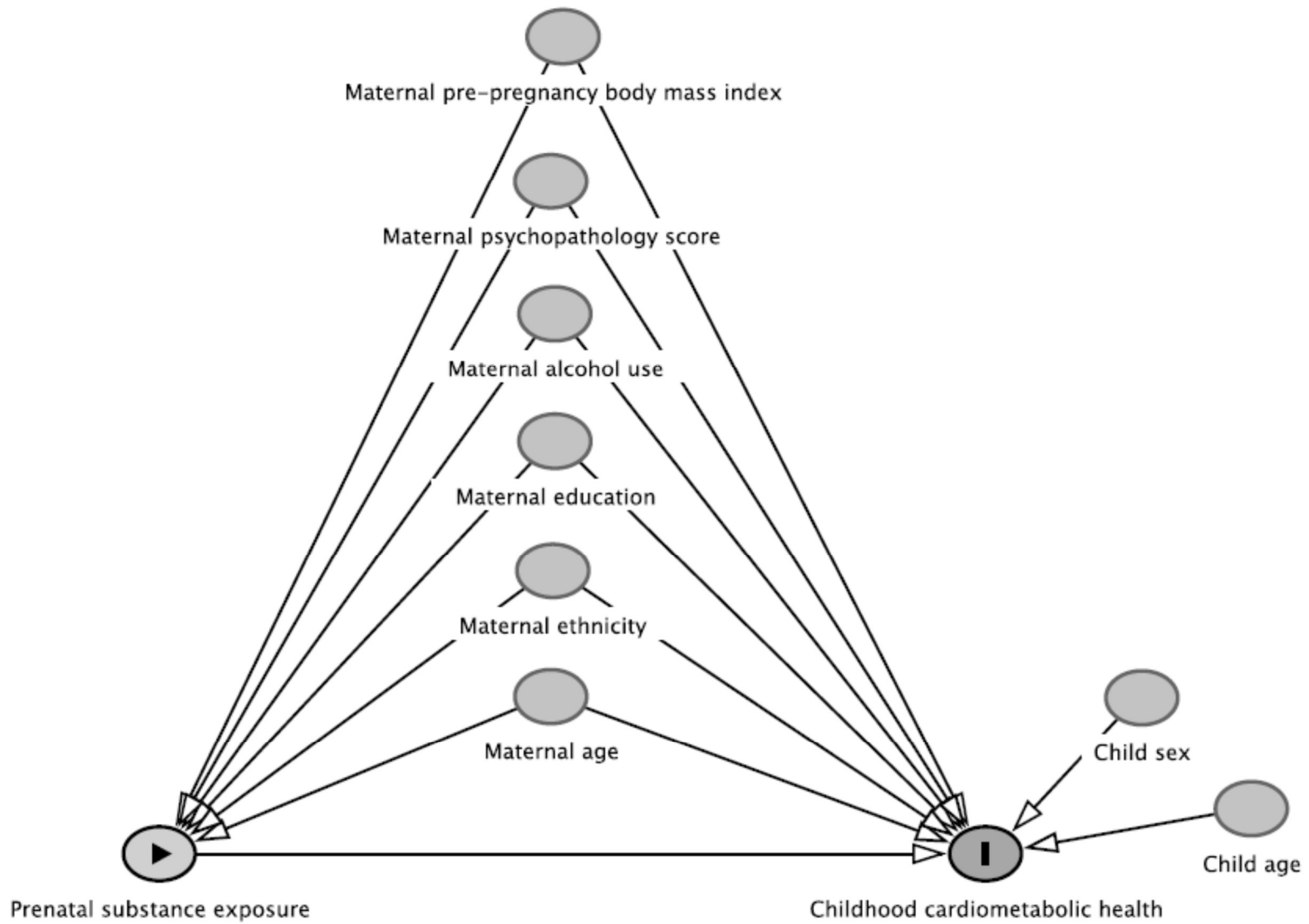


Table S4. Associations of maternal and paternal tobacco and cannabis use during pregnancy with childhood body fat outcomes at age 10 years stratified for child sex

	Body mass index (SDS) ^a		Android-gynoid ratio (SDS) ^a		Fat mass index (SDS) ^a		Fat-free mass index (SDS) ^a		Overweight ^b	
	Boys (n = 2078)	Girls (n = 2174)	Boys (n = 2056)	Girls (n = 2152)	Boys (n = 2049)	Girls (n = 2150)	Boys (n = 2049)	Girls (n = 2150)	Boys (n = 2078)	Girls (n = 2174)
Tobacco only	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	OR (95% CI)	OR (95% CI)
Maternal use										
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
First trimester only	0.04 (-0.12, 0.20)	-0.01 (-0.15, 0.14)	0.06 (-0.09, 0.21)	0.14 (-0.01, 0.28)	-0.02 (-0.17, 0.13)	-0.02 (-0.15, 0.10)	-0.01 (-0.15, 0.13)	0.05 (-0.09, 0.19)	0.86 (0.49, 1.48)	1.39 (0.92, 2.08)
Continued smoking	0.11 (-0.02, 0.23)	0.23 (0.10, 0.35)**	0.15 (0.03, 0.26)**	0.29 (0.16, 0.41)**	0.11 (-0.01, 0.23)	0.30 (0.19, 0.41)**	0.07 (-0.04, 0.18)	0.10 (-0.03, 0.22)	1.35 (0.96, 1.91)	1.38 (0.99, 1.91)
< 5 per day	-0.02 (-0.19, 0.15)	0.26 (0.08, 0.45)**	0.01 (-0.15, 0.17)	0.27 (0.08, 0.46)**	-0.05 (-0.21, 0.11)	0.30 (0.14, 0.46)**	0.01 (-0.14, 0.16)	0.11 (-0.08, 0.29)	1.16 (0.73, 1.87)	1.14 (0.69, 1.87)
≥ 5 per day	0.23 (0.06, 0.40)**	0.20 (0.05, 0.36)**	0.27 (0.12, 0.43)**	0.30 (0.14, 0.46)**	0.26 (0.10, 0.41)**	0.30 (0.16, 0.43)**	0.13 (-0.02, 0.27)	0.09 (-0.07, 0.24)	1.54 (1.00, 2.39)	1.55 (1.04, 2.31)*
p-value interaction model [#]		0.22		0.19		0.12		0.60		0.42
Paternal use										
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Yes	0.16 (0.07, 0.25)**	0.09 (0.00, 0.18)*	0.19 (0.11, 0.27)**	0.14 (0.05, 0.23)**	0.17 (0.08, 0.25)**	0.13 (0.06, 0.20)**	0.05 (-0.03, 0.13)	0.01 (-0.08, 0.09)	1.38 (1.06, 1.80)**	1.24 (0.97, 1.57)
< 5 per day	0.10 (-0.03, 0.22)	0.04 (-0.08, 0.17)	0.10 (-0.02, 0.21)	0.07 (-0.05, 0.20)	0.10 (-0.01, 0.21)	0.02 (-0.09, 0.12)	0.01 (-0.09, 0.12)	0.04 (-0.09, 0.16)	1.29 (0.89, 1.88)	0.98 (0.67, 1.41)
≥ 5 per day	0.21 (0.10, 0.31)**	0.12 (0.02, 0.22)*	0.26 (0.16, 0.35)**	0.18 (0.07, 0.28)**	0.21 (0.11, 0.31)**	0.20 (0.11, 0.29)**	0.07 (-0.03, 0.16)	-0.01 (-0.11, 0.09)	1.43 (1.06, 1.93)*	1.38 (1.05, 1.81)*
p-value interaction model [#]		0.36		0.50		0.50		0.83		0.76

	Body mass index (SDS) ^a		Android-gynoid ratio (SDS) ^a		Fat mass index (SDS) ^a		Fat-free mass index (SDS) ^a		Overweight ^b	
	Boys (n = 2363)	Girls (n = 2418)	Boys (n = 2338)	Girls (n = 2394)	Boys (n = 2330)	Girls (n = 2391)	Boys (n = 2330)	Girls (n = 2391)	Boys (n = 2363)	Girls (n = 2418)
Cannabis	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	OR (95% CI)	OR (95% CI)
Maternal use										
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Before pregnancy	-0.08 (-0.33, 0.17)	0.24 (-0.01, 0.48)	-0.16 (-0.39, 0.06)	0.20 (-0.05, 0.45)	-0.12 (-0.35, 0.11)	0.18 (-0.03, 0.39)	0.03 (-0.20, 0.25)	0.27 (0.02, 0.51)*	0.76 (0.31, 1.86)	1.80 (0.94, 3.45)
During pregnancy	0.12 (-0.12, 0.36)	0.45 (0.18, 0.73)**	0.04 (-0.18, 0.26)	0.46 (0.18, 0.74)**	0.01 (-0.22, 0.23)	0.32 (0.08, 0.55)**	0.16 (-0.06, 0.38)	0.36 (0.09, 0.63)**	0.67 (0.30, 1.47)	2.72 (1.39, 5.33)**

Continued tobacco use	0.11 (-0.02, 0.23)	0.23 (0.11, 0.35)**	0.14 (0.03, 0.26)**	0.28 (0.15, 0.41)**	0.11 (0.00, 0.23)	0.30 (0.19, 0.40)**	0.06 (-0.06, 0.17)	0.09 (-0.03, 0.21)	1.33 (0.96, 1.86)	1.38 (1.00, 1.90)
p-value interaction model [#]		0.04		0.01		0.02		0.21		0.03

Paternal use

No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Cannabis use	-0.04 (-0.18, 0.11)	0.27 (0.14, 0.41)**	0.00 (-0.13, 0.13)	0.23 (0.09, 0.37)**	-0.04 (-0.18, 0.09)	0.19 (0.07, 0.31)**	0.01 (-0.11, 0.14)	0.31 (0.17, 0.45)**	1.13 (0.75, 1.71)	1.46 (1.02, 2.10)*
p-value interaction model [#]		< 0.01		0.02		0.01		< 0.01		0.12

Note: Confounder model were adjusted for maternal age, maternal education, maternal ethnicity, maternal alcohol use, maternal psychopathology score, pre-pregnancy body mass index (BMI) and child age. *p-value < 0.05, **p-value < 0.017 (Bonferroni corrected values for multiple testing).

[#] p-values when linear model and model with interaction term were compared.

Abbreviations: Android-gynoid ratio (Android/gynoid fat mass ratio).

^a Values represent regression coefficients (difference) and 95% confidence interval (95% CI) from linear regression models that reflects the differences in childhood outcomes standard deviation score (SDS) for maternal or paternal tobacco and/or cannabis use during pregnancy, compared to the reference group.

^b Values are odds ratio (OR) and 95% CI from logistic regression models that reflect the risk of childhood overweight for maternal or paternal tobacco and /or cannabis use during pregnancy, compared to the reference group.

Table S5. Associations of maternal and paternal tobacco and cannabis use during pregnancy with childhood blood pressure and metabolic outcomes at age 10 years stratified for child sex

	Systolic blood pressure (SDS)		Diastolic blood pressure (SDS)		Total cholesterol (SDS)		HDL-Cholesterol (SDS)		Triglyceride (SDS)	
	Boys (n = 2000)	Girls (n = 2109)	Boys (n = 2001)	Girls (n = 2108)	Boys (n = 1448)	Girls (n = 1511)	Boys (n = 1449)	Girls (n = 1511)	Boys (n = 1448)	Girls (n = 1502)
Tobacco only	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)
Maternal use										
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
First trimester only	-0.09 (-0.25, 0.08)	-0.04 (-0.19, 0.11)	-0.02 (-0.18, 0.15)	-0.02 (-0.17, 0.12)	0.06 (-0.14, 0.25)	0.04 (-0.14, 0.21)	-0.08 (-0.27, 0.12)	0.09 (-0.08, 0.26)	0.19 (-0.01, 0.39)	-0.01 (-0.18, 0.16)
Continued smoking	0.12 (-0.01, 0.25)	0.05 (-0.08, 0.19)	0.05 (-0.08, 0.18)	0.10 (-0.03, 0.23)	0.07 (-0.09, 0.22)	0.04 (-0.12, 0.20)	-0.03 (-0.19, 0.13)	-0.13 (-0.28, 0.03)	0.25 (0.09, 0.41)**	0.06 (-0.09, 0.21)
< 5 per day	0.08 (-0.10, 0.25)	-0.06 (-0.25, 0.14)	-0.03 (-0.20, 0.15)	0.03 (-0.16, 0.23)	0.11 (-0.10, 0.31)	0.00 (-0.23, 0.23)	-0.12 (-0.33, 0.09)	-0.06 (-0.29, 0.16)	0.26 (0.05, 0.47)**	-0.07 (-0.3, 0.15)
≥ 5 per day	0.16 (0.00, 0.33)	0.13 (-0.04, 0.29)	0.13 (-0.04, 0.30)	0.14 (-0.02, 0.30)	0.03 (-0.18, 0.23)	0.07 (-0.13, 0.26)	0.07 (-0.15, 0.28)	-0.17 (-0.36, 0.02)	0.23 (0.01, 0.45)*	0.15 (-0.04, 0.34)
p-value interaction model [#]		0.53		0.98		0.75		0.29		0.19
Paternal use										
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Yes	0.08 (-0.01, 0.17)	-0.01 (-0.10, 0.08)	0.07 (-0.02, 0.16)	0.00 (-0.09, 0.09)	0.09 (-0.01, 0.20)	0.00 (-0.11, 0.11)	0.03 (-0.08, 0.14)	-0.07 (-0.17, 0.04)	0.09 (-0.02, 0.20)	0.02 (-0.09, 0.12)
< 5 per day	0.03 (-0.09, 0.16)	-0.03 (-0.16, 0.10)	0.07 (-0.06, 0.19)	-0.03 (-0.16, 0.10)	0.07 (-0.08, 0.21)	-0.03 (-0.18, 0.13)	0.00 (-0.14, 0.15)	-0.11 (-0.26, 0.04)	0.14 (-0.01, 0.30)	0.05 (-0.10, 0.19)
≥ 5 per day	0.12 (0.01, 0.22)*	0.01 (-0.10, 0.11)	0.07 (-0.04, 0.18)	0.02 (-0.09, 0.12)	0.11 (-0.02, 0.23)	0.01 (-0.11, 0.14)	0.05 (-0.08, 0.17)	-0.04 (-0.16, 0.08)	0.06 (-0.07, 0.19)	0.00 (-0.12, 0.12)
p-value interaction model [#]		0.10		0.12		0.09		0.16		0.30
Cannabis										
	Systolic blood pressure (SDS)		Diastolic blood pressure (SDS)		Total cholesterol (SDS)		HDL-Cholesterol (SDS)		Triglyceride (SDS)	
	Boys (n = 2273)	Girls (n = 2346)	Boys (n = 2274)	Girls (n = 2345)	Boys (n = 1644)	Girls (n = 1680)	Boys (n = 1645)	Girls (n = 1681)	Boys (n = 1643)	Girls (n = 1672)
Maternal use	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Before pregnancy	-0.08 (-0.33, 0.17)	0.11 (-0.15, 0.36)	0.03 (-0.23, 0.29)	0.11 (-0.15, 0.36)	-0.41 (-0.70, -0.11)**	0.22 (-0.08, 0.52)	0.12 (-0.19, 0.42)	0.03 (-0.26, 0.32)	-0.38 (-0.68, -0.07)*	0.10 (-0.19, 0.39)
During pregnancy	0.10 (-0.14, 0.35)	0.24 (-0.05, 0.53)	0.05 (-0.21, 0.30)	-0.02 (-0.31, 0.26)	-0.05 (-0.35, 0.25)	0.04 (-0.32, 0.39)	0.01 (-0.29, 0.32)	-0.37 (-0.71, -0.03)*	-0.19 (-0.50, 0.13)	0.19 (-0.14, 0.53)

Continued tobacco use	0.13 (0.01, 0.26)*	0.06 (-0.07, 0.19)	0.06 (-0.07, 0.19)	0.10 (-0.03, 0.22)	0.05 (-0.10, 0.20)	0.04 (-0.11, 0.20)	-0.05 (-0.20, 0.10)	-0.15 (-0.30, 0.00)	0.25 (0.09, 0.40)**	0.08 (-0.07, 0.23)
p-value interaction model [#]		0.48		0.92		0.06		0.22		0.02
Paternal use										
No Cannabis use	Reference -0.04 (-0.19, 0.10)	Reference 0.11 (-0.03, 0.26)	Reference -0.08 (-0.23, 0.07)	Reference 0.11 (-0.03, 0.25)	Reference -0.12 (-0.30, 0.05)	Reference 0.15 (-0.02, 0.32)	Reference 0.23 (0.05, 0.40)**	Reference -0.06 (-0.23, 0.10)	Reference -0.20 (-0.38, -0.02)*	Reference 0.10 (-0.06, 0.27)
p-value interaction model [#]		0.19		0.15		0.11		< 0.01		< 0.01

Note: Confounder model were adjusted for maternal age, maternal education, maternal ethnicity, maternal alcohol use, maternal psychopathology score, pre-pregnancy body mass index (BMI), and child age. *p-value < 0.05, **p-value < 0.017 (Bonferroni corrected values for multiple testing).

[#] p-values when linear model and model with interaction term were compared.

Values are regression coefficients (difference), 95% confidence interval (95% CI) from linear regression models that reflects the differences in childhood outcomes standard deviation score (SDS) for maternal or paternal tobacco and/or cannabis use during pregnancy, compared to the reference group.

Abbreviations: HDL-cholesterol: high-density lipoprotein cholesterol.

Table S6. Associations of maternal and paternal tobacco and cannabis use during pregnancy with childhood cardio-metabolic risk factors at age 10 years stratified for child sex

	Glucose (SDS) ^a		Insulin (SDS) ^a		Cardio-metabolic clustering ^b	
	Boys (n = 1449)	Girls (n = 1509)	Boys (n = 1447)	Girls (n = 1507)	Boys (n = 1397)	Girls (n = 1465)
Tobacco only	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	OR (95% CI)	OR (95% CI)
Maternal use						
No	Reference	Reference	Reference	Reference	Reference	Reference
First trimester only	-0.05 (-0.25, 0.15)	0.05 (-0.12, 0.23)	-0.10 (-0.29, 0.10)	-0.05 (-0.23, 0.12)	0.97 (0.43, 2.22)	0.81 (0.48, 1.38)
Continued smoking	0.02 (-0.13, 0.18)	0.01 (-0.15, 0.17)	0.00 (-0.16, 0.15)	0.07 (-0.08, 0.23)	1.31 (0.80, 2.12)	1.33 (0.89, 1.99)
< 5 per day	0.04 (-0.17, 0.24)	-0.03 (-0.26, 0.20)	0.00 (-0.20, 0.21)	-0.05 (-0.28, 0.19)	1.21 (0.63, 2.31)	0.81 (0.41, 1.60)
≥ 5 per day	0.01 (-0.20, 0.22)	0.04 (-0.16, 0.23)	-0.01 (-0.22, 0.20)	0.15 (-0.04, 0.35)	1.41 (0.75, 2.64)	1.74 (1.08, 2.80)*
p-value interaction model [#]		0.63		0.75		0.96
Paternal use						
No	Reference	Reference	Reference	Reference	Reference	Reference
Yes	-0.03 (-0.14, 0.08)	0.03 (-0.08, 0.13)	-0.08 (-0.19, 0.03)	0.03 (-0.07, 0.14)	1.57 (1.09, 2.24)**	0.96 (0.71, 1.29)
< 5 per day	-0.10 (-0.25, 0.05)	-0.17 (-0.32, -0.02)*	-0.02 (-0.17, 0.13)	-0.06 (-0.21, 0.1)	1.67 (1.01, 2.76)*	0.82 (0.51, 1.30)
≥ 5 per day	0.02 (-0.11, 0.15)	0.14 (0.02, 0.27)*	-0.12 (-0.24, 0.01)	0.09 (-0.04, 0.21)	1.50 (1.00, 2.26)*	1.03 (0.73, 1.46)
p-value interaction model [#]		0.68		0.12		0.03
Cannabis						
	Glucose (SDS) ^a		Insulin (SDS) ^a		Cardio-metabolic clustering ^b	
	Boys (n = 1645)	Girls (n = 1679)	Boys (n = 1643)	Girls (n = 1677)	Boys (n = 1582)	Girls (n = 1630)
Maternal use	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	OR (95% CI)	OR (95% CI)
No	Reference	Reference	Reference	Reference	Reference	Reference
Cannabis before	-0.17 (-0.47, 0.13)	0.08 (-0.22, 0.38)	-0.02 (-0.32, 0.28)	0.20 (-0.09, 0.50)	0.00 (0.00, Inf)	0.90 (0.36, 2.20)
Cannabis during	0.09 (-0.22, 0.39)	-0.08 (-0.43, 0.27)	-0.23 (-0.53, 0.07)	0.27 (-0.08, 0.61)	1.06 (0.39, 2.89)	2.74 (1.21, 6.22)**
Continued tobacco	0.00 (-0.15, 0.15)	-0.01 (-0.17, 0.14)	-0.01 (-0.16, 0.15)	0.07 (-0.08, 0.22)	1.27 (0.79, 2.03)	1.40 (0.94, 2.07)
p-value interaction model [#]		0.52		0.16		0.06
Paternal use						
No	Reference	Reference	Reference	Reference	Reference	Reference
Cannabis use	-0.14 (-0.32, 0.04)	-0.01 (-0.18, 0.16)	-0.08 (-0.26, 0.10)	0.22 (0.05, 0.39)**	0.49 (0.23, 1.01)	1.30 (0.84, 2.02)
p-value interaction model [#]		0.45		0.01		< 0.01

Note: Confounder model were adjusted for maternal age, education, ethnicity, alcohol use, psychopathology score, pre-pregnancy body mass index (BMI), and child age. *p-value < 0.05, **p-value < 0.017 (Bonferroni corrected values for multiple testing).

[#] p-values when linear model and model with interaction term were compared.

^a Values represent regression coefficients (difference) and 95% confidence interval (95% CI) from linear regression models that reflects the differences in childhood outcomes standard deviation score (SDS) for maternal or paternal tobacco and/or cannabis use during pregnancy, compared to the reference group.

^b Values are odds ratio (OR) and 95% CI from logistic regression models that reflect the risk of childhood cardio-metabolic clustering risk for maternal or paternal tobacco and/or cannabis use during pregnancy compared with the reference group.

Table S7. Associations of maternal and paternal tobacco and cannabis use with childhood body fat outcomes only for children at age 10 years of Dutch mothers

	Body mass index (SDS)^a (n = 2431)	Android-gynoid ratio (SDS)^a (n = 2404)	Fat mass index (SDS)^a (n = 2403)	Fat-free mass index (SDS)^a (n = 2403)	Overweight^b (n = 2431)
Tobacco only	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	OR (95% CI)
Maternal use					
No	Reference	Reference	Reference	Reference	Reference
First trimester only	-0.02 (-0.14, 0.11)	0.05 (-0.08, 0.17)	-0.05 (-0.16, 0.06)	0.01 (-0.11, 0.13)	1.29 (0.81, 2.06)
Continued smoking	0.24 (0.12, 0.35)**	0.24 (0.13, 0.35)**	0.27 (0.17, 0.37)**	0.11 (0.00, 0.21)*	1.63 (1.14, 2.33)**
< 5 per day	0.13 (-0.04, 0.29)	0.09 (-0.07, 0.25)	0.14 (-0.01, 0.29)	0.06 (-0.09, 0.22)	1.23 (0.68, 2.21)
≥ 5 per day	0.31 (0.17, 0.45)**	0.34 (0.20, 0.48)**	0.36 (0.23, 0.48)**	0.14 (0.01, 0.26)*	1.89 (1.24, 2.89)**
p-value interaction model [#]	0.42	0.19	0.39	0.65	0.07
Paternal use					
No	Reference	Reference	Reference	Reference	Reference
Yes	0.09 (0.01, 0.16)*	0.11 (0.04, 0.18)**	0.09 (0.03, 0.16)**	0.03 (-0.04, 0.1)	1.16 (0.88, 1.53)
< 5 per day	0.05 (-0.05, 0.16)	0.00 (-0.10, 0.10)	-0.01 (-0.10, 0.09)	0.08 (-0.01, 0.18)	0.98 (0.64, 1.49)
≥ 5 per day	0.12 (0.02, 0.21)**	0.19 (0.10, 0.28)**	0.17 (0.09, 0.25)**	-0.01 (-0.10, 0.07)	1.26 (0.92, 1.73)
p-value interaction model [#]	0.46	0.02	0.10	0.95	0.50
<hr/>					
	Body mass index (SDS)^a (n = 2726)	Android-gynoid ratio (SDS)^a (n = 2697)	Fat mass index (SDS)^a (n = 2694)	Fat-free mass index (SDS)^a (n = 2694)	Overweight^b (n = 2726)
Cannabis	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	OR (95% CI)
Maternal use					
No	Reference	Reference	Reference	Reference	Reference
Cannabis before	0.07 (-0.13, 0.27)	-0.07 (-0.27, 0.12)	-0.01 (-0.18, 0.17)	0.22 (0.03, 0.41)*	1.56 (0.79, 3.10)
Cannabis during	0.24 (0.03, 0.46)*	0.31 (0.10, 0.52)**	0.19 (-0.01, 0.38)	0.14 (-0.07, 0.34)	1.00 (0.46, 2.19)
Continued tobacco	0.24 (0.12, 0.35)**	0.23 (0.12, 0.34)**	0.27 (0.17, 0.37)**	0.1 (-0.01, 0.20)	1.56 (1.10, 2.21)**
p-value interaction model [#]	0.69	0.41	0.40	0.35	0.12
Paternal use					
No	Reference	Reference	Reference	Reference	Reference
Cannabis use	0.16 (0.04, 0.28)**	0.25 (0.13, 0.37)**	0.17 (0.06, 0.27)**	0.13 (0.02, 0.24)*	1.69 (1.15, 2.48)**
p-value interaction model [#]	0.42	0.03	0.14	0.01	0.20

Note: Confounder models were adjusted for maternal age, maternal education, maternal alcohol use, maternal psychopathology score, pre-pregnancy body mass index (BMI), child sex, and child age. *p-value < 0.05, **p-value < 0.017 (Bonferroni corrected values for multiple testing).

Abbreviations: Android-gynoid ratio (Android/gynoid fat mass ratio). # p-values when linear model and model with interaction term were compared.

^a Values represent regression coefficients (difference) and 95% confidence interval (95% CI) from linear regression models that reflects the differences in childhood outcomes standard deviation score (SDS) for maternal or paternal tobacco and/or cannabis use during pregnancy, compared to the reference group.

^b Values are odds ratio (OR) and 95% CI from logistic regression models that reflect the risk of childhood overweight for maternal or paternal tobacco and/or cannabis use during pregnancy, compared to the reference group.

Table S8. Associations of maternal and paternal tobacco and cannabis use with childhood cardio-metabolic risk factors only for children at age 10 years of Dutch mothers

	Systolic blood pressure (SDS) ^a (n = 2344)	Diastolic blood pressure (SDS) ^a (n = 2344)	Total Cholesterol (SDS) ^a (n = 1676)	HDL-Cholesterol (SDS) ^a (n = 1677)	Triglyceride (SDS) ^a (n = 1673)	Glucose (SDS) ^a (n = 1676)	Insulin (SDS) ^a (n = 1676)	Cardio-metabolic clustering ^b (n = 1622)
Tobacco only	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	OR (95% CI)
Maternal use								
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
First trimester only	-0.07 (-0.21, 0.07)	0.01 (-0.13, 0.15)	-0.02 (-0.18, 0.15)	0.07 (-0.10, 0.23)	-0.04 (-0.20, 0.13)	0.04 (-0.13, 0.22)	-0.09 (-0.25, 0.07)	0.86 (0.45, 1.65)
Continued smoking	0.05 (-0.07, 0.18)	0.01 (-0.12, 0.14)	0.05 (-0.1, 0.19)	0.02 (-0.13, 0.16)	-0.03 (-0.18, 0.12)	0.04 (-0.11, 0.20)	0.03 (-0.12, 0.17)	1.12 (0.68, 1.85)
< 5 per day	-0.07 (-0.26, 0.12)	-0.12 (-0.31, 0.07)	-0.01 (-0.22, 0.2)	-0.08 (-0.29, 0.13)	-0.03 (-0.25, 0.18)	0.06 (-0.17, 0.28)	0 (-0.21, 0.21)	0.95 (0.43, 2.10)
≥ 5 per day	0.13 (-0.02, 0.29)	0.10 (-0.06, 0.25)	0.09 (-0.09, 0.28)	0.09 (-0.10, 0.27)	-0.03 (-0.22, 0.16)	0.03 (-0.16, 0.23)	0.05 (-0.14, 0.23)	1.23 (0.67, 2.26)
p-value interaction model [#]	0.57	0.08	0.56	0.25	< 0.01	0.94	0.66	0.54
Paternal use								
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Yes	-0.03 (-0.11, 0.06)	0.00 (-0.08, 0.09)	0.12 (0.02, 0.21)*	0.03 (-0.07, 0.12)	0.03 (-0.07, 0.13)	-0.04 (-0.15, 0.06)	-0.04 (-0.14, 0.06)	0.98 (0.68, 1.41)
< 5 per day	-0.03 (-0.15, 0.08)	0.00 (-0.12, 0.11)	0.06 (-0.07, 0.19)	-0.03 (-0.17, 0.10)	0.07 (-0.07, 0.20)	-0.18 (-0.33, -0.04)**	-0.06 (-0.19, 0.08)	0.82 (0.47, 1.43)
≥ 5 per day	-0.02 (-0.12, 0.08)	0.00 (-0.10, 0.10)	0.15 (0.04, 0.27)**	0.07 (-0.05, 0.19)	0.01 (-0.12, 0.13)	0.06 (-0.07, 0.18)	-0.03 (-0.15, 0.09)	1.07 (0.71, 1.63)
p-value interaction model [#]	0.07	0.45	0.12	0.07	0.10	0.05	0.32	0.16
Cannabis								
	Systolic blood pressure (SDS) ^a (n = 2633)	Diastolic blood pressure (SDS) ^a (n = 2633)	Total Cholesterol (SDS) ^a (n = 1874)	HDL-Cholesterol (SDS) ^a (n = 1875)	Triglyceride (SDS) ^a (n = 1871)	Glucose (SDS) ^a (n = 1874)	Insulin (SDS) ^a (n = 1874)	Cardio-metabolic clustering ^b (n = 1812)
Cannabis	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	OR (95% CI)
Maternal use								
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Cannabis before	0.00 (-0.22, 0.22)	0.01 (-0.21, 0.24)	0.12 (-0.13, 0.38)	0.24 (-0.01, 0.49)	-0.18 (-0.44, 0.08)	0.05 (-0.22, 0.31)	0.17 (-0.08, 0.41)	0.56 (0.17, 1.85)
Cannabis during	0.18 (-0.06, 0.42)	0.15 (-0.10, 0.39)	-0.14 (-0.44, 0.15)	-0.17 (-0.46, 0.13)	-0.12 (-0.42, 0.19)	0.04 (-0.27, 0.36)	0.02 (-0.27, 0.32)	1.44 (0.55, 3.74)
Continued tobacco	0.06 (-0.06, 0.19)	0.00 (-0.12, 0.12)	0.04 (-0.10, 0.19)	-0.02 (-0.16, 0.13)	0.00 (-0.15, 0.15)	0.02 (-0.14, 0.17)	0.03 (-0.11, 0.17)	1.15 (0.71, 1.89)
p-value interaction model [#]	0.81	0.08	0.14	0.14	0.03	0.64	0.90	0.36
Paternal use								
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Cannabis use	0.10 (-0.04, 0.23)	0.04 (-0.09, 0.17)	0.01 (-0.15, 0.16)	-0.01 (-0.17, 0.15)	0.03 (-0.13, 0.19)	0.01 (-0.16, 0.18)	0.18 (0.02, 0.34)*	1.17 (0.69, 1.98)
p-value interaction model [#]	0.24	0.84	0.93	0.27	0.49	0.23	0.32	0.16

Note: Confounder models were adjusted for maternal age, education, alcohol use, psychopathology score, pre-pregnancy body mass index (BMI), child sex, and child age.

Abbreviations: HDL-cholesterol: high-density lipoprotein cholesterol. *p-value < 0.05, **p-value < 0.017 (Bonferroni corrected values for multiple testing).

^a Values represent regression coefficients (difference) and 95% confidence interval (95% CI) from linear regression models that reflects the differences in childhood outcomes standard deviation score (SDS) for maternal or paternal tobacco and/or cannabis use during pregnancy, compared to the reference group.

^b Values are odds ratio (OR) and 95% CI from logistic regression models that reflect the risk of childhood cardio-metabolic clustering risk for maternal or paternal tobacco and/or cannabis use during pregnancy, compared to the reference group. [#] p-values when linear model and model with interaction term were compared.

Methods S1. Calculation of the continuous composite cardio-metabolic risk z-score

To establish a continuous composite cardio-metabolic risk score, we calculated the standardized residuals (z-scores) for individual risk factors by regression on selected demographic variables such as child sex and child age.¹ The individual risk factors were body mass index (BMI), mean arterial pressure (MAP) ($[\text{systolic blood pressure} + 2 \times (\text{diastolic blood pressure})] / 3$), log-natural transformed homeostasis assessment model of insulin resistance (HOMA) ($[\text{Glucose (mmol/L)} \times \text{Insuline (mU/L)}] / 22.5$), log-natural transformed triglycerides, and HDL-cholesterol.¹ Since the standardized HDL-cholesterol is inversely related to metabolic risk it is multiplied by -1. Then, the standardized residuals (z-scores) for the individual risk factors were summed to create the metabolic syndrome z-score. Since waist circumference was not available, body mass index was used. A higher score is interpreted as a indicative of a less favorable metabolic syndrome profile.¹

Reference

1. Eisenmann JC. On the use of a continuous metabolic syndrome score in pediatric research. *Cardiovascular diabetology*. 2008;7:17-17. doi:10.1186/1475-2840-7-17

Table S9. Associations of maternal and paternal tobacco and cannabis use with childhood continuous composite cardio-metabolic z-score at age 10 years

	Cardio-metabolic z-score
Tobacco only	Difference (95% CI)
Maternal use	
No	Reference
First trimester only	-0.08 (-0.47, 0.31)
Continued smoking	0.48 (0.16, 0.80)**
< 5 per day	0.29 (-0.16, 0.75)
≥ 5 per day	0.64 (0.22, 1.05)**
Paternal use	
No	Reference
Yes	0.20 (-0.02, 0.42)
< 5 per day	0.13 (-0.18, 0.44)
≥ 5 per day	0.24 (-0.02, 0.51)
Cannabis	
Maternal use	
No	Reference
Cannabis before	0.01 (-0.61, 0.63)
Cannabis during	0.27 (-0.41, 0.95)
Continued tobacco	0.50 (0.18, 0.82)**
Paternal use	
No	Reference
Cannabis use	0.04 (-0.32, 0.40)

Note: Confounder models were adjusted for maternal age, ethnicity, education, alcohol use, psychopathology score, pre-pregnancy body mass index (BMI). *p-value < 0.05, **p-value < 0.017 (Bonferroni corrected values for multiple testing). Values represent regression coefficients (difference) and 95% confidence interval (95% CI) from linear regression models that reflects the differences in childhood continuous cardio-metabolic z-score for maternal or paternal tobacco and/or cannabis use during pregnancy, compared to the reference group.