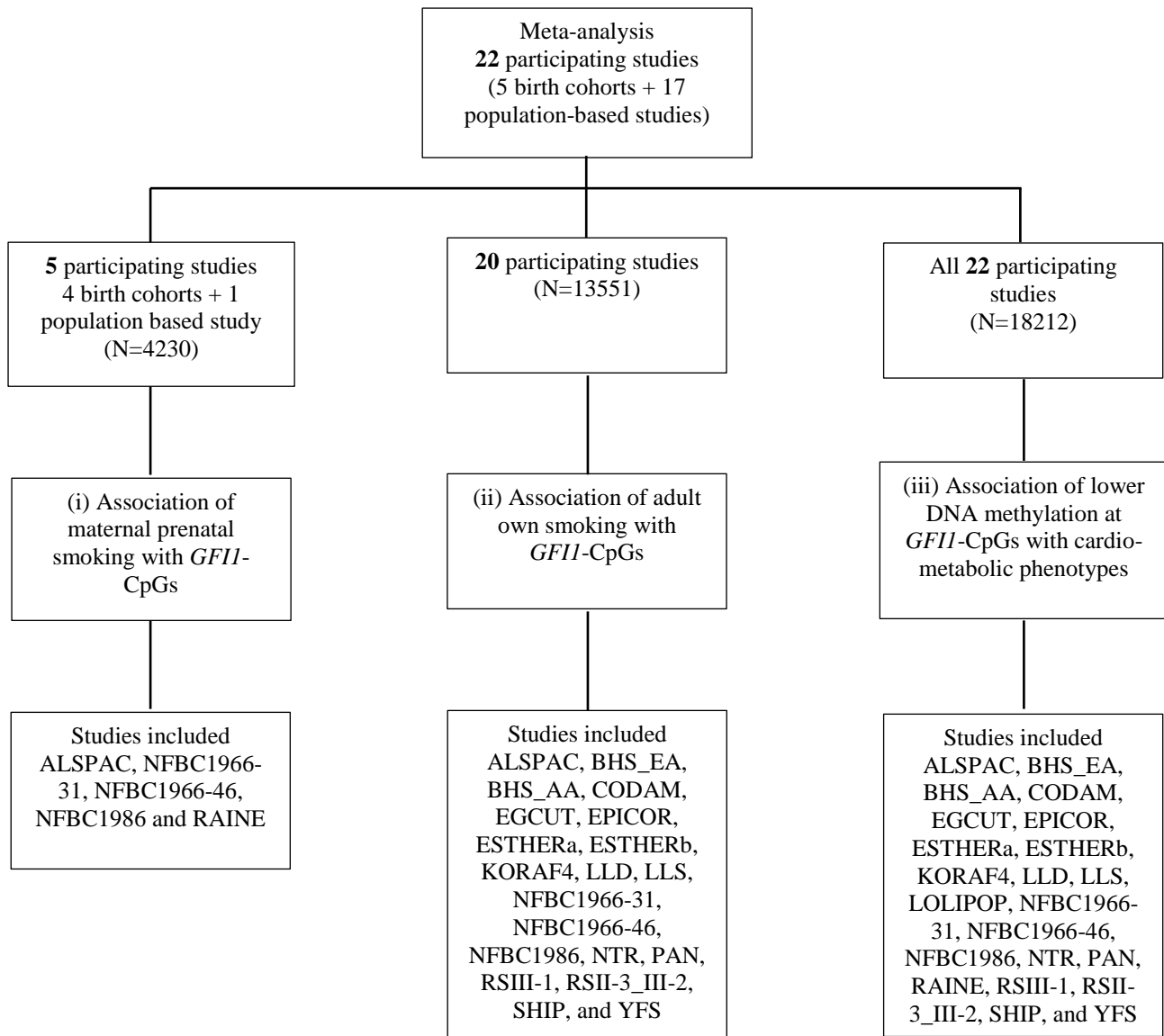


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**Figure S1: Flowchart of the study design**

Studies names: The Avon Longitudinal Study of Parents and Children (ALSPAC), BIOS consortium, the two studies from Bogalusa Heart Study (BHS – European American and African American), the Estonian Genome Centre, University of Tartu (EGCUT), the Italian cardiovascular section of EPIC (EPICOR), the Cooperative Gesundheitsforschung in der Region Augsburg (Cooperative Health Research in the Augsburg Region) F4 (KORAF4), the two independent subsets of the Epidemiologische Studie zu Chancen der Verhütung, Früherkennung und optimierten Therapie chronischer Erkrankungen in der älteren Bevölkerung (ESTHERa and ESTHERb), the Lifelines Deep (LLD), the London Life Science Population study (LOLIPOP), the two follow-up datasets from Northern Finland Birth cohort 1966 (NFBC1966-31years and NFBC1966-46years), Northern Finland Birth cohort 1986 (NFBC1986), The Western Australian Pregnancy Cohort study (RAINE), the two independent studies from Rotterdam Study (RS) –RSIII-1 and RSII-3\_III-2, the Study of Health in Pomerania – Trend (SHIP-Trend) and the Young Finns Study 2011 (YFS). BIOS consortium includes the Cohort On Diabetes And Atherosclerosis Maastricht (CODAM), the Leiden Longevity Study (LLS), the Netherlands Twin Register study (NTR) and the Prospective Amyotrophic Lateral Sclerosis (ALS) study Netherlands (PAN)

**Table S1: Characteristics of the participants based on exposure to maternal prenatal smoking (n=4,230)**

Studies <sup>1</sup>	ALSPAC (n=1443)			NFBC1966-31 yr (n=740)			NFBC1966-46 yr (n=716) <sup>3</sup>			NFBC1986 (n=512)			RAINE (n=819)		
Maternal smoking	Unexposed	Exposed	P-value	Unexposed	Exposed	P-value	Unexposed	Exposed	P-value	Unexposed	Exposed	P-value	Unexposed	Exposed	P-value
N (%)	1220 (80)	223 (15)	-	587 (79)	163 (21)	-	558 (79)	146 (21)	-	467 (91)	45 (9)	-	661 (81)	158 (19)	-
Males n (%)	415 (34)	68 (31)	-	255 (43)	70 (47)	-	242 (43)	67 (46)	-	217 (46)	15 (33)	-	345 (52)	73 (46)	-
Age (yr)	49.1 (5.4)	48.0 (7.0)	0.04	31	31	-	46	46	-	16	16	-	17	17	-
Adult smoking n (%)	115 (9)	38 (17)	0.001	138 (24)	56 (37)	0.001	76 (14)	34 (23)	0.006	84 (17)	17 (38)	0.002	NA	NA	-
<b>Cardio-metabolic Phenotypes<sup>2</sup></b>															
BMI (kg/m <sup>2</sup> )	26.7 (4.8)	27.3 (4.8)	0.13	24.4 (4.0)	24.8 (4.1)	0.28	26.6 (4.5)	27.5 (5.7)	0.09	21.2 (3.2)	22.9 (4.4)	0.002	22.8 (4.3)	24.9 (5.3)	<0.0001
WC (cm)	88.5 (13.3)	90.2 (12.8)	0.12	82.4 (11.2)	82.9 (12.0)	0.65	91.1 (12.8)	92.8 (15.0)	0.23	74.0 (8.5)	76.3 (11.5)	0.08	79.1 (11.2)	82.5 (13.1)	0.002
TG (mmol/l)	1.1 (0.6)	1.3 (0.8)	0.03	1.1 (0.7)	1.1 (0.7)	0.5	1.2 (1.0)	1.3 (0.9)	0.40	0.8 (0.4)	1.0 (0.5)	0.002	1.0 (0.5)	1.2 (0.8)	<0.0001
HDL-C (mmol/l)	1.4 (0.4)	1.3 (0.3)	<0.0001	1.6 (0.4)	1.6 (0.3)	0.7	1.6 (0.4)	1.6 (0.4)	0.65	1.4 (1.4)	1.4 (1.3)	0.82	1.3 (0.3)	1.3 (0.3)	0.17
FG (mmol/l)	5.4 (1.1)	5.5 (1.0)	0.33	5.0 (0.8)	5.04 (0.5)	0.45	5.5 (0.6)	5.6 (0.6)	0.03	5.2 (0.5)	5.1 (0.1)	0.37	4.7 (0.6)	4.8 (0.4)	0.79
SBP (mmHg)	122(14)	122 (14)	0.74	124 (13)	124 (14)	0.67	124 (14)	124 (14)	0.79	129 (17)	129 (17)	0.76	113 (10)	114 (10)	0.34
DBP (mmHg)	74 (10)	74 (10)	0.41	76 (0.5)	76 (1)	0.36	77 (12)	76 (11)	0.30	86 (11)	87 (12)	0.73	58 (6)	58 (6)	0.69
<b>Mean methylation<sup>2</sup></b>															
cg14179389	0.14 (0.08)	0.12 (0.08)	0.02	0.27 (0.06)	0.25 (0.05)	<0.0001	0.26 (0.06)	0.23 (0.05)	<0.0001	0.31 (0.06)	0.26 (0.05)	<0.0001	0.30 (0.06)	0.26 (0.05)	<0.0001
cg09935388	0.75 (0.11)	0.71 (0.14)	<0.0001	0.78 (0.06)	0.76 (0.08)	<0.0001	0.81 (0.06)	0.76 (0.08)	<0.0001	0.82 (0.06)	0.79 (0.05)	0.003	0.80 (0.06)	0.77 (0.08)	<0.0001
cg12876356	0.79 (0.13)	0.74 (0.16)	<0.0001	0.83 (0.06)	0.82 (0.07)	0.08	0.93 (0.06)	0.90 (0.07)	0.009	0.85 (0.03)	0.84 (0.01)	0.29	0.87 (0.07)	0.85 (0.09)	0.01
cg18316974	0.91 (0.07)	0.89 (0.11)	0.01	0.96 (0.05)	0.96 (0.04)	0.6	0.94 (0.05)	0.94 (0.04)	0.16	0.97 (0.04)	0.96 (0.04)	0.71	0.91 (0.04)	0.90 (0.05)	0.07
cg09662411	0.68 (0.10)	0.68 (0.11)	0.51	0.78 (0.05)	0.78 (0.05)	0.69	0.92 (0.05)	0.91 (0.05)	0.04	0.80 (0.05)	0.79 (0.06)	0.40	0.82 (0.06)	0.81 (0.07)	0.007
cg18146737	0.92 (0.11)	0.89 (0.15)	0.003	0.95 (0.08)	0.94 (0.08)	0.41	0.94 (0.08)	0.93 (0.08)	0.19	0.96 (0.08)	0.95 (0.08)	0.77	0.91 (0.06)	0.90 (0.08)	0.23
cg04535902	0.74 (0.09)	0.74 (0.09)	0.47	0.83 (0.06)	0.83 (0.05)	0.39	0.93 (0.06)	0.90 (0.05)	0.001	0.85 (0.05)	0.85 (0.06)	0.79	0.83 (0.08)	0.82 (0.08)	0.25
cg10399789	0.78 (0.10)	0.76 (0.13)	0.03	0.77 (0.04)	0.76 (0.04)	0.29	0.83 (0.04)	0.82 (0.04)	0.19	0.79 (0.03)	0.78 (0.04)	0.39	0.80 (0.04)	0.79 (0.05)	0.009

<sup>1</sup>Studies names: The Avon Longitudinal Study of Parents and Children (ALSPAC), the two subsets of the Northern Finland Birth cohort 1966 (NFBC1966-31years and NFBC1966-46years), the Northern Finland Birth cohort 1986 (NFBC1986), The Western Australian Pregnancy Cohort study (RAINE).

<sup>2</sup>Values are mean (SD).

<sup>3</sup>Data on maternal smoking has 12 missing.

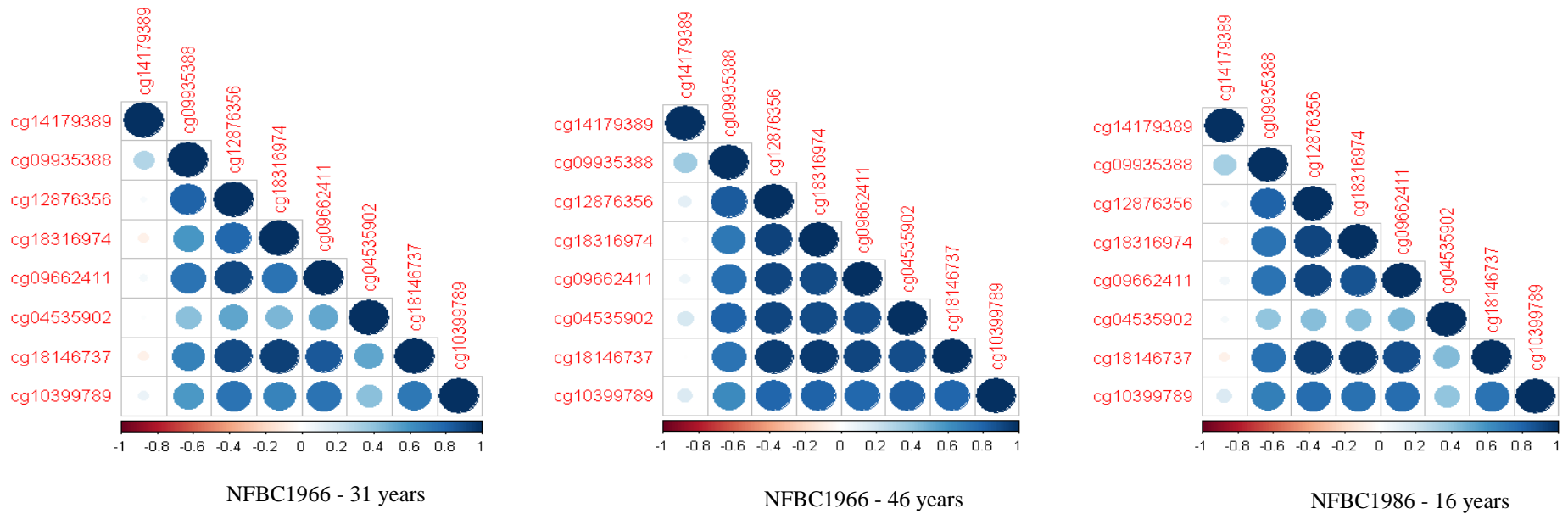
Unexposed group was defined as no maternal smoking during pregnancy and exposed group as any smoking during pregnancy.

Adult smoking is defined as cigarette  $\geq 1$  per day.

*P*-values are given for independent samples t-test (continuous) or chi-square test (categorical).

Abbreviations: BMI – Body Mass Index; WC – Waist Circumference; TG – Triglycerides; HDL-C – High Density Lipoprotein Cholesterol; FG – Fasting Glucose; DBP – Diastolic Blood Pressure; SBP – Systolic Blood Pressure; NA – Not available.

**Table S2: Correlation matrix for the eight *GFII*-CpGs in NFBC66-31, NFBC66-46 and NFBC86-16 years (n=1,968)**



Blue circle represents positive correlations and red circle represents negative correlations. Strength of correlation between the CpGs is reflected by the size of the dot.  
 Studies included: The two follow-up datasets from Northern Finland Birth cohort 1966 (NFBC1966-31years and NFBC1966-46years) and Northern Finland Birth cohort 1986 (NFBC1986).

**Table S3: Meta-analysis effect size of DNA methylation at the eight *GFI1*-CpGs by maternal prenatal smoking across the five participating studies (n=4,230)**

	Model 1					Model 2				
	Estimate ( $\beta$ )	SE	<i>P</i> -value	Direction	<i>F</i> <sup>2</sup>	Estimate ( $\beta$ )	SE	<i>P</i> -value	Direction	<i>F</i> <sup>2</sup>
cg14179389	-0.03	0.003	6.30E-30	-----	12.7	-0.03	0.003	2.00E-27	-----	19.3
cg09935388	-0.03	0.004	9.21E-11	-----	12	-0.02	0.004	1.54E-09	-----	18.1
cg12876356	-0.01	0.005	0.008	-----	86.6	-0.01	0.005	0.01	-----	83
cg18316974	-0.004	0.003	0.15	-----	70.9	-0.004	0.003	0.18	-----	62.6
cg09662411	-0.009	0.004	0.01	-----	0	-0.009	0.004	0.02	---+--	0
cg18146737	-0.005	0.004	0.23	-----	74.7	-0.005	0.004	0.26	-----	66.9
cg04535902	-0.003	0.004	0.54	-----	56.1	-0.0005	0.004	0.91	-+---	41.7
cg10399789	-0.006	0.003	0.03	-----	60	-0.005	0.003	0.05	-----	49.6

Model 1: CpG = maternal smoking + technical covariates; Model 2: CpG = maternal smoking + technical covariates + sex + adult own smoking + age.  
Bonferroni corrected *P*-value threshold of  $P \leq 0.012$  has been used for the analysis.  
Maternal smoking was defined as any maternal smoking during pregnancy.  
Studies included: The Avon Longitudinal Study of Parents and Children (ALSPAC), the two subsets of the Northern Finland Birth cohort 1966 (NFBC1966-31years and NFBC1966-46years), the Northern Finland Birth cohort 1986 (NFBC1986), the Western Australian Pregnancy Cohort study (RAINE).

**Table S4: Meta-analysis effect size of DNA methylation at the eight *GFII*-CpGs by adult own smoking across the 20 participating studies (n=13,551)**

	Model 1					Model 2				
	Estimate ( $\beta$ )	SE	P-value	Direction	$I^2$	Estimate ( $\beta$ )	SE	P-value	Direction	$I^2$
cg14179389	-0.02	0.003	2.65E-10	-----+-----	93.4	-0.02	0.003	5.96E-09	-----+-----	91.1
cg09935388	-0.07	0.004	2.88E-75	-----	98.8	-0.07	0.004	4.44E-67	-----	98.8
cg12876356	-0.04	0.004	2.29E-25	-----	97.7	-0.04	0.004	4.27E-22	-----	97.5
cg18316974	-0.02	0.003	1.99E-12	-----	97.1	-0.02	0.003	8.15E-11	-----	96.7
cg09662411	-0.02	0.003	6.79E-15	-----	96.6	-0.02	0.003	4.35E-13	-----	96.2
cg18146737	-0.04	0.005	4.68E-19	-----	96.9	-0.04	0.005	7.31E-16	-----	96.6
cg04535902	-0.02	0.004	4.59E-09	-----+-----	95.6	-0.02	0.004	7.50E-08	-----+-----	95
cg10399789	-0.01	0.003	3.19E-07	-----	94.5	-0.01	0.003	1.80E-06	-----	93.7

Model 1: CpG = Adult own smoking + technical covariates; Model 2: CpG = Adult own smoking + technical covariates + sex + age.

Bonferroni corrected  $P$ -value threshold of  $P \leq 0.012$  has been used for the analysis.

Adult own smoking was defined as cigarette  $\geq 1$  per day.

Studies included: The Avon Longitudinal Study of Parents and Children (ALSPAC), BIOS consortium, the two studies from Bogalusa Heart Study (BHS – European American and African American), the Estonian Genome Centre University of Tartu (EGCUT), the Italian cardiovascular section of EPIC (EPICOR), the two independent subsets of the Epidemiologische Studie zu Chancen der Verhütung, Früherkennung und optimierten Therapie chronischer Erkrankungen in der älteren Bevölkerung (ESTHERa and ESTHERb), the Cooperative Gesundheitsforschung in der Region Augsburg (Cooperative Health Research in the Augsburg Region) F4 (KORAF4), the Lifelines Deep (LLD), the two follow-up datasets from Northern Finland Birth cohort 1966 (NFBC1966-31years and NFBC1966-46years), Northern Finland Birth cohort 1986 (NFBC1986), the Western Australian Pregnancy Cohort study (RAINE), the two independent studies from Rotterdam Study (RS) –RSIII-1 and RSII-3\_III-2, the Study of Health in Pomerania – Trend (SHIP-Trend) and the Young Finns Study 2011 (YFS). BIOS consortium includes the Cohort On Diabetes And Atherosclerosis Maastricht (CODAM), the Leiden Longevity Study (LLS), the Netherlands Twin Register study (NTR) and the Prospective Amyotrophic Lateral Sclerosis (ALS) study Netherlands (PAN).

**Table S5: Conditional analysis of meta-analysis effect size of DNA methylation at the eight *GFII*-CpGs by adult own smoking additionally adjusted for other CpGs in the 20 participating studies (n=13,551)**

	Model 1					Model 2				
	Estimate ( $\beta$ )	SE	P-value	Direction	I <sup>2</sup>	Estimate ( $\beta$ )	SE	P-value	Direction	I <sup>2</sup>
cg14179389	0.004	0.003	0.18	---++++-+-+-----	42.6	0.005	0.003	0.12	+-----+-----	30.4
cg09935388	-0.03	0.002	2.37E-47	-----	96.8	-0.03	0.002	6.98E-46	-----	96.6
cg12876356	-0.001	0.001	0.29	+-----+-----	22.5	-0.001	0.001	0.32	--+-----+-----	28
cg18316974	-0.004	0.001	0.0006	++-----+-----	57.7	-0.004	0.001	0.0005	+-----+-----	50.6
cg09662411	0.004	0.002	0.01	---+++++-----	52	0.003	0.002	0.04	+-----+-----	58.8
cg18146737	0.008	0.001	9.84E-08	+++++-----	69.8	0.008	0.001	5.80E-08	++0+++++-----	73
cg04535902	-0.001	0.003	0.66	-----+-----	0	-0.001	0.003	0.64	--+-----+-----	0
cg10399789	-0.0001	0.002	0.98	+-----+-----	59.9	0.0001	0.002	0.94	+-----+-----	48

Model 1: CpG = Adult smoking + technical covariates + other CpGs; Model 2: CpG = Adult smoking + technical covariates + other CpGs + sex + age.

Bonferroni corrected p-value threshold of  $P$ -value  $\leq 0.012$  has been used for the analysis.

Adult own smoking was defined as cigarette  $\geq 1$  per day.

Studies included: The Avon Longitudinal Study of Parents and Children (ALSPAC), BIOS consortium, the two studies from Bogalusa Heart Study (BHS – European American and African American), the Estonian Genome Centre, University of Tartu (EGCUT), the Italian cardiovascular section of EPIC (EPICOR), the two independent subsets of the Epidemiologische Studie zu Chancen der Verhütung, Früherkennung und optimierten Therapie chronischer Erkrankungen in der älteren Bevölkerung (ESTHERa and ESTHERb), the Cooperative Gesundheitsforschung in der Region Augsburg (Cooperative Health Research in the Augsburg Region) F4 (KORAF4), the Lifelines Deep (LLD), the two follow-up datasets from Northern Finland Birth cohort 1966 (NFBC1966-31years and NFBC1966-46years), Northern Finland Birth cohort 1986 (NFBC1986), the Western Australian Pregnancy Cohort study (RAINE), the two independent studies from Rotterdam Study (RS) –RSIII-1 and RSII-3\_III-2, the Study of Health in Pomerania – Trend (SHIP-Trend) and the Young Finns Study 2011 (YFS). BIOS consortium includes the Cohort On Diabetes And Atherosclerosis Maastricht (CODAM), the Leiden Longevity Study (LLS), the Netherlands Twin Register study (NTR) and the Prospective Amyotrophic Lateral Sclerosis (ALS) study Netherlands (PAN).



**Table S6: Meta-analysis effect size of cardio-metabolic phenotypes by lower DNA methylation at the eight *GFII*-CpGs across all the participating studies (n=18,212)**

	Cardio-metabolic Phenotype	Model 1					Model 2				
		Estimate ( $\beta$ )	SE	P-value	Direction	$I^2$	Estimate ( $\beta$ )	SE	P-value	Direction	$I^2$
cg14179389	BMI	0.01	0.01	0.44	+-----+-----+-----+	37.5	0.02	0.01	0.05	-+-----+-----+-----+	21.4
	WC	0.03	0.01	0.03	+-----+-----+-----+	27	0.04	0.01	0.0002	+-----+-----+-----+	15.2
	FG	0.01	0.01	0.37	+-----+-----+-----+	11	0.02	0.01	0.14	+-----+-----+-----+	0
	HDL-C	-0.001	0.01	0.92	+-----+-----+-----+	9.6	-0.002	0.008	0.79	+-----+-----+-----+	4.3
	TG	0.03	0.01	0.01	+-----+-----+-----+	53.4	0.02	0.01	0.02	+-----+-----+-----+	45.7
	DBP	0.02	0.01	0.05	+-----+-----+-----+	0	0.04	0.01	0.006	+-----+-----+-----+	0
	SBP	0.04	0.01	0.002	+-----+-----+-----+	32	0.04	0.01	0.001	+-----+-----+-----+	25.4
cg09935388	BMI	-0.07	0.01	8.1E-11	-----+-----+-----+	58.4	-0.06	0.01	1.5E-07	-----+-----+-----+	40.1
	WC	-0.05	0.01	1.8E-05	-----+-----+-----+	61.8	-0.05	0.01	0.0001	-----+-----+-----+	45
	FG	0.001	0.01	0.93	+-----+-----+-----+	0	-0.0002	0.01	0.98	+-----+-----+-----+	0
	HDL-C	-0.003	0.01	0.74	+-----+-----+-----+	47.6	0.02	0.008	0.02	+-----+-----+-----+	37.4
	TG	0.06	0.01	1.0E-09	+-----+-----+-----+	57.6	0.01	0.005	0.006	+-----+-----+-----+	51.6
	DBP	-0.04	0.01	0.0002	+-----+-----+-----+	0	-0.03	0.01	0.009	+-----+-----+-----+	0
	SBP	-0.04	0.01	0.0006	+-----+-----+-----+	4.9	-0.03	0.01	0.01	+-----+-----+-----+	0
cg12876356	BMI	-0.07	0.01	4.6E-10	-----+-----+-----+	53.9	-0.06	0.01	5.4E-08	-----+-----+-----+	38.4
	WC	-0.05	0.01	9.3E-07	+-----+-----+-----+	69.8	-0.05	0.01	6.8E-06	+-----+-----+-----+	59.3
	FG	-0.004	0.01	0.69	+-----+-----+-----+	0	-0.007	0.01	0.56	+-----+-----+-----+	0
	HDL-C	0.04	0.01	0.0001	+-----+-----+-----+	17.9	0.02	0.01	0.02	+-----+-----+-----+	0
	TG	0.04	0.01	0.001	+-----+-----+-----+	19.8	0.03	0.01	0.03	+-----+-----+-----+	0.2
	DBP	-0.03	0.01	0.002	+-----+-----+-----+	0	-0.02	0.01	0.03	+-----+-----+-----+	0
	SBP	-0.03	0.01	0.01	+-----+-----+-----+	1.7	-0.02	0.01	0.11	+-----+-----+-----+	11.1
cg18316974	BMI	-0.07	0.01	3.7E-09	-----+-----+-----+	46.4	-0.06	0.01	4.1E-07	-----+-----+-----+	33.6
	WC	-0.05	0.01	1.1E-06	-----+-----+-----+	57.1	-0.05	0.01	4.9E-06	-----+-----+-----+	44.6
	FG	-0.01	0.01	0.34	+-----+-----+-----+	0	-0.01	0.01	0.35	+-----+-----+-----+	0
	HDL-C	0.01	0.0074	0.13	+-----+-----+-----+	50.8	0.02	0.01	0.015	+-----+-----+-----+	43

	TG	0.006	0.0044	0.20	+++++-----+	30.6	0.02	0.01	0.08	+++++-----+	0
	DBP	-0.03	0.01	0.005	-----+-----+	0	-0.02	0.01	0.03	-----+-----+	0
	SBP	-0.03	0.01	0.007	-----+-----+	0	-0.02	0.01	0.04	-----+-----+	0
cg09662411	BMI	-0.05	0.01	3.1E-06	-----+-----+	40.9	-0.05	0.01	3.8E-05	+++++-----+	23.7
	WC	-0.05	0.01	2.6E-05	-----+-----+	58.7	-0.04	0.01	9.3E-05	-----+-----+	45.3
	FG	-0.01	0.01	0.39	+++++-----+	0	-0.006	0.01	0.60	+++++-----+	0
	HDL-C	0.01	0.008	0.30	-----+-----+	35	0.02	0.008	0.018	+++++-----+	19.9
	TG	0.03	0.0106	0.002	+++++-----+	0	0.02	0.01	0.07	+++++-----+	0
	DBP	-0.03	0.01	0.01	-----+-----+	0	-0.03	0.01	0.03	-----+-----+	0
	SBP	-0.03	0.01	0.006	-----+-----+	0	-0.02	0.01	0.03	-----+-----+	16.1
cg18146737	BMI	-0.07	0.01	2.0E-09	-----+-----+	47.9	-0.06	0.01	1.4E-07	-----+-----+	36.1
	WC	-0.06	0.01	1.9E-07	-----+-----+	60.8	-0.05	0.01	7.8E-07	-----+-----+	51.9
	FG	-0.01	0.01	0.46	+++++-----+	0	-0.003	0.01	0.77	+++++-----+	0
	HDL-C	0.002	0.0074	0.80	+++++-----+	51.3	0.01	0.007	0.24	+++++-----+	42.1
	TG	0.03	0.0101	0.002	+++++-----+	0	0.02	0.01	0.06	+++++-----+	0
	DBP	-0.03	0.01	0.02	-----+-----+	0	-0.02	0.01	0.09	-----+-----+	0
	SBP	-0.02	0.01	0.09	+++++-----+	0	-0.01	0.01	0.36	+++++-----+	0
cg04535902	BMI	-0.04	0.01	0.001	+++++-----+	53	-0.04	0.01	0.001	-----+-----+	26.1
	WC	-0.03	0.01	0.02	+++++-----+	44.2	-0.03	0.01	0.03	+++++-----+	18.7
	FG	-0.01	0.01	0.30	-----+-----+	0	-0.01	0.01	0.25	+++++-----+	0
	HDL-C	0.03	0.0109	0.006	+++++-----+	40.6	0.02	0.01	0.10	+++++-----+	30.3
	TG	0.03	0.01	0.01	+++++-----+	43.4	0.02	0.01	0.12	+++++-----+	36.7
	DBP	-0.02	0.01	0.07	-----+-----+	0	-0.02	0.01	0.17	-----+-----+	0
	SBP	-0.02	0.01	0.05	+++++-----+	0	-0.02	0.01	0.18	+++++-----+	12.2
cg10399789	BMI	-0.02	0.01	0.07	-----+-----+	22.1	-0.02	0.01	0.07	-----+-----+	11.5
	WC	-0.01	0.01	0.28	+++++-----+	59.4	-0.02	0.01	0.16	+++++-----+	47.4
	FG	0.002	0.01	0.86	+++++-----+	0	0.002	0.01	0.86	+++++-----+	0
	HDL-C	0.001	0.008	0.90	-----+-----+	40.6	0.01	0.01	0.04	+++++-----+	38.6
	TG	0.03	0.01	0.001	+++++-----+	49.7	0.02	0.01	0.08	+++++-----+	30.8
	DBP	0.004	0.01	0.72	+++++-----+	18.9	0.004	0.01	0.71	+++++-----+	14.9

	SBP	0.001	0.01	0.91	+++++-----+++++	25.1	0.003	0.01	0.77	+-----+++++	31.5
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Model 1: cardio-metabolic phenotype = CpG + technical covariate; Model 2: cardio-metabolic phenotype = CpG + technical covariates + age + sex + adult own smoking.  
Direction of estimate of the cardio-metabolic phenotypes is in correspondence to lower DNA methylation at the CpGs.  
Standardized values with mean=0 and standard deviation (SD) =1 were used for cardio-metabolic phenotypes and CpG methylation across all the studies in the meta-analysis.  
 $\beta$  can be interpreted as 1-SD change in cardio-metabolic phenotype per 1-SD decrease in methylation.  
According to availability in the participating studies, BMI was available in 18212, WC in 14665, HDL-C in 18212, TG in 18212, FG in 16529, DBP in 16529, and SBP in 16529 of the total individuals.  
Abbreviations: BMI – Body Mass Index; WC – Waist Circumference; TG – Triglycerides; HDL-C – High Density Lipoprotein Cholesterol; FG – Fasting Glucose; DBP – Diastolic Blood Pressure; SBP – Systolic Blood Pressure.  
Bonferroni corrected p-value threshold of  $p \leq 0.012$  has been used for the analysis.  
Studies included: The Avon Longitudinal Study of Parents and Children (ALSPAC), BIOS consortium, the two studies from Bogalusa Heart Study (BHS – European American and African American), the Estonian Genome Centre, University of Tartu (EGCUT), the Italian cardiovascular section of EPIC (EPICOR), the two independent subsets of the Epidemiologische Studie zu Chancen der Verhütung, Früherkennung und optimierten Therapie chronischer Erkrankungen in der älteren Bevölkerung (ESTHERa and ESTHERb), the Cooperative Gesundheitsforschung in der Region Augsburg (Cooperative Health Research in the Augsburg Region) F4 (KORAF4), the Lifelines Deep (LLD), The London Life Science Population study (LOLIPOP), the two follow-up datasets from Northern Finland Birth cohort 1966 (NFBC1966-31years and NFBC1966-46years), Northern Finland Birth cohort 1986 (NFBC1986), the Western Australian Pregnancy Cohort study (RAINE), the two independent studies from Rotterdam Study (RS) –RSIII-1 and RSII-3\_III-2, the Study of Health in Pomerania – Trend (SHIP-Trend) and the Young Finns Study 2011 (YFS). BIOS consortium includes the Cohort On Diabetes And Atherosclerosis Maastricht (CODAM), the Leiden Longevity Study (LLS), the Netherlands Twin Register study (NTR) and the Prospective Amyotrophic Lateral Sclerosis (ALS) study Netherlands (PAN).

**Table S7: Sensitivity analysis showing meta-analysis effect size of cardio-metabolic phenotypes by lower DNA methylation at eight *GFII*-CpGs in a subset of the European ethnicity studies (n=13,690)**

	Cardio-metabolic Phenotypes	Model 1					Model 2				
		Estimate (β)	SE	P-value	Direction	I <sup>2</sup>	Estimate (β)	SE	P-value	Direction	I <sup>2</sup>
cg14179389	BMI	0.01	0.01	0.29	+++++-----	35.3	0.03	0.01	0.03	+++++-----	16.7
	WC	0.03	0.01	0.02	+++++-----	9	0.04	0.01	0.0001	+++++-----	0.2
	FG	0.01	0.01	0.37	+++++-----	19.9	0.02	0.01	0.11	+++++-----	0
	HDL-C	-0.004	0.01	0.67	+++++-----	14.7	-0.004	0.01	0.69	+++++-----	17.1
	TG	0.03	0.01	0.02	+++++-----	60	0.02	0.01	0.05	+++++-----	52.3
	DBP	0.02	0.01	0.05	+++++-----	4.1	0.04	0.01	0.001	+++++-----	2.3
	SBP	0.03	0.01	0.009	+++++-----	37.6	0.04	0.01	0.001	+++++-----	33.8
cg09935388	BMI	-0.07	0.01	7.52E-09	-----+	41.9	-0.06	0.01	6.02E-06	-----+	8.5
	WC	-0.04	0.01	2.70E-04	-----+	41	-0.04	0.01	7.69E-04	-----+	0
	FG	0.001	0.01	9.66E-01	+++++-----	0	-0.0003	0.01	9.80E-01	+++++-----	0
	HDL-C	-0.003	0.01	0.70	+++++-----	44	0.02	0.01	1.31E-01	+++++-----	35.6
	TG	0.05	0.01	8.24E-06	+++++-----	59.1	0.01	0.01	1.78E-02	+++++-----	51.8
	DBP	-0.05	0.01	8.84E-05	-----+	0	-0.03	0.01	5.00E-03	-----+	0
	SBP	-0.04	0.01	4.90E-04	-----+	0	-0.03	0.01	6.28E-03	-----+	0
cg12876356	BMI	-0.06	0.01	6.11E-08	-----+	34.4	-0.06	0.01	4.56E-06	-----+	5.3
	WC	-0.05	0.01	3.22E-05	+++++-----	60	-0.04	0.01	1.15E-04	+++++-----	39.9
	FG	-0.00	0.01	6.66E-01	+++++-----	0	-0.01	0.01	6.63E-01	+++++-----	0
	HDL-C	0.01	0.01	0.37	+++++-----	58.3	0.02	0.01	3.67E-02	+++++-----	52.1
	TG	-0.04	0.01	2.52E-03	+++++-----	25.1	0.02	0.01	4.48E-02	+++++-----	0
	DBP	-0.04	0.01	2.23E-03	-----+	0	-0.02	0.01	3.56E-02	-----+	0
	SBP	-0.03	0.01	1.36E-02	+++++-----	0	-0.02	0.01	1.11E-01	+++++-----	7
cg18316974	BMI	-0.06	0.01	3.24E-07	+++++-----	19.6	-0.05	0.01	1.75E-05	+++++-----	7
	WC	-0.05	0.01	2.77E-05	-----+	30.3	-0.04	0.01	7.21E-05	-----+	0
	FG	-0.01	0.01	3.37E-01	+++++-----	0	-0.01	0.01	3.49E-01	+++++-----	0

	HDL-C	0.01	0.01	0.16	---+-----+	53	0.02	0.01	1.69E-02	---+-----+	46.1
	TG	0.004	0.01	3.28E-01	++++-----+	37.3	0.02	0.01	7.62E-02	++++-----+	3.3
	DBP	-0.03	0.01	5.56E-03	-+-----+	0	-0.02	0.01	2.87E-02	-+-----+	0
	SBP	-0.03	0.01	9.49E-03	-+-----+	0	-0.02	0.01	4.83E-02	-+-----+	0
cg09662411	BMI	-0.05	0.01	8.67E-05	-----+	7.1	-0.04	0.01	7.52E-04	-----+	0
	WC	-0.04	0.01	4.08E-04	-----+	39.4	-0.04	0.01	8.81E-04	-----+	12.3
	FG	-0.01	0.01	3.77E-01	+-----+	0	-0.01	0.01	5.61E-01	+-----+	0
	HDL-C	0.01	0.01	0.23	-+-----+	40.1	0.03	0.01	1.74E-02	+-----+	28.1
	TG	0.03	0.01	1.65E-02	++++-----+	0	0.02	0.01	1.39E-01	++++-----+	0
	DBP	-0.03	0.01	7.45E-03	-----+	0	-0.03	0.01	3.06E-02	-----+	0
	SBP	-0.03	0.01	9.57E-03	-----+	0	-0.02	0.01	3.99E-02	-----+	7.9
cg18146737	BMI	-0.06	0.01	2.13E-07	-----+	8.9	-0.05	0.01	9.65E-06	-----+	0
	WC	-0.05	0.01	7.89E-06	-----+	33.5	-0.05	0.01	1.89E-05	-----+	7.5
	FG	-0.01	0.01	4.67E-01	+-----+	0	-0.002	0.01	8.39E-01	+-----+	0
	HDL-C	-0.001	0.01	0.90	-+-----+	49.9	0.01	0.01	5.45E-01	-+-----+	41
	TG	0.03	0.01	5.05E-03	++++-----+	0.5	0.02	0.01	5.58E-02	++++-----+	0
	DBP	-0.03	0.01	1.54E-02	-----+	0	-0.02	0.01	7.42E-02	-----+	0
	SBP	-0.02	0.01	1.35E-01	+-----+	0	-0.01	0.01	3.73E-01	+-----+	0
cg04535902	BMI	-0.04	0.01	0.005	+-----+	43.7	-0.04	0.01	0.002	+-----+	16
	WC	-0.02	0.01	0.06	+-----+	27.8	-0.02	0.01	0.07	+-----+	0
	FG	-0.01	0.01	0.30	-+-----+	0	-0.01	0.01	0.30	-+-----+	0
	HDL-C	0.0009	0.01	0.92	++++-----+	47.7	0.01	0.01	0.42	++++-----+	38.8
	TG	0.03	0.01	0.008	++++-----+	49.9	0.02	0.01	0.09	++++-----+	36.9
	DBP	-0.02	0.01	0.09	-+-----+	0	-0.02	0.01	0.15	-+-----+	0
	SBP	-0.02	0.01	0.15	-+-----+	0	-0.01	0.01	0.24	-+-----+	14.5
cg10399789	BMI	-0.02	0.01	0.15	-----+	0	-0.02	0.01	0.19	-----+	0
	WC	-0.01	0.01	0.56	+-----+	38.6	-0.01	0.01	0.32	+-----+	13.1
	FG	0.001	0.01	0.96	+-----+	0	0.0001	0.01	0.99	+-----+	0
	HDL-C	0.01	0.01	0.53	+-----+	38.9	0.02	0.01	0.07	+-----+	38.1
	TG	0.03	0.01	0.02957	++++-----+	54.8	0.02	0.01	0.17	++++-----+	38.9

	DBP	0.004	0.01	0.75	+++++-----+++	25.9	0.002	0.01	0.83	+++++-----+++	19.4
	SBP	0.004	0.01	0.70	+++++-----+++	24.1	0.004	0.01	0.72	+++++-----+++	30.1

Model 1: cardio-metabolic phenotype = CpG + technical covariate; Model 2: cardio-metabolic phenotype = CpG + technical covariates + age + sex + adult own smoking.  
Direction of estimate of the cardio-metabolic phenotypes is in correspondence to lower DNA methylation at the CpGs.  
Standardized values with mean=0 and standard deviation (SD) =1 were used for cardio-metabolic phenotypes and CpG methylation across all the studies in the meta-analysis.  
 $\beta$  can be interpreted as 1-SD change in cardio-metabolic phenotype per 1-SD decrease in methylation.  
Abbreviations: BMI – Body Mass Index; WC – Waist Circumference; TG – Triglycerides; HDL-C – High Density Lipoprotein Cholesterol; FG – Fasting Glucose; DBP – Diastolic Blood Pressure; SBP – Systolic Blood Pressure.  
Bonferroni corrected p-value threshold of  $P \leq 0.012$  has been used for the analysis.  
Studies excluded: the Bogalusa Heart Study (BHS –African American) and The London Life Science Population study (LOLIPOP).

**Table S8: Sensitivity analysis of the association of eight *GFI1*-CpGs with former and current adult own smoking in the NFBC1966 at 31 and 46 years (n=1,456)**

<b>NFBC1966-31</b>		<b>Model 1</b>			<b>Model 2</b>		
		Estimate ( $\beta$ )	SE	<i>P</i> -value	Estimate ( $\beta$ )	SE	<i>P</i> -value
cg14179389	Former smoking	-0.18	0.08	0.03	-0.18	0.08	0.02
	Current smoking	-0.44	0.08	<.0001	-0.45	0.08	<.0001
cg09935388	Former smoking	-0.18	0.08	0.02	-0.19	0.08	0.02
	Current smoking	-0.95	0.08	<.0001	-0.95	0.08	<.0001
cg12876356	Former smoking	-0.06	0.09	0.52	-0.06	0.09	0.52
	Current smoking	-0.48	0.09	<.0001	-0.48	0.09	<.0001
cg18316974	Former smoking	-0.01	0.09	0.93	-0.01	0.09	0.93
	Current smoking	-0.28	0.09	0.002	-0.28	0.09	0.002
cg09662411	Former smoking	-0.02	0.09	0.81	-0.02	0.09	0.81
	Current smoking	-0.37	0.09	<.0001	-0.37	0.09	<.0001
cg18146737	Former smoking	-0.01	0.08	0.94	-0.01	0.08	0.95
	Current smoking	-0.27	0.08	0.001	-0.27	0.08	0.002
cg04535902	Former smoking	-0.14	0.09	0.12	-0.15	0.09	0.12
	Current smoking	-0.26	0.09	0.005	-0.26	0.09	0.01
cg10399789	Former smoking	0.01	0.09	0.92	0.01	0.09	0.89
	Current smoking	-0.22	0.09	0.01	-0.22	0.09	0.02
<b>NFBC1966-46</b>							
cg14179389	Former smoking	-0.26	0.08	0.001	-0.26	0.08	0.001
	Current smoking	-0.53	0.10	<.0001	-0.53	0.10	<.0001
cg09935388	Former smoking	-0.28	0.07	0.0002	-0.29	0.07	0.0002
	Current smoking	-1.35	0.10	<.0001	-1.35	0.10	<.0001
cg12876356	Former smoking	-0.13	0.09	0.12	-0.13	0.09	0.12
	Current smoking	-0.90	0.11	<.0001	-0.89	0.11	<.0001
cg18316974	Former smoking	-0.10	0.09	0.25	-0.10	0.09	0.25
	Current smoking	-0.76	0.12	<.0001	-0.75	0.12	<.0001
cg09662411	Former smoking	-0.04	0.09	0.65	-0.04	0.09	0.64
	Current smoking	-0.68	0.11	<.0001	-0.68	0.11	<.0001
cg18146737	Former smoking	-0.06	0.09	0.50	-0.06	0.09	0.49
	Current smoking	-0.69	0.12	<.0001	-0.69	0.12	<.0001
cg04535902	Former smoking	-0.06	0.09	0.51	-0.06	0.09	0.50
	Current smoking	-0.75	0.11	<.0001	-0.75	0.11	<.0001
cg04535902	Former smoking	-0.11	0.09	0.19	-0.11	0.09	0.19
	Current smoking	-0.61	0.11	<.0001	-0.61	0.11	<.0001

Model 1: CpG = Adult own smoking + technical covariates; Model 2: CpG = Adult own smoking + technical covariates + sex + age.  
Former smoking was defined as participants who last smoked regularly or occasionally six months ago.  
Current smoking was defined as cigarette  $\geq 1$  per day.  
Reference group included non-smokers (participants who never smoked).  
Observe that current smoking is associated with all the eight *GFI*-CpGs however, former smoking is significantly associated with only cg14179389 and cg09935388.  
Also decrease in methylation ( $\beta$ ) is observed higher in current smoking than former smoking. Thus in our study we included current smoking in the meta-analysis.  
Studies included: The two follow up subsets of Northern Finland Birth Cohort 1966 (NFBC1966) at 31 and 46 years.