Supplemental Material

Genome-Wide DNA Methylation in Peripheral Blood and Long-Term Exposure to Source-Specific Transportation Noise and Air Pollution: The SAPALDIA Study

Ikenna C. Eze, Ayoung Jeong, Emmanuel Schaffner, Faisal I. Rezwan, Akram Ghantous, Maria Foraster, Danielle Vienneau, Florian Kronenberg, Zdenko Herceg, Paolo Vineis, Mark Brink, Jean-Marc Wunderli, Christian Schindler, Christian Cajochen, Martin Röösli, John W. Holloway, Medea Imboden, and Nicole Probst-Hensch

Table of Contents

Figure S1. Distributions of the BMIQ-normalized beta values (A) and technical bias-corrected residuals (B) in the SAPALDIA study. SAPALDIA: Swiss cohort study on air pollution and lung and heart diseases in adults.

Figure S2. Distribution of transportation noise and air pollution parameters in the present study.

Additional File- Excel Document

Table S1. Spearman rank correlations of transportation noise and air pollutions exposures among the SAPALDIA participants included in the present study.

	Aircraft Lden (dB)	Railway Lden (dB)	Road traffic Lden (dB)	Aircraft Lnight (dB)	Railway Lnight (dB)	Road traffic Lnight (dB)	NO_2 ($\mu g/m^3$)	$PM_{2.5}$ ($\mu g/m^3$)
All; $n = 2,542$								
Aircraft Lden (dB)	1							
Railway Lden (dB)	0.15	1						
Road traffic Lden (dB)	0.017	0.08	1					
Aircraft Lnight (dB)	0.76	0.01	0.06	1				
Railway Lnight(dB)	0.17	0.97	0.07	0.02	1			
Road traffic Lnight (dB)	0.02	0.08	0.99	0.06	0.07	1		
NO_2 ($\mu g/m^3$)	0.09	0.23	0.40	0.15	0.25	0.40	1	
$PM_{2.5}$ ($\mu g/m^3$)	0.25	0.19	0.19	0.23	0.21	0.20	0.65	1
SAPALDIA2; $n = 1,170$								
Aircraft Lden (dB)	1							
Railway Lden (dB)	0.22	1						
Road traffic Lden (dB)	0.04	0.09	1					
Aircraft Lnight (dB)	0.89	0.16	0.11	1				
Railway Lnight(dB)	0.24	0.98	0.08	0.17	1			
Road traffic Lnight (dB)	0.04	0.09	0.99	0.11	0.08	1		
NO_2 ($\mu g/m^3$)	0.20	0.17	0.39	0.36	0.19	0.40	1	
$PM_{2.5}$ ($\mu g/m^3$)	0.25	0.20	0.20	0.34	0.22	0.20	0.72	1
SAPALDIA3; $n = 1,372$								
Aircraft Lden (dB)	1							
Railway Lden (dB)	0.13	1						
Road traffic Lden (dB)	-0.01	0.07	1					
Aircraft Lnight (dB)	0.61	-0.06	0.03	1				
Railway Lnight(dB)	0.15	0.97	0.06	-0.06	1			
Road traffic Lnight (dB)	-0.01	0.08	0.99	0.03	0.07	1		
NO_2 ($\mu g/m^3$)	0.07	0.25	0.42	0.03	0.26	0.42	1	
$PM_{2.5}$ ($\mu g/m^3$)	0.28	0.13	0.23	0.22	0.14	0.23	0.58	1

SAPALDIA: Swiss cohort study on air pollution and lung and heart diseases in adults. SAPALDIA2 and SAPALDIA3 represent the second and third waves of the SAPALDIA study. Lden: day-evening night noise level; Lnight: nighttime noise level; NO_2: nitrogen dioxide; $PM_{2.5}$: particulate matter with aerodynamic diameter <2.5 μm.

Table S2. Summary of the included participants, stratified and survey and nested study

	SAPALDIA2 [a]			SAPALDIA3 [a]		
Categorical variables, *n* (%)	All	ALEC	EXPOs-OMICS	All	ALEC	EXPOs-OMICS
All	1,170 (100)	972 (100)	198 (100)	1,372 (100)	970 (100)	402 (100)
Women	623 (53)	521 (54)	102 (52)	737 (54)	519 (54)	218 (54)
Formal education, ≤9 years	56 (5)	54 (6)	2 (1)	62 (4)	54 (5)	8 (2)
Formal education, 10-12 years	759 (65)	634 (65)	125 (63)	887 (65)	636 (66)	251 (62)
Formal education, >12 years	355 (30)	284 (29)	71 (36)	423 (31)	280 (29)	143 (36)
Smoking status, never	539 (46)	402 (41)	137 (69)	659 (48)	396 (41)	263 (65)
Smoking status, former	355 (30)	294 (30)	61 (31)	496 (36)	157 (37)	139 (35)
Smoking status, current	276 (24)	276 (29)	0 (0)	217 (16)	217 (22)	0 (0)
Passive smoke exposure	289 (25)	257 (26)	32 (16)	159 (12)	136 (14)	23 (6)
Alcohol intake >1 glass per day	456 (39)	377 (39)	79 (40)	529 (38)	374 (39)	147 (37)
Fruit intake ≤3days/week	326 (28)	183 (29)	43 (22)	280 (20)	212 (22)	68 (17)
Vegetable intake ≤ 3days/week	86 (7)	74 (7)	12 (6)	100 (7)	73 (8)	27 (7)
Urban area	689 (59)	588 (60)	101 (51)	897 (60)	587 (61)	230 (57)
Prevalent asthma	161 (14)	161 (17)	0 (0)	398 (21)	194 (20)	204 (51)
MVPA <150 minutes per week	330 (28)	286 (29)	44 (22)	354 (26)	263 (27)	91 (23)
Regular nighttime opening of windows	971 (83)	808 (83)	163 (82)	1,131 (82)	797 (82)	334 (83)
Continuous variables, median (IQR)						
Age	50 (18)	50 (18)	49 (15)	58 (18)	59 (18)	57 (18)
Body mass index (kg/m^2)	24.9 (5)	25.1 (6)	24.1 (4)	25.8 (6)	24.8 (5)	24.6 (5)
Smoking pack years	0.4 (15)	2.0 (18)	0 (1)	0 (14)	2.1 (21)	0 (3)
Neighborhood index of socio-economic position (%)	64.6 (13)	64.4 (13)	65.1 (13)	64.8 (13)	64.7 (13)	65.1 (13)
Greenness index within 1 km buffer	0.61 (0.2)	0.61 (0.2)	0.63 (0.2)	0.62 (0.2)	0.62 (0.2)	0.63 (0.2)
Aircraft Lden (dB)	30 (9)	30 (10)	30 (8)	32.7 (8)	33.4 (8)	31.7 (7)
Railway Lden (dB)	30 (11)	30.4 (11)	30 (10)	30 (7)	30 (7)	30 (7)
Road traffic Lden (dB)	53.7 (11)	53.8 (11)	53.2 (10)	53.9 (11)	53.9 (11)	53.5 (11)
NO$_2$ (µg/m^3)	20.2 (14)	20.4 (14)	19.7 (15)	16.7 (10)	16.7 (9)	16.7 (10)
PM$_{2.5}$ (µg/m^3)	14.3 (5)	14.3 (5)	13.9 (5)	12.9 (2)	12.9 (2)	12.9 (2)

SAPALDIA: Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults. ALEC: Aging lungs in European cohorts. ALEC and EXPOsOMICS are European cohort consortia in which SAPALDIA participates. MVPA: moderate to vigorous physical activity. PM$_{2.5}$: particulate matter with aerodynamic diameter <2.5 µm. NO$_2$: nitrogen dioxide. [a] Population included in the analysis was limited to participants with complete methylome, exposure, and covariate data.

Table S3. Top ten CpGs independently associated with source-specific transportation noise and air pollution in the SAPALDIA study, single exposure models.

Exposure	CpG ID	CHR	Location	Gene	Feature	Model 1				Model 2		
						Beta	SE	P-value	P (FDR)	Beta	SE	P-value
Aircraft Lden	cg02286155	5	176826262	*N.A*	N.A.	-0.007	0.001	8.05E-07	0.347	-0.007	0.001	1.08E-06
	cg21602842	18	46291908	*KIAA0427*	Body	-0.005	0.001	6.91E-06	0.579	-0.005	0.001	6.65E-06
	cg09042449	10	44064225	*ZNF239*	5UTR	-0.002	0.0004	7.30E-06	0.579	-0.002	0.000	8.33E-06
	cg16218477	7	1066167	*C7orf50*	Body	-0.004	0.001	8.15E-06	0.579	-0.004	0.001	6.82E-06
	cg10975000	13	28371375	*N.A*	N.A.	-0.002	0.001	1.12E-05	0.579	-0.002	0.001	1.15E-05
	cg22979422	12	56694490	*CS*	TSS1500	-0.010	0.002	1.27E-05	0.579	-0.010	0.002	1.22E-05
	cg15063530	2	17716941	*N.A*	N.A.	-0.009	0.002	1.29E-05	0.579	-0.009	0.002	1.28E-05
	cg21903378	14	104686811	*N.A*	N.A.	-0.009	0.002	1.52E-05	0.579	-0.008	0.002	2.18E-05
	cg04635504	11	2829241	*KCNQ1*	Body	-0.005	0.001	1.63E-05	0.579	-0.005	0.001	1.59E-05
	cg25462190	5	177547067	*N4BP3*	Body	-0.007	0.002	1.66E-05	0.579	-0.007	0.002	1.40E-05
Railway Lden	cg25201280	15	35838552	*ATPBD4*	TSS200	-0.001	0.0002	1.78E-07	0.077	-0.001	0.0002	2.07E-07
	cg24653263	5	38258335	*EGFLAM*	TSS200	-0.003	0.001	1.24E-06	0.233	-0.003	0.001	1.42E-06
	cg16825060	8	144242342	*LY6H*	TSS1500	-0.003	0.001	2.45E-06	0.233	-0.003	0.001	2.72E-06
	cg23468045	5	12669584	*N.A*	N.A.	0.001	0.0002	2.46E-06	0.233	0.001	0.0002	2.25E-06
	cg07461273	7	99697172	*MCM7*	Body	-0.004	0.001	2.71E-06	0.233	-0.004	0.001	2.73E-06
	cg01301319	7	27153580	*HOXA3*	5UTR	-0.003	0.001	4.42E-06	0.261	-0.003	0.001	4.29E-06
	cg19270309	17	77712853	*ENPP7*	3UTR	0.002	0.0005	4.48E-06	0.261	0.002	0.0005	4.85E-06
	cg13402217	1	151584375	*SNX27*	TSS1500	-0.003	0.001	5.26E-06	0.261	-0.003	0.001	4.63E-06
	cg18076500	19	11640020	*ECSIT*	TSS200	-0.001	0.0001	6.44E-06	0.261	-0.001	0.0001	6.16E-06
	cg20497635	17	998504	*ABR*	Body	0.004	0.001	6.90E-06	0.261	0.004	0.001	8.21E-06
Road traffic Lden	cg01836943	12	23267824	*N.A*	N.A.	0.001	0.0002	8.50E-07	0.366	0.001	0.0002	1.09E-06
	cg14328230	19	17830207	*MAP1S*	TSS200	-0.0003	0.0001	4.65E-06	0.492	-0.0003	0.0001	6.51E-06
	cg01066220	6	31696240	*DDAH2*	Body	0.0005	0.0001	5.40E-06	0.492	0.0005	0.0001	7.15E-06
	cg09129334	13	111837676	*ARHGEF7*	Body	-0.007	0.001	7.12E-06	0.492	-0.007	0.001	8.81E-06
	cg17765713	4	128801754	*PLK4*	TSS1500	-0.001	0.0003	1.07E-05	0.492	-0.002	0.0003	7.97E-06
	cg22530293	1	2458418	*PANK4*	TSS1500	-0.001	0.0002	1.22E-05	0.492	-0.001	0.0002	1.42E-05
	cg14748795	10	101283090			-0.005	0.001	1.25E-05	0.492	-0.005	0.001	1.41E-05

Exposure	CpG	CHR	Position	Gene	Region	Beta	SE	P-value	FDR	Beta	SE	P-value
	cg10447111	12	4647897	*RAD51AP1*	TSS200	-0.001	0.0003	1.55E-05	0.492	-0.001	0.0003	1.01E-05
	cg07929259	14	38031240	*N.A*	N.A.	0.001	0.0002	1.67E-05	0.492	0.001	0.0002	2.19E-05
	cg06646021	1	229406520	*RAB4A*	TSS1500	-0.004	0.001	1.91E-05	0.492	-0.004	0.001	2.08E-05
NO$_2$	cg04337651	2	239344738	*ASB1*	Body	0.003	0.001	1.08E-06	0.421	0.003	0.001	1.78E-06
	cg01493658	9	133588893	*ABL1*	TSS1500	-0.0004	0.0001	2.08E-06	0.421	-0.0004	0.0001	2.50E-06
	cg06826760	1	193076307	*GLRX2*	TSS1500	0.005	0.001	3.05E-06	0.421	0.005	0.001	3.46E-06
	cg26814835	20	30195969	*N.A*	N.A.	0.001	0.0003	4.66E-06	0.421	0.001	0.0003	4.47E-06
	cg18601596	6	39283313	*KCNK16*	Body	0.005	0.001	4.89E-06	0.421	0.005	0.001	5.71E-06
	cg18809706	7	143209945	*N.A*	N.A.	0.001	0.0002	6.62E-06	0.452	0.001	0.0002	4.32E-06
	cg10145926	14	95875792	*C14orf139*	Body	0.002	0.0005	7.35E-06	0.452	0.0022	0.0005	7.49E-06
	cg11844697	17	80935769	*B3GNTL1*	Body	0.0004	0.0001	9.08E-06	0.471	0.0004	0.0001	1.46E-05
	cg18156543	17	48172978	*PDK2*	Body	-0.001	0.0003	9.85E-06	0.471	-0.001	0.0003	1.77E-05
	cg11856476	12	77064229	*N.A*	N.A.	0.001	0.0002	1.48E-05	0.556	0.0008	0.0002	1.35E-05
PM$_{2.5}$	cg26704043	6	5282702	*FARS2*	5UTR	0.014	0.003	9.21E-08 [a]	0.040	0.013	0.003	1.66E-07
	cg20099458	7	5272275	*WIPI2*	3UTR	0.014	0.003	5.08E-07	0.109	0.014	0.003	5.30E-07
	cg25029903	2	44105057	*ABCG8*	3UTR	0.017	0.004	8.22E-07	0.118	0.017	0.004	1.28E-06
	cg25162533	17	81032067	*N.A*	N.A.	0.019	0.004	1.15E-06	0.124	0.020	0.004	4.73E-07
	cg14531665	9	91058614	*SPIN1*	Body	0.011	0.002	2.00E-06	0.133	0.011	0.002	2.89E-06
	cg20703242	1	230279135	*GALNT2*	Body	0.014	0.003	2.86E-06	0.133	0.014	0.003	3.56E-06
	cg00486143	7	127774154	*N.A*	N.A.	0.011	0.002	2.95E-06	0.133	0.011	0.002	3.12E-06
	cg02194396	19	427162	*SHC2*	Body	0.017	0.004	2.95E-06	0.133	0.017	0.004	3.67E-06
	cg02740308	2	132414348	*N.A*	N.A.	0.020	0.004	3.31E-06	0.133	0.020	0.004	3.31E-06
	cg17112266	7	150737198	*ABCB8*	Body	0.009	0.002	3.50E-06	0.133	0.009	0.002	4.18E-06

CpG: Cytosine-phosphate-Guanine. SAPALDIA: Swiss cohort study on air pollution and lung and heart diseases in adults. CHR: chromosome. SE: standard error. FDR: false discovery rate. Lden: day-evening-night noise level. NO$_2$: nitrogen dioxide. PM$_{2.5}$: particulate matter with aerodynamic diameter <2.5 µm. Beta coefficients represent increase or decrease in DNA methylation per 10dB increase in aircraft, railway or road traffic Lden or 10 µg/m^3 increase in NO$_2$ or PM$_{2.5}$. All estimates were from single exposure epigenome-wide linear mixed-effects models, with random intercept at the level of participant. In a preliminary step, DNA methylation β-values were regressed on the Illumina control probe-derived first 30 principal components to correct for correlation structures and technical bias, and residuals of these regressions covering 430,477 CpGs were used as the technical bias-corrected methylation level at the CpG sites. Extreme values of the residuals (lying beyond three times the interquartile range below the first quartile and above the third quartile at each CpG site) were replaced with their corresponding detection threshold value ("modified winsorization"). The "winsorized" data were then used as the dependent variables in the epigenome-wide association study. N.A.: not annotated. [a] Significant at Bonferroni-corrected p-value of 1.16E-07. Model 1: adjusted for age, sex, educational level, area, and neighborhood socio-economic status, greenness index, smoking status and pack years, exposure to passive smoke, consumption of fruits, vegetables and alcohol, nested study, asthma status, survey, source-specific noise truncation indicator (for Lden models) and leukocyte composition. Model 2: Model 1 + body mass index and physical activity.

Table S4. Top ten CpGs independently associated with source-specific transportation noise and air pollution in the multi-exposure model, stratified by nested study.

					All				ALEC			EXPOs OMICS		
Exposure	CpG ID	CHR	Location	Gene	Beta	SE	P-value	P (FDR)	Beta	SE	P-value	Beta	SE	P-value
Aircraft Lden	cg02286155	5	176826262	*N.A.*	-0.007	0.001	1.48E-06	0.637	-0.006	0.002	1.65E-04	-0.008	0.003	9.11E-03
	cg15063530	2	17716941	*N.A.*	-0.009	0.002	8.14E-06	0.659	-0.012	0.002	3.38E-07	-0.001	0.004	7.44E-01
	cg16218477	7	1066167	*C7orf50*	-0.004	0.001	8.53E-06	0.659	-0.004	0.001	1.03E-04	-0.004	0.002	7.11E-02
	cg21602842	18	46291908	*KIAA0427*	-0.005	0.001	9.84E-06	0.659	-0.004	0.001	1.48E-03	-0.008	0.002	1.14E-03
	cg09042449	10	44064225	*ZNF239*	-0.002	0.0004	1.06E-05	0.659	-0.002	0.0005	2.88E-04	-0.002	0.001	2.02E-02
	cg10975000	13	28371375	*N.A.*	-0.002	0.0005	1.12E-05	0.659	-0.003	0.001	4.58E-06	-0.001	0.001	2.79E-01
	cg06220958	17	10452851	*MYH2*	0.011	0.002	1.24E-05	0.659	0.010	0.003	1.64E-04	0.011	0.005	3.72E-02
	cg25462190	5	177547067	*N4BP3*	-0.007	0.002	1.32E-05	0.659	-0.005	0.002	9.91E-04	-0.009	0.004	1.19E-02
	cg11944797	13	99135711	*STK24*	-0.001	0.0003	1.38E-05	0.659	-0.001	0.0003	1.86E-02	-0.003	0.001	1.12E-04
	cg04635504	11	2829241	*KCNQ1*	-0.005	0.001	1.61E-05	0.664	-0.006	0.001	9.97E-06	-0.003	0.003	3.31E-01
Railway Lden	cg25201280	15	35838552	*ATPBD4*	-0.001	0.0002	1.74E-07	0.075	-0.001	0.0002	1.39E-05	-0.001	0.0003	1.60E-03
	cg24653263	5	38258335	*EGFLAM*	-0.003	0.001	8.97E-07	0.193	-0.003	0.001	8.98E-05	-0.005	0.002	1.63E-03
	cg16825060	8	144242342	*LY6H*	-0.003	0.001	2.34E-06	0.256	-0.003	0.001	6.62E-05	-0.003	0.001	3.24E-02
	cg23468045	5	12669584	*N.A.*	0.001	0.0002	2.37E-06	0.256	0.001	0.0003	1.99E-04	0.002	0.001	9.36E-03
	cg19270309	17	77712853	*ENPP7*	0.002	0.0005	3.25E-06	0.266	0.002	0.001	4.87E-05	0.002	0.001	1.40E-02
	cg07461273	7	99697172	*MCM7*	-0.004	0.001	3.78E-06	0.266	-0.003	0.001	1.21E-03	-0.006	0.002	6.75E-04
	cg01301319	7	27153580	*HOXA3*	-0.003	0.001	4.60E-06	0.266	-0.002	0.001	5.57E-04	-0.005	0.001	1.43E-03
	cg23113715	22	25800663	*N.A.*	-0.004	0.001	5.79E-06	0.266	-0.005	0.001	6.26E-06	-0.003	0.002	1.24E-01
	cg13402217	1	151584375	*SNX27*	-0.003	0.001	6.03E-06	0.266	-0.002	0.001	9.42E-04	-0.005	0.002	3.95E-03
	cg24047259	14	65347275	*N.A.*	-0.001	0.0003	7.35E-06	0.266	-0.001	0.0003	4.26E-04	-0.002	0.001	1.36E-02
Road traffic Lden	cg09129334	13	111837676	*ARHGEF7*	-0.007	0.001	1.73E-06	0.384	-0.007	0.002	2.39E-05	-0.007	0.004	4.62E-02
	cg17383236	7	100167504	*N.A.*	-0.002	0.0005	2.76E-06	0.384	-0.002	0.001	3.24E-04	-0.003	0.001	1.97E-02
	cg01066220	6	31696240	*DDAH2*	0.001	0.0001	3.48E-06	0.384	0.0005	0.0001	7.43E-05	0.001	0.0003	1.95E-02
	cg23910243	16	31484618	*TGFB1I1*	-0.002	0.0005	4.32E-06	0.384	-0.002	0.001	7.61E-05	-0.002	0.001	2.27E-02
	cg06646021	1	229406520	*RAB4A*	-0.005	0.001	4.47E-06	0.384	-0.005	0.001	7.03E-06	-0.002	0.002	2.88E-01

Exposure	CpG	CHR	Position	Gene	Beta	SE	p	FDR	Beta	SE	p	Beta	SE	p
	cg03066594	20	10415919	*C20orf94*	0.0005	0.0001	6.00E-06	0.386	0.0005	0.0001	2.97E-06	0.0002	0.0002	2.86E-01
	cg03966094	22	21058792	*TMEM191A*	-0.003	0.001	7.06E-06	0.386	-0.002	0.001	1.18E-03	-0.005	0.001	6.86E-04
	cg13948857	5	131763756	*C5orf56*	-0.003	0.001	7.17E-06	0.386	-0.002	0.001	3.33E-03	-0.005	0.002	7.71E-03
	cg08351004	2	172965650	*DLX2*	-0.002	0.0005	9.53E-06	0.456	-0.002	0.001	9.02E-05	-0.002	0.001	3.34E-02
	cg13777730	1	234793300	*N.A.*	-0.003	0.001	1.07E-05	0.458	-0.002	0.001	3.56E-03	-0.006	0.002	1.87E-03
NO_2	cg04337651	2	239344738	*ASB1*	0.004	0.001	2.06E-06	0.657	0.003	0.001	1.28E-04	0.005	0.002	8.00E-03
	cg18776472	10	50732819	*ERCC6*	-0.001	0.0002	8.20E-06	0.657	-0.0004	0.0001	1.20E-02	-0.002	0.001	1.16E-04
	cg18601596	6	39283313	*KCNK16*	0.006	0.001	8.21E-06	0.657	0.004	0.001	1.73E-03	0.012	0.003	1.00E-04
	cg12392998	17	79550668	*NPLOC4*	-0.002	0.0004	8.72E-06	0.657	-0.002	0.0005	3.46E-05	-0.001	0.001	1.21E-01
	cg16550606	13	50160670	*RCBTB1*	0.004	0.001	1.33E-05	0.657	0.005	0.001	5.39E-06	0.0004	0.002	8.53E-01
	cg25266109	19	12404608	*ZNF44*	-0.0004	0.0001	1.38E-05	0.657	-0.0004	0.0001	2.90E-04	-0.0004	0.0002	7.85E-02
	cg01746514	14	24520922	*LRRC16B*	-0.001	0.0002	1.43E-05	0.657	-0.001	0.0003	9.85E-05	-0.001	0.0005	4.20E-02
	cg15811902	15	75918385	*SNUPN*	-0.002	0.0005	1.61E-05	0.657	-0.003	0.001	7.41E-06	-0.001	0.001	3.74E-01
	cg26898336	17	15244519	*TEKT3*	0.002	0.0005	1.65E-05	0.657	0.002	0.001	8.41E-04	0.004	0.001	3.09E-03
	cg21099332	5	39270715	*N.A.*	0.004	0.001	1.66E-05	0.657	0.004	0.001	3.11E-05	0.003	0.002	2.52E-01
$PM_{2.5}$	cg26704043	6	5282702	*FARS2*	0.014	0.003	4.18E-07	0.180	0.009	0.003	1.98E-03	0.023	0.007	7.68E-04
	cg05157625	14	93153553	*RIN3*	0.021	0.004	1.08E-06	0.231	0.020	0.005	2.00E-05	0.024	0.012	4.59E-02
	cg20099458	7	5272275	*WIPI2*	0.014	0.003	1.61E-06	0.231	0.010	0.003	1.41E-03	0.026	0.007	3.56E-04
	cg06587257	12	50452135	*ACCN2*	0.022	0.005	2.71E-06	0.292	0.018	0.005	8.16E-04	0.043	0.011	5.78E-05
	cg14531665	9	91058614	*SPIN1*	0.012	0.003	5.91E-06	0.398	0.009	0.003	2.72E-04	0.010	0.007	1.64E-01
	cg06526020	6	34308880	*NUDT3*	0.029	0.006	6.43E-06	0.398	0.022	0.007	1.25E-03	0.035	0.016	3.01E-02
	cg21058520	6	100914733	*N.A.*	0.004	0.001	6.76E-06	0.398	0.002	0.001	8.41E-02	0.010	0.002	5.09E-06
	cg16259904	10	134146220	*LRRC27*	0.027	0.006	8.90E-06	0.398	0.023	0.007	4.20E-04	0.024	0.015	9.98E-02
	cg12770741	17	883776	*NXN*	0.018	0.004	9.15E-06	0.398	0.020	0.005	8.90E-06	0.005	0.009	6.17E-01
	cg26750893	2	38043481	*N.A.*	0.016	0.004	1.05E-05	0.398	0.017	0.004	8.33E-06	0.007	0.010	4.57E-01

CpG: Cytosine-phosphate-Guanine. ALEC: Aging lungs in European cohorts. CHR: chromosome. SE: standard error. FDR: false discovery rate. Lden: day-evening-night noise level. NO_2: nitrogen dioxide. $PM_{2.5}$: particulate matter with aerodynamic diameter <2.5 µm. Beta coefficients represent increase or decrease in DNA methylation per 10 dB increase in aircraft, railway or road traffic Lden or 10 µg/m^3 increase in NO_2 or $PM_{2.5}$. All estimates were from multi-exposure epigenome-wide mixed linear models, with random intercept at the level of participant, adjusted for age, sex, educational level, area, neighborhood socio-economic status, greenness index, smoking status, smoking pack years, exposure to passive smoke, consumption of fruits, vegetables and alcohol, asthma status, survey, noise truncation indicators and leukocyte composition. Multi-exposure models included all five exposures (Aircraft, railway, road traffic Lden, NO_2 and $PM_{2.5}$) at the same time. In a preliminary step, DNA methylation β-values were regressed on the Illumina control probe-derived first 30 principal components to correct for correlation structures and technical bias, and residuals of these regressions covering 430,477 CpGs were used as the technical bias-corrected methylation level at the CpG sites. Extreme values of the residuals (lying beyond three times the interquartile range below the first quartile and above the third quartile at each CpG site) were replaced with their corresponding detection threshold value ("modified

winsorization"). The "winsorized" data were then used as the dependent variables in the epigenome-wide association study. N (all) = 1,389 (2542 observations). N (ALEC) = 985 (1942 observations). N (EXPOsOMICS) = 404 (600 observations). ALEC and EXPOsOMICS are European cohort consortia in which SAPALDIA participates. *N.A.*: not annotated.

Table S5. Sensitivity of source-specific transportation noise and air pollution-related CpGs to nighttime window-opening behavior of participants

Exposure	CpG ID	CHR	Location	Gene	Main model; all				Main model; regular open windows		
					Beta	SE	P-value	P (FDR)	Beta	SE	P-value
Aircraft Lden	cg02286155	5	176826262	*N.A.*	-0.007	0.001	1.48E-06	0.637	-0.008	0.002	1.30E-06
	cg15063530	2	17716941	*N.A.*	-0.009	0.002	8.14E-06	0.659	-0.009	0.002	4.76E-05
	cg16218477	7	1066167	*C7orf50*	-0.004	0.001	8.53E-06	0.659	-0.004	0.001	7.82E-05
	cg21602842	18	46291908	*KIAA0427*	-0.005	0.001	9.84E-06	0.659	-0.005	0.001	1.07E-04
	cg09042449	10	44064225	*ZNF239*	-0.002	0.0004	1.06E-05	0.659	-0.002	0.0004	3.69E-05
	cg10975000	13	28371375	*N.A.*	-0.002	0.0005	1.12E-05	0.659	-0.002	0.001	9.62E-05
	cg06220958	17	10452851	*MYH2*	0.011	0.002	1.24E-05	0.659	0.012	0.003	9.60E-06
	cg25462190	5	177547067	*N4BP3*	-0.007	0.002	1.32E-05	0.659	-0.006	0.002	9.72E-04
	cg11944797	13	99135711	*STK24*	-0.001	0.0003	1.38E-05	0.659	-0.002	0.0004	1.12E-05
	cg04635504	11	2829241	*KCNQ1*	-0.005	0.001	1.61E-05	0.664	-0.005	0.001	1.05E-04
Railway Lden	cg25201280	15	35838552	*ATPBD4*	-0.001	0.0002	1.74E-07	0.075	-0.001	0.0002	8.85E-07
	cg24653263	5	38258335	*EGFLAM*	-0.003	0.001	8.97E-07	0.193	-0.004	0.001	2.62E-06
	cg16825060	8	144242342	*LY6H*	-0.003	0.001	2.34E-06	0.256	-0.003	0.001	9.78E-07
	cg23468045	5	12669584	*N.A.*	0.001	0.0002	2.37E-06	0.256	0.001	0.0003	7.97E-05
	cg19270309	17	77712853	*ENPP7*	0.002	0.0005	3.25E-06	0.266	0.002	0.0005	4.41E-04
	cg07461273	7	99697172	*MCM7*	-0.004	0.001	3.78E-06	0.266	-0.004	0.001	2.29E-05
	cg01301319	7	27153580	*HOXA3*	-0.003	0.001	4.60E-06	0.266	-0.003	0.001	1.95E-04
	cg23113715	22	25800663	*N.A.*	-0.004	0.001	5.79E-06	0.266	-0.005	0.001	5.72E-06
	cg13402217	1	151584375	*SNX27*	-0.003	0.001	6.03E-06	0.266	-0.003	0.001	2.82E-06
	cg24047259	14	65347275	*N.A.*	-0.001	0.0003	7.35E-06	0.266	-0.001	0.0003	2.55E-06
Road traffic Lden	cg09129334	13	111837676	*ARHGEF7*	-0.007	0.001	1.73E-06	0.384	-0.008	0.002	1.35E-05
	cg17383236	7	100167504	*N.A.*	-0.002	0.0005	2.76E-06	0.384	-0.002	0.001	1.26E-03
	cg01066220	6	31696240	*DDAH2*	0.001	0.0001	3.48E-06	0.384	0.0004	0.0001	9.77E-04
	cg23910243	16	31484618	*TGFB1I1*	-0.002	0.0005	4.32E-06	0.384	-0.002	0.0005	3.61E-06

	CpG	CHR	Position	Gene	Beta	SE	P-value	FDR	Beta	SE	P-value
	cg06646021	1	229406520	*RAB4A*	-0.005	0.001	4.47E-06	0.384	-0.005	0.001	1.57E-05
	cg03066594	20	10415919	*C20orf94*	0.0005	0.0001	6.00E-06	0.386	0.0005	0.0001	5.26E-05
	cg03966094	22	21058792	*TMEM191A*	-0.003	0.001	7.06E-06	0.386	-0.003	0.001	1.34E-05
	cg13948857	5	131763756	*C5orf56*	-0.003	0.001	7.17E-06	0.386	-0.003	0.001	1.96E-04
	cg08351004	2	172965650	*DLX2*	-0.002	0.0005	9.53E-06	0.456	-0.003	0.0005	1.60E-06
	cg13777730	1	234793300	*N.A.*	-0.003	0.001	1.07E-05	0.458	-0.003	0.001	3.88E-05
NO$_2$	cg04337651	2	239344738	*ASB1*	0.004	0.001	2.06E-06	0.657	0.003	0.001	5.08E-05
	cg18776472	10	50732819	*ERCC6*	-0.001	0.0002	8.20E-06	0.657	-0.001	0.0002	1.08E-04
	cg18601596	6	39283313	*KCNK16*	0.006	0.001	8.21E-06	0.657	0.006	0.002	4.05E-05
	cg12392998	17	79550668	*NPLOC4*	-0.002	0.0004	8.72E-06	0.657	-0.002	0.0005	1.07E-05
	cg16550606	13	50160670	*RCBTB1*	0.004	0.001	1.33E-05	0.657	0.004	0.001	4.67E-05
	cg25266109	19	12404608	*ZNF44*	-0.0004	0.0001	1.38E-05	0.657	-0.0005	0.0001	5.83E-05
	cg01746514	14	24520922	*LRRC16B*	-0.001	0.0002	1.43E-05	0.657	-0.001	0.0003	5.17E-07
	cg15811902	15	75918385	*SNUPN*	-0.002	0.0005	1.61E-05	0.657	-0.002	0.001	2.55E-05
	cg26898336	17	15244519	*TEKT3*	0.002	0.0005	1.65E-05	0.657	0.003	0.001	2.36E-06
	cg21099332	5	39270715	*N.A.*	0.004	0.001	1.66E-05	0.657	0.005	0.001	3.90E-06
PM$_{2.5}$	cg26704043	6	5282702	*FARS2*	0.014	0.003	4.18E-07	0.180	0.014	0.003	1.28E-05
	cg05157625	14	93153553	*RIN3*	0.021	0.004	1.08E-06	0.231	0.022	0.005	2.00E-05
	cg20099458	7	5272275	*WIPI2*	0.014	0.003	1.61E-06	0.231	0.014	0.003	4.66E-05
	cg06587257	12	50452135	*ACCN2*	0.022	0.005	2.71E-06	0.292	0.024	0.006	2.48E-05
	cg14531665	9	91058614	*SPIN1*	0.012	0.003	5.91E-06	0.398	0.013	0.003	7.31E-06
	cg06526020	6	34308880	*NUDT3*	0.029	0.006	6.43E-06	0.398	0.031	0.007	3.07E-05
	cg21058520	6	100914733	*N.A.*	0.004	0.001	6.76E-06	0.398	0.004	0.001	7.15E-05
	cg16259904	10	134146220	*LRRC27*	0.027	0.006	8.90E-06	0.398	0.026	0.007	1.95E-04
	cg12770741	17	883776	*NXN*	0.018	0.004	9.15E-06	0.398	0.015	0.005	9.64E-04
	cg26750893	2	38043481	*N.A.*	0.016	0.004	1.05E-05	0.398	0.018	0.004	5.28E-05

CpG: Cytosine-phosphate-Guanine. CHR: chromosome. SE: standard error. FDR: false discovery rate. Lden: day-evening-night noise level. NO$_2$: nitrogen dioxide. PM$_{2.5}$: particulate matter with aerodynamic diameter <2.5 μm. Beta coefficients represent increase or decrease in DNA methylation per 10 dB increase in aircraft, railway or road traffic Lden or 10 μg/m^3 increase in NO$_2$ or PM$_{2.5}$. All estimates were from multi-exposure linear mixed-effects models (containing all exposures), with participant-level random intercept, adjusted for age, sex, education, area, neighborhood socio-economic status, greenness index, smoking status, pack years, passive smoke, consumption of fruits, vegetables and alcohol, asthma status, survey and leukocyte composition. In a preliminary step, DNA methylation β-values were regressed on the Illumina control probe-derived first 30 principal components to correct for correlation structures and technical bias, and residuals of these regressions covering 430,477 CpGs were used as the technical bias-corrected methylation level at the CpG sites. Extreme values of the residuals (lying beyond three times the interquartile range

below the first quartile and above the third quartile at each CpG site) were replaced with their corresponding detection threshold value ("modified winsorization"). The "winsorized" data were then used as the dependent variables in the epigenome-wide association study. N (all) = 1,389 (2,542 observations); N (nighttime regular open windows) = 1,150 (2,517 observations). *N.A.*: not annotated.

Table S6. Sensitivity of source-specific transportation noise and air pollution-related CpGs to "non-winsorization" of extreme methylation values

Exposure	CpG ID	CHR	Location	Gene	Main model				"Non-winsorized" model			N (EV)
					Beta	SE	P-value	P (FDR)	Beta	SE	P-value	
Aircraft Lden	cg02286155	5	176826262	*N.A.*	-0.007	0.001	1.48E-06	0.637	-0.007	0.002	2.87E-06	4
	cg15063530	2	17716941	*N.A.*	-0.009	0.002	8.14E-06	0.659	-0.010	0.002	9.20E-06	32
	cg16218477	7	1066167	*C7orf50*	-0.004	0.001	8.53E-06	0.659	-0.004	0.001	1.18E-05	2
	cg21602842	18	46291908	*KIAA0427*	-0.005	0.001	9.84E-06	0.659	-0.005	0.001	9.84E-06	1
	cg09042449	10	44064225	*ZNF239*	-0.002	0.0004	1.06E-05	0.659	-0.002	0.0004	1.24E-05	3
	cg10975000	13	28371375	*N.A.*	-0.002	0.0005	1.12E-05	0.659	-0.003	0.001	1.02E-04	28
	cg06220958	17	10452851	*MYH2*	0.011	0.002	1.24E-05	0.659	0.011	0.002	1.10E-05	7
	cg25462190	5	177547067	*N4BP3*	-0.007	0.002	1.32E-05	0.659	-0.007	0.002	2.45E-05	6
	cg11944797	13	99135711	*STK24*	-0.001	0.0003	1.38E-05	0.659	-0.001	0.001	2.02E-02	8
	cg04635504	11	2829241	*KCNQ1*	-0.005	0.001	1.61E-05	0.664	-0.005	0.001	2.12E-05	5
Railway Lden	cg25201280	15	35838552	*ATPBD4*	-0.001	0.0002	1.74E-07	0.075	-0.001	0.0002	2.07E-05	13
	cg24653263	5	38258335	*EGFLAM*	-0.003	0.001	8.97E-07	0.193	-0.004	0.001	1.05E-05	29
	cg16825060	8	144242342	*LY6H*	-0.003	0.001	2.34E-06	0.256	-0.003	0.001	1.41E-06	6
	cg23468045	5	12669584	*N.A.*	0.001	0.0002	2.37E-06	0.256	0.001	0.0003	6.01E-06	13
	cg19270309	17	77712853	*ENPP7*	0.002	0.0005	3.25E-06	0.266	0.003	0.0005	2.19E-06	37
	cg07461273	7	99697172	*MCM7*	-0.004	0.001	3.78E-06	0.266	-0.004	0.001	3.23E-06	2
	cg01301319	7	27153580	*HOXA3*	-0.003	0.001	4.60E-06	0.266	-0.003	0.001	5.43E-06	7
	cg23113715	22	25800663	*N.A.*	-0.004	0.001	5.79E-06	0.266	-0.005	0.001	1.22E-05	38
	cg13402217	1	151584375	*SNX27*	-0.003	0.001	6.03E-06	0.266	-0.003	0.001	6.03E-06	0
	cg24047259	14	65347275	*N.A.*	-0.001	0.0003	7.35E-06	0.266	-0.001	0.0003	7.86E-06	9
Road traffic Lden	cg09129334	13	111837676	*ARHGEF7*	-0.007	0.001	1.73E-06	0.384	-0.007	0.002	1.80E-06	3
	cg17383236	7	100167504	*N.A.*	-0.002	0.0005	2.76E-06	0.384	-0.003	0.001	2.10E-06	4
	cg01066220	6	31696240	*DDAH2*	0.001	0.0001	3.48E-06	0.384	0.0005	0.0001	3.72E-06	8

	CpG	CHR	Position	Gene	Beta	SE	P-value	FDR	Beta	SE	P-value	EV
	cg23910243	16	31484618	*TGFB1I1*	-0.002	0.0005	4.32E-06	0.384	-0.002	0.0005	2.68E-06	20
	cg06646021	1	229406520	*RAB4A*	-0.005	0.001	4.47E-06	0.384	-0.005	0.001	4.31E-06	8
	cg03066594	20	10415919	*C20orf94*	0.0005	0.0001	6.00E-06	0.386	0.0005	0.0001	7.00E-06	3
	cg03966094	22	21058792	*TMEM191A*	-0.003	0.001	7.06E-06	0.386	-0.003	0.001	7.06E-06	0
	cg13948857	5	131763756	*C5orf56*	-0.003	0.001	7.17E-06	0.386	-0.003	0.001	7.17E-06	0
	cg08351004	2	172965650	*DLX2*	-0.002	0.0005	9.53E-06	0.456	-0.002	0.0005	1.95E-04	24
	cg13777730	1	234793300	*N.A.*	-0.003	0.001	1.07E-05	0.458	-0.003	0.001	1.07E-05	0
NO$_2$	cg04337651	2	239344738	*ASB1*	0.004	0.001	2.06E-06	0.657	0.004	0.001	2.06E-06	0
	cg18776472	10	50732819	*ERCC6*	-0.001	0.0002	8.20E-06	0.657	-0.001	0.0002	3.32E-04	28
	cg18601596	6	39283313	*KCNK16*	0.006	0.001	8.21E-06	0.657	0.006	0.001	8.21E-06	0
	cg12392998	17	79550668	*NPLOC4*	-0.002	0.0004	8.72E-06	0.657	-0.002	0.001	1.05E-03	10
	cg16550606	13	50160670	*RCBTB1*	0.004	0.001	1.33E-05	0.657	0.004	0.001	1.06E-05	1
	cg25266109	19	12404608	*ZNF44*	-0.0004	0.0001	1.38E-05	0.657	-0.0005	0.0001	1.06E-06	12
	cg01746514	14	24520922	*LRRC16B*	-0.001	0.0002	1.43E-05	0.657	-0.001	0.0003	2.27E-05	38
	cg15811902	15	75918385	*SNUPN*	-0.002	0.0005	1.61E-05	0.657	-0.002	0.0005	1.74E-05	3
	cg26898336	17	15244519	*TEKT3*	0.002	0.0005	1.65E-05	0.657	0.002	0.001	2.87E-04	22
	cg21099332	5	39270715	*N.A.*	0.004	0.001	1.66E-05	0.657	0.004	0.001	1.66E-05	0
PM$_{2.5}$	cg26704043	6	5282702	*FARS2*	0.014	0.003	4.18E-07	0.180	0.014	0.003	7.73E-07	2
	cg05157625	14	93153553	*RIN3*	0.021	0.004	1.08E-06	0.231	0.021	0.004	1.08E-06	0
	cg20099458	7	5272275	*WIPI2*	0.014	0.003	1.61E-06	0.231	0.014	0.003	2.61E-06	11
	cg06587257	12	50452135	*ACCN2*	0.022	0.005	2.71E-06	0.292	0.022	0.005	4.91E-06	14
	cg14531665	9	91058614	*SPIN1*	0.012	0.003	5.91E-06	0.398	0.013	0.003	2.25E-06	4
	cg06526020	6	34308880	*NUDT3*	0.029	0.006	6.43E-06	0.398	0.029	0.006	6.43E-06	0
	cg21058520	6	100914733	*N.A.*	0.004	0.001	6.76E-06	0.398	0.009	0.001	3.14E-10	21
	cg16259904	10	134146220	*LRRC27*	0.027	0.006	8.90E-06	0.398	0.027	0.006	8.90E-06	0
	cg12770741	17	883776	*NXN*	0.018	0.004	9.15E-06	0.398	0.018	0.004	1.13E-05	10
	cg26750893	2	38043481	*N.A.*	0.016	0.004	1.05E-05	0.398	0.019	0.004	1.03E-06	2

CpG: Cytosine-phosphate-Guanine. CHR: chromosome. SE: standard error. FDR: false discovery rate. EV: extreme methylation values. Lden: day-evening-night noise level. NO$_2$: nitrogen dioxide. PM$_{2.5}$: particulate matter with aerodynamic diameter <2.5 μm. Beta coefficients represent increase or decrease in DNA methylation per 10 dB increase in aircraft, railway or road traffic Lden or 10 μg/m^3 increase in NO$_2$ or PM$_{2.5}$. All estimates were from multi-exposure linear mixed-effects models (containing all exposures), with participant-level random intercept, adjusted for age, sex, education, area, neighborhood socio-economic status, greenness index, smoking status, pack years, passive smoke, consumption of fruits, vegetables and alcohol, asthma status, survey and leukocyte composition. In a preliminary step, DNA methylation β-values were regressed on the Illumina control probe-derived first 30 principal components to correct for correlation structures and technical

bias, and residuals of these regressions covering 430,477 CpGs were used as the technical bias-corrected methylation level at the CpG sites. Extreme values of the residuals (lying beyond three times the interquartile range below the first quartile and above the third quartile at each CpG site) were replaced with their corresponding detection threshold value ("modified winsorization"). The "winsorized" data were then used as the dependent variables in the epigenome-wide association study (main model). N (all) and N ("non-winsorized") = 1,389 (2,542 observations). *N.A.*: not annotated.

Table S7. Sensitivity of source-specific transportation noise and air pollution-related CpGs to exclusion of leukocyte composition from main model.

Exposure	CpG ID	CHR	Location	Gene	Main model				Main model without leukocytes		
					Beta	SE	P-value	P (FDR)	Beta	SE	P-value
Aircraft Lden	cg02286155	5	176826262	*N.A.*	-0.007	0.001	1.48E-06	0.637	-0.006	0.001	1.25E-05
	cg15063530	2	17716941	*N.A.*	-0.009	0.002	8.14E-06	0.659	-0.009	0.002	9.17E-06
	cg16218477	7	1066167	*C7orf50*	-0.004	0.001	8.53E-06	0.659	-0.004	0.001	1.63E-05
	cg21602842	18	46291908	*KIAA0427*	-0.005	0.001	9.84E-06	0.659	-0.005	0.001	1.12E-05
	cg09042449	10	44064225	*ZNF239*	-0.002	0.0004	1.06E-05	0.659	-0.002	0.0004	1.47E-05
	cg10975000	13	28371375	*N.A.*	-0.002	0.0005	1.12E-05	0.659	-0.002	0.001	6.39E-05
	cg06220958	17	10452851	*MYH2*	0.011	0.002	1.24E-05	0.659	0.010	0.002	2.70E-05
	cg25462190	5	177547067	*N4BP3*	-0.007	0.002	1.32E-05	0.659	-0.006	0.002	2.07E-04
	cg11944797	13	99135711	*STK24*	-0.001	0.0003	1.38E-05	0.659	-0.001	0.0003	1.22E-05
	cg04635504	11	2829241	*KCNQ1*	-0.005	0.001	1.61E-05	0.664	-0.005	0.001	3.48E-05
Railway Lden	cg25201280	15	35838552	*ATPBD4*	-0.001	0.0002	1.74E-07	0.075	-0.001	0.0001	2.14E-07
	cg24653263	5	38258335	*EGFLAM*	-0.003	0.001	8.97E-07	0.193	-0.004	0.001	4.50E-07
	cg16825060	8	144242342	*LY6H*	-0.003	0.001	2.34E-06	0.256	-0.003	0.001	1.99E-06
	cg23468045	5	12669584	*N.A.*	0.001	0.0002	2.37E-06	0.256	0.001	0.0002	1.91E-06
	cg19270309	17	77712853	*ENPP7*	0.002	0.0005	3.25E-06	0.266	0.002	0.0005	2.96E-06
	cg07461273	7	99697172	*MCM7*	-0.004	0.001	3.78E-06	0.266	-0.003	0.001	1.11E-02
	cg01301319	7	27153580	*HOXA3*	-0.003	0.001	4.60E-06	0.266	-0.003	0.001	6.34E-06
	cg23113715	22	25800663	*N.A.*	-0.004	0.001	5.79E-06	0.266	-0.005	0.001	3.16E-06
	cg13402217	1	151584375	*SNX27*	-0.003	0.001	6.03E-06	0.266	-0.003	0.001	7.94E-06
	cg24047259	14	65347275	*N.A.*	-0.001	0.0003	7.35E-06	0.266	-0.001	0.0003	8.18E-06
Road traffic Lden	cg09129334	13	111837676	*ARHGEF7*	-0.007	0.001	1.73E-06	0.384	-0.006	0.002	1.17E-04
	cg17383236	7	100167504	*N.A.*	-0.002	0.0005	2.76E-06	0.384	-0.002	0.001	8.03E-03

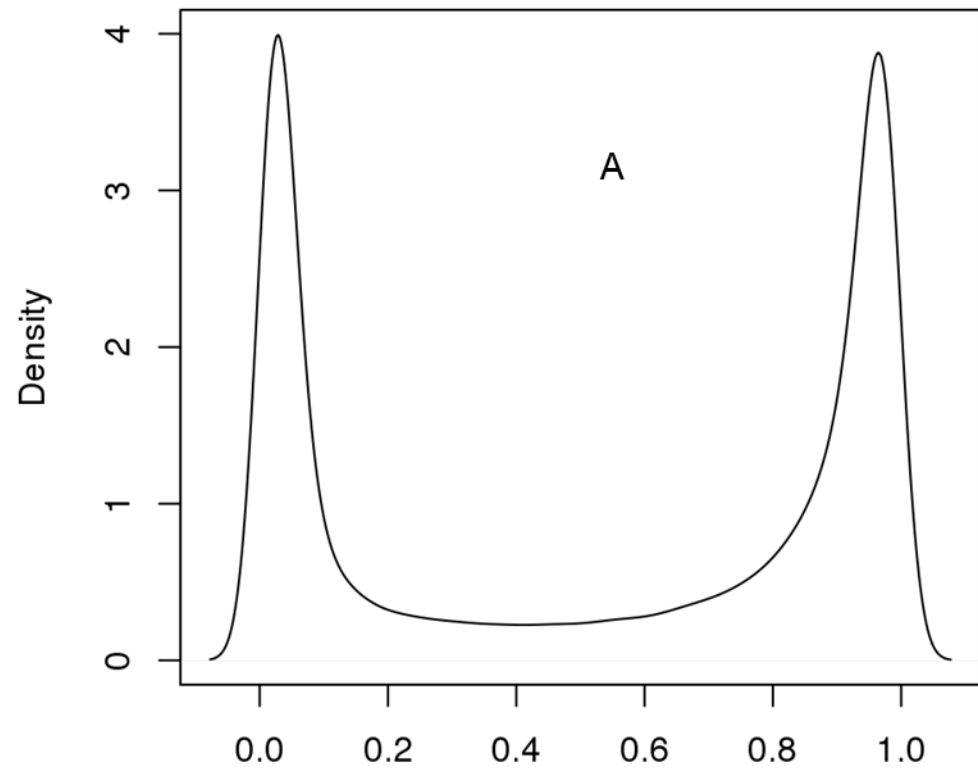| Exposure	CpG	CHR	Position	Gene	Beta	SE	EWAS P		Beta	SE	P
	cg01066220	6	31696240	*DDAH2*	0.001	0.0001	3.48E-06	0.384	0.001	0.0001	8.52E-07
	cg23910243	16	31484618	*TGFB1I1*	-0.002	0.0005	4.32E-06	0.384	-0.002	0.0005	1.56E-05
	cg06646021	1	229406520	*RAB4A*	-0.005	0.001	4.47E-06	0.384	-0.004	0.001	2.32E-04
	cg03066594	20	10415919	*C20orf94*	0.0005	0.0001	6.00E-06	0.386	0.0004	0.0001	1.56E-05
	cg03966094	22	21058792	*TMEM191A*	-0.003	0.001	7.06E-06	0.386	-0.003	0.001	3.27E-04
	cg13948857	5	131763756	*C5orf56*	-0.003	0.001	7.17E-06	0.386	-0.0002	0.002	9.04E-01
	cg08351004	2	172965650	*DLX2*	-0.002	0.0005	9.53E-06	0.456	-0.002	0.0005	3.41E-03
	cg13777730	1	234793300	*N.A.*	-0.003	0.001	1.07E-05	0.458	-0.001	0.001	6.03E-01
NO₂	cg04337651	2	239344738	*ASB1*	0.004	0.001	2.06E-06	0.657	0.004	0.001	1.83E-06
	cg18776472	10	50732819	*ERCC6*	-0.001	0.0002	8.20E-06	0.657	-0.001	0.0002	4.64E-06
	cg18601596	6	39283313	*KCNK16*	0.006	0.001	8.21E-06	0.657	0.004	0.002	6.14E-03
	cg12392998	17	79550668	*NPLOC4*	-0.002	0.0004	8.72E-06	0.657	-0.002	0.0004	1.19E-05
	cg16550606	13	50160670	*RCBTB1*	0.004	0.001	1.33E-05	0.657	0.004	0.001	2.69E-04
	cg25266109	19	12404608	*ZNF44*	-0.0004	0.0001	1.38E-05	0.657	-0.0004	0.0001	2.29E-05
	cg01746514	14	24520922	*LRRC16B*	-0.001	0.0002	1.43E-05	0.657	-0.001	0.0002	1.31E-05
	cg15811902	15	75918385	*SNUPN*	-0.002	0.0005	1.61E-05	0.657	-0.002	0.0005	2.38E-05
	cg26898336	17	15244519	*TEKT3*	0.002	0.0005	1.65E-05	0.657	0.002	0.002	1.18E-04
	cg21099332	5	39270715	*N.A.*	0.004	0.001	1.66E-05	0.657	0.001	0.002	5.21E-01
PM₂.₅	cg26704043	6	5282702	*FARS2*	0.014	0.003	4.18E-07	0.180	0.012	0.006	4.32E-02
	cg05157625	14	93153553	*RIN3*	0.021	0.004	1.08E-06	0.231	0.021	0.004	6.14E-07
	cg20099458	7	5272275	*WIPI2*	0.014	0.003	1.61E-06	0.231	0.013	0.003	1.12E-05
	cg06587257	12	50452135	*ACCN2*	0.022	0.005	2.71E-06	0.292	0.022	0.005	4.27E-06
	cg14531665	9	91058614	*SPIN1*	0.012	0.003	5.91E-06	0.398	0.009	0.006	1.47E-01
	cg06526020	6	34308880	*NUDT3*	0.029	0.006	6.43E-06	0.398	0.022	0.013	8.43E-02
	cg21058520	6	100914733	*N.A.*	0.004	0.001	6.76E-06	0.398	0.004	0.001	3.61E-06
	cg16259904	10	134146220	*LRRC27*	0.027	0.006	8.90E-06	0.398	0.027	0.006	1.07E-05
	cg12770741	17	883776	*NXN*	0.018	0.004	9.15E-06	0.398	0.018	0.004	9.29E-06
	cg26750893	2	38043481	*N.A.*	0.016	0.004	1.05E-05	0.398	0.018	0.007	6.61E-03

CpG: Cytosine-phosphate-Guanine. CHR: chromosome. SE: standard error. EWAS: epigenome-wide association study. Lden: day-evening-night noise level. NO₂: nitrogen dioxide. PM₂.₅: particulate matter with aerodynamic diameter <2.5 μm. Beta coefficients represent increase or decrease in DNA methylation per 10 dB increase in aircraft, railway or road traffic Lden or 10 μg/m³ increase in NO₂ or PM₂.₅. Main model estimates were from multi-exposure linear mixed-effects models (containing all five exposures), with participant-level random intercept, adjusted for age, sex, educational level, study area, neighborhood socio-economic status, greenness index, smoking status, smoking pack years, passive smoke, consumption of fruits,

vegetables and alcohol, asthma status, survey and leukocyte composition. In a preliminary step, DNA methylation β-values were regressed on the Illumina control probe-derived first 30 principal components to correct for correlation structures and technical bias, and residuals of these regressions covering 430,477 CpGs were used as the technical bias-corrected methylation level at the CpG sites. Extreme values of the residuals (lying beyond three times the interquartile range below the first quartile and above the third quartile at each CpG site) were replaced with their corresponding detection threshold value ("modified winsorization"). The "winsorized" data were then used as the dependent variables in the EWAS. *N.A.*: not annotated.
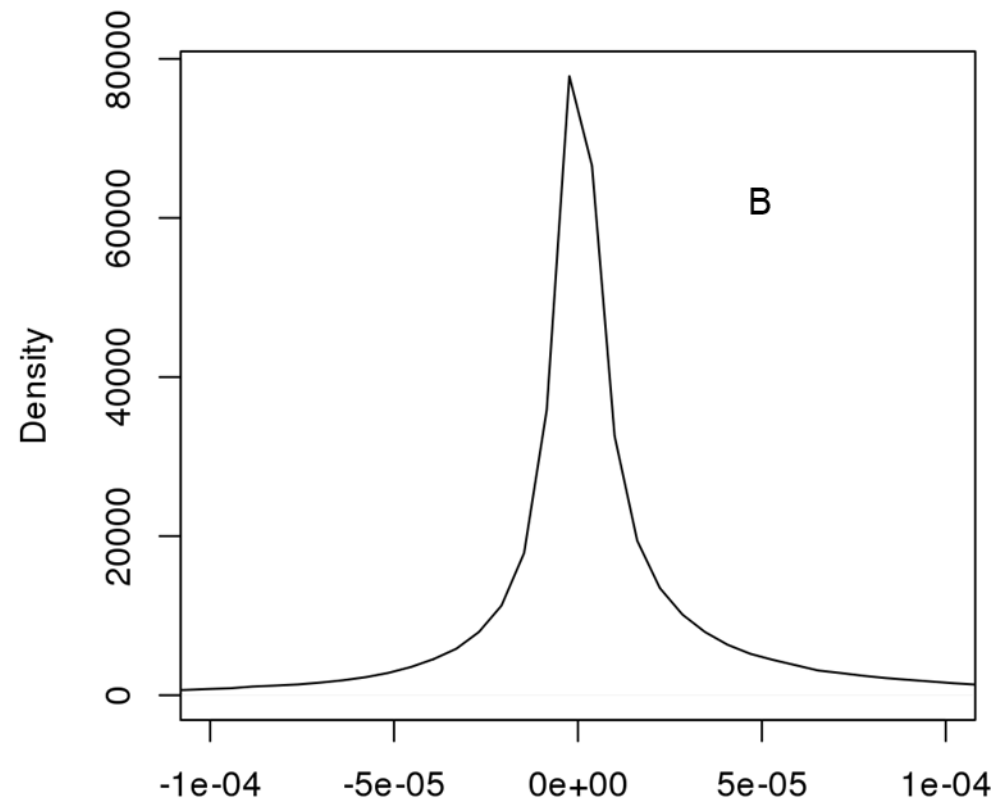
Table S8. Association between source-specific transportation noise and air pollution exposures, and leukocyte composition in the SAPALDIA study

Exposure	Statistic	B cell	CD4T	CD8T	Eosinophils	Monocytes	Neutrophils	Natural killer cells
Aircraft Lden	β (95% CI)	0.003 (0.001, 0.005)	0.008 (0.003, 0.013)	0.007 (0.003, 0.010)	-0.001 (-0.002, -0.0003)	-0.001 (-0.003, 0.001)	-0.015 (-0.023, -0.007)	0.001 (-0.003, 0.004)
	P-value	*0.021*	*0.003*	*7.55E-05*	*0.136*	*0.238*	*4.01E-04*	*0.691*
Railway Lden	β (95% CI)	0.001 (-0.001, 0.002)	-0.002 (-0.005, 0.002)	-0.001 (-0.003, 0.002)	0.001 (-0.0001, 0.002)	0.001 (-0.001, 0.002)	0.002 (-0.004, 0.008)	-0.002 (-0.004, 0.001)
	P-value	*0.332*	*0.309*	*0.553*	*0.077*	*0.380*	*0.491*	*0.256*
Road traffic Lden	β (95% CI)	-0.0004 (-0.002, 0.001)	0.003 (-0.0004, 0.006)	-0.001 (-0.003, 0.004)	-0.0003 (-0.001, 0.0005)	-0.001 (-0.002, 0.001)	-0.003 (-0.008, 0.003)	0.002 (-0.0002, 0.005)
	P-value	*0.572*	*0.080*	*0.453*	*0.437*	*0.310*	*0.375*	*0.077*
NO$_2$	β (95% CI)	0.00001 (-0.001, 0.001)	-0.002 (-0.005, 0.001)	0.001 (-0.001, 0.001)	0.0001 (-0.001, 0.001)	-0.001 (-0.002, 0.001)	-0.00001 (0.006, 0.006)	0.0004 (-0.002, 0.003)
	P-value	*0.991*	*0.171*	*0.171*	*0.718*	*0.458*	*0.998*	*0.743*
PM$_{2.5}$	β (95% CI)	0.005 (0.002, 0.008)	0.005 (-0.001, 0.012)	0.013 (0.009, 0.017)	0.0004 (-0.001, 0.002)	-0.004 (-0.006, -0.001)	-0.009 (-0.020, 0.001)	-0.003 (-0.008, 0.001)
	P-value	*2.44E-04*	*0.090*	*3.05E-09*	*0.586*	*0.011*	*0.087*	*0.176*

SAPALDIA: Swiss cohort study on air pollution and lung and heart diseases in adults. Lden: day-evening-night noise level. NO$_2$: nitrogen dioxide. PM$_{2.5}$: particulate matter with aerodynamic diameter <2.5 μm. All estimates represent change in mean leukocyte type per 10 dB of aircraft, railway or road traffic Lden, and per 10 μg/m^3 of NO$_2$ or PM$_{2.5}$, and derive from linear mixed-effects multi-exposure models adjusted for noise truncation indicators, with random intercept at the level of the participant. Multi-exposure models contained all five exposures and noise truncation indicators at the same time.

Figure S1. Distributions of the BMIQ-normalized beta values (A) and technical bias-corrected residuals (B) in the SAPALDIA study. SAPALDIA: Swiss cohort study on air pollution and lung and heart diseases in adults.
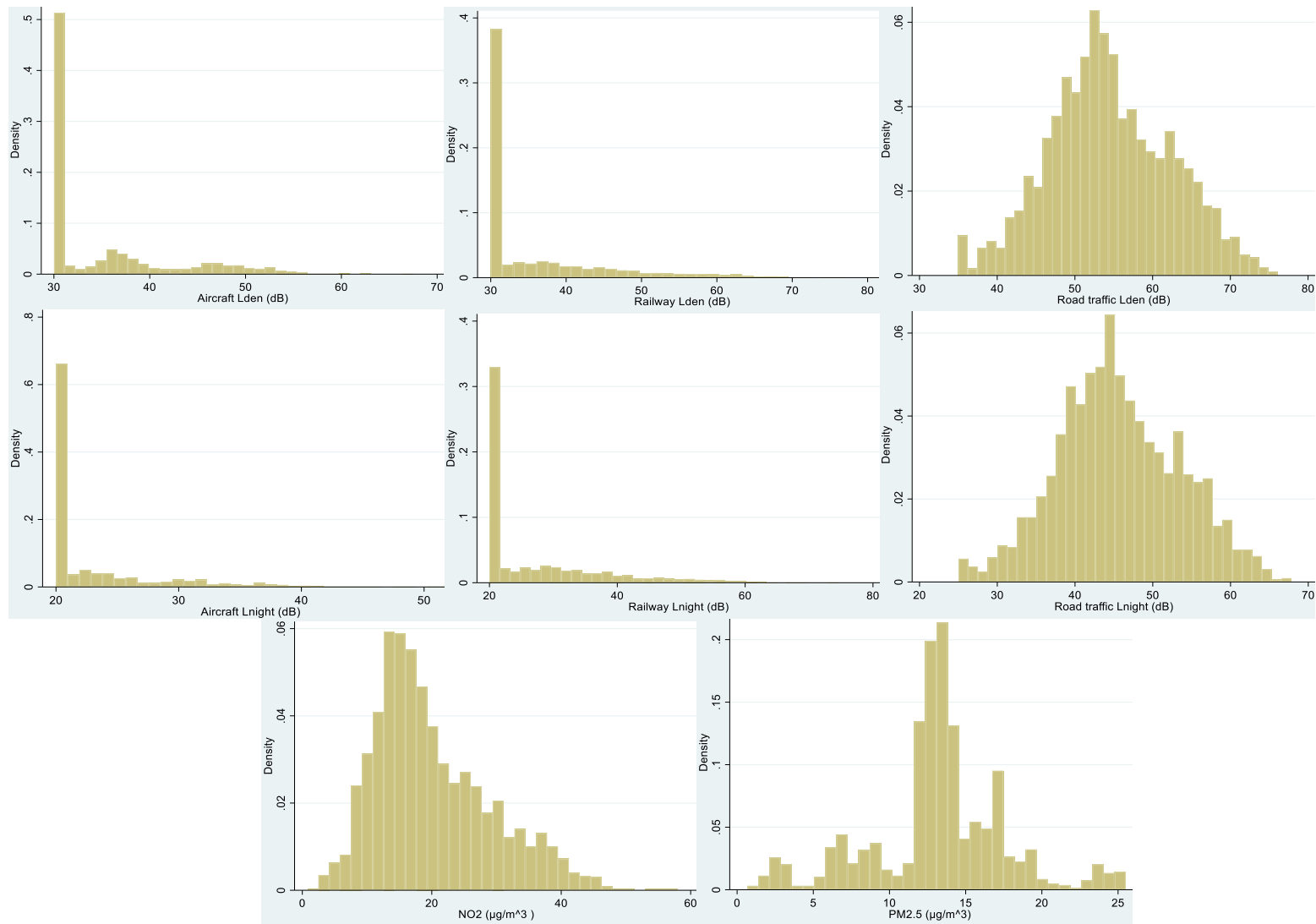
Figure S2. Distribution of transportation noise and air pollution parameters in the present study.

Lden: day-evening night noise level. Lnight: nighttime noise level. NO$_2$: nitrogen dioxide; PM$_{2.5}$: particulate matter with aerodynamic diameter <2.5 μm.