Supplemental Material

Table S1. Characteristics of the study population (at visit 4) by the presence of carotid plaques at visit 4.

Patients` characteristics at V4	No plaque	Plaque at V4	p-value
N. total =997	794	203	
Age (yr)	58.7 ± 5.8	61.4 ± 5.2	<0.001
Male sex	387 (48.7%)	122 (60.1%)	0.004
BMI (Kg/m2)	26.9 ± 4.8	27.4 ± 4.8	0.16
Waist circumference (cm)	92.6 ± 13.3	95.7 ± 13.6	0.003
Smoking	99 (12.5%)	29 (14.4%)	0.46
SBP (mmHg)	128.2 ± 15.5	134.4 ± 16.9	<0.001
DBP (mmHg)	74.3 ± 8.8	74.4 ± 9.0	0.87
Heart rate (bpm)	63.5 ± 8.9	62.7 ± 10.5	0.28
Diabetes	57 (7.3%)	21 (10.7%)	0.27
Glucose (g/L)	0.9 ± 0.2	1.0 ± 0.2	<0.001
Hypertension history	225 (28.4%)	76 (37.8%)	0.010
Total cholesterol (g/L)	2.2 ± 0.4	2.2 ± 0.4	0.46
HDL cholesterol (g/L)	0.6 ± 0.1	0.6 ± 0.1	0.59
LDL cholesterol (g/L)	1.4 ± 0.3	1.4 ± 0.4	0.11
Triglycerides (g/L)	1.1 ± 0.8	1.2 ± 0.6	0.033
Lipid lowering therapy	181 (22.8%)	71 (35.0%)	<0.001
eGFR (ml/min)	88.3 ± 12.0	89.1 ± 12.9	0.41
Carotid stenosis 20-50%	0 (0.0%)	15 (100.0%)	<0.001
cIMT (µm)	691 ± 138	722 ± 132	0.005
PWV (m/s)	9.0 ± 1.7	9.8 ± 2.1	<0.001
PCSK9 (NPX)	2.9 ± 0.4	3.0 ± 0.4	<0.001
LDL receptor (NPX)	5.5 ± 0.6	5.6 ± 0.5	0.016

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate calculated by the CKD-EPI formula; LDL, low-density lipoprotein; cIMT, carotid intima-media thickness; PWV, pulse-wave velocity; PCSK9, proprotein convertase subtilisin/kexin type 9; NPX, Olink® log2 standardized units.

Table S2. Factors associated with carotid artery plaque at visit 4.

Variable	OR (95%CI)	p-value
"Best" clinical model		
Age (per 5 yr)	1.48 (1.26-1.73)	<0.001
SBP (per 10 mmHg)	1.18 (1.07-1.30)	0.001
Lipid-lowering therapy	1.39 (0.98-1.97)	0.062
PCSK9 plus LDLr on top of the "best" clinical model		
PCSK9 (NPX)	1.66 (1.01-2.72)	0.045
LDLr (NPX)	1.12 (0.82-1.53)	0.48
PCSK9/LDLr ratio on top of the "best" clinical model		
PCSK9/LDLr (ratio)	1.13 (0.89-1.43)	0.33

N =997; N. Plaque =203.

LDLc, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; LDLr, LDL receptor; NPX, Olink® log2 standardized units.

Table S3. Plaque at visit 4 in the "children".

Children at V1	No plaque	Plaque at V4
N. total =647	641 (99.1%)	6 (0.9%)

Table S4. Association of PCSK9 and LDLr (visit 1 and visit 4) with IMT and PWV (at visit 4).

Visit 1 (PCSK9 and LDLr)		
IMT above the 90th percentile	**OR (95%CI)**	**p-value**
PCSK9 (NPX)	1.03 (0.67-1.61)	0.87
LDLr (NPX)	1.11 (0.84-1.47)	0.45
IMT (mm) continuous	**Coef. (95%CI)**	**p-value**
PCSK9 (NPX)	16.1 (-10.7 to +42.8)	0.24
LDLr (NPX)	11.8 (-5.2 to +28.7)	0.18
PWV above the 90th percentile	**OR (95%CI)**	**p-value**
PCSK9 (NPX)	1.01 (0.46-2.20)	0.98
LDLr (NPX)	1.23 (0.75-2.01)	0.41
PWV (m/s) continuous	**Coef. (95%CI)**	**p-value**
PCSK9 (NPX)	-0.1 (-0.4 to +0.3)	0.60
LDLr (NPX)	0.4 (+0.1 to +0.6)	0.002
Visit 4 (PCSK9 and LDLr)		
IMT above the 90th percentile	**OR (95%CI)**	**p-value**
PCSK9 (NPX)	0.87 (0.58-1.30)	0.51
LDLr (NPX)	1.32 (1.00-1.73)	0.042
IMT (mm) continuous	**Coef. (95%CI)**	**p-value**
PCSK9 (NPX)	-2.9 (-27.4 to +21.5)	0.81
LDLr (NPX)	20.9 (+4.5 to +37.2)	0.012
PWV above the 90th percentile	**OR (95%CI)**	**p-value**
PCSK9 (NPX)	1.09 (0.55-2.18)	0.79
LDLr (NPX)	1.17 (0.74-1.84)	0.51
PWV (m/s) continuous	**Coef. (95%CI)**	**p-value**
PCSK9 (NPX)	0.1 (-0.3 to +0.3)	0.92
LDLr (NPX)	0.1 (-0.1 to +0.3)	0.27

Model adjusted on age, sex, smoking and LDLc.

Table S5. Association between presence of plaques and PCSK9 polymorphisms (n=949).

id	Allele 1	Allele 2	freqA2	beta	sd	p	BH
rs2479394	G	A	0.702	0.124	0.132	0.348	0.566
rs11588151	G	A	0.778	0.151	0.151	0.318	0.566
rs11206510	C	T	0.795	0.256	0.157	0.103	0.269
rs17192725	A	G	0.900	0.013	0.200	0.950	0.950
rs2182833	G	A	0.800	-0.141	0.150	0.348	0.566
rs2479409	G	A	0.655	-0.281	0.125	0.025	0.130
rs11591147	T	G	0.985	0.120	0.513	0.814	0.847
rs11583680	T	C	0.856	0.409	0.190	0.032	0.137
rs499718	T	C	0.815	0.101	0.159	0.524	0.632
rs28385708	T	C	0.932	0.163	0.245	0.507	0.632
rs41294821	T	C	0.990	-0.559	0.545	0.305	0.566
rs7552841	T	C	0.600	0.037	0.124	0.768	0.832
rs58255540	G	A	0.948	-0.209	0.255	0.412	0.630
rs634272	T	C	0.741	0.412	0.147	0.005	0.032
rs11808052	T	C	0.948	-0.134	0.259	0.604	0.683
rs540796	A	G	0.838	0.578	0.188	0.002	0.024
rs562556	G	A	0.838	0.584	0.188	0.002	0.024
rs114162366	A	G	0.981	-0.301	0.403	0.455	0.632
rs631220	A	G	0.838	0.562	0.187	0.003	0.024
rs505151	G	A	0.968	0.248	0.377	0.510	0.632
rs41294827	T	G	0.973	-0.653	0.333	0.050	0.143
rs77011887	T	C	0.979	-0.443	0.386	0.251	0.544
rs77868073	C	T	0.974	-0.673	0.334	0.044	0.142
rs487230	A	G	0.784	0.327	0.159	0.039	0.142
rs114527615	A	G	0.980	0.289	0.466	0.535	0.632
rs17111584	C	T	0.968	-0.487	0.309	0.114	0.271

Table S6. Crude odd ratios for association between plaques at V4 and genotype at rs562556.

	Plaques (n=184)	No plaques (n=718)	OR (95%CI) (risk per A allele)	P trend
Rs562556				
GG	0	24		
GA	41	201	1.67 (1.17-2.38)	P = 0.004
AA	143	493		

Table S7. Association between *PCSK9* polymorphisms and circulating LDL at visit 4 (n=895).

id	Allele 1	Allele 2	freqA2	beta	sd	p	BH
rs2479394	G	A	0.703	-0.019	0.017	0.273	0.671
rs11588151	G	A	0.777	-0.010	0.019	0.617	0.895
rs11206510	C	T	0.794	-0.017	0.020	0.382	0.671
rs17192725	A	G	0.899	-0.013	0.026	0.619	0.895
rs2182833	G	A	0.800	-0.016	0.020	0.416	0.675
rs2479409	G	A	0.654	-0.006	0.017	0.703	0.918
rs11591147	T	G	0.985	0.080	0.065	0.218	0.671
rs11583680	T	C	0.856	-0.025	0.023	0.269	0.671
rs499718	T	C	0.815	-0.007	0.020	0.747	0.925
rs28385708	T	C	0.931	-0.027	0.031	0.387	0.671
rs41294821	T	C	0.990	-0.004	0.079	0.964	0.964
rs7552841	T	C	0.601	-0.018	0.016	0.269	0.671
rs58255540	G	A	0.948	0.032	0.035	0.358	0.671
rs634272	T	C	0.741	-0.007	0.018	0.706	0.918
rs11808052	T	C	0.948	0.033	0.035	0.343	0.671
rs540796	A	G	0.837	0.053	0.021	0.012	0.088
rs562556	G	A	0.837	0.052	0.021	0.014	0.088
rs114162366	A	G	0.980	-0.005	0.057	0.929	0.964
rs631220	A	G	0.838	0.053	0.021	0.011	0.088
rs505151	G	A	0.968	-0.006	0.045	0.888	0.964
rs41294827	T	G	0.973	0.069	0.049	0.161	0.671
rs77011887	T	C	0.979	-0.005	0.055	0.930	0.964
rs77868073	C	T	0.974	0.063	0.049	0.202	0.671
rs487230	A	G	0.783	0.048	0.019	0.013	0.088
rs114527615	A	G	0.980	-0.013	0.056	0.815	0.963
rs17111584	C	T	0.968	0.042	0.044	0.340	0.671

Table S8. Association between *PCSK9* polymorphisms and circulating LDL at visit 1 (n=861).

id	Allele 1	Allele 2	freqA2	beta	sd	p	BH
rs2479394	G	A	0.699	-0.011	0.018	0.534	0.816
rs11588151	G	A	0.776	0.050	0.020	0.015	0.077
rs11206510	C	T	0.793	0.033	0.021	0.113	0.327
rs17192725	A	G	0.899	-0.056	0.028	0.042	0.156
rs2182833	G	A	0.797	-0.025	0.021	0.248	0.538
rs2479409	G	A	0.653	-0.034	0.018	0.054	0.176
rs11591147	T	G	0.985	0.190	0.068	0.005	0.077
rs11583680	T	C	0.856	0.012	0.024	0.605	0.828
rs499718	T	C	0.814	-0.006	0.021	0.778	0.963
rs28385708	T	C	0.932	0.007	0.033	0.824	0.974
rs41294821	T	C	0.990	0.025	0.084	0.765	0.963
rs7552841	T	C	0.598	-0.024	0.017	0.155	0.393
rs58255540	G	A	0.948	0.029	0.037	0.439	0.761
rs634272	T	C	0.744	0.021	0.019	0.274	0.549
rs11808052	T	C	0.948	0.030	0.037	0.427	0.761
rs540796	A	G	0.838	0.057	0.022	0.011	0.077
rs562556	G	A	0.837	0.056	0.022	0.012	0.077
rs114162366	A	G	0.983	0.000	0.064	0.996	0.996
rs631220	A	G	0.839	0.059	0.022	0.009	0.077
rs505151	G	A	0.969	-0.112	0.048	0.021	0.090
rs41294827	T	G	0.974	0.007	0.053	0.897	0.996
rs77011887	T	C	0.979	-0.032	0.059	0.589	0.828
rs77868073	C	T	0.975	-0.001	0.054	0.984	0.996
rs487230	A	G	0.787	0.028	0.020	0.166	0.393
rs114527615	A	G	0.980	0.039	0.059	0.511	0.816
rs17111584	C	T	0.971	-0.004	0.050	0.935	0.996

Table S9. Association between *PCSK9* polymorphisms and circulating PCSK9 at visit 1 (n=894).

id	Allele 1	Allele 2	freqA2	beta	sd	p	BH
rs2479394	G	A	0.702	-0.026	0.019	1.7E-01	2.9E-01
rs11588151	G	A	0.777	0.061	0.021	3.8E-03	9.5E-03
rs11206510	C	T	0.794	0.061	0.021	4.4E-03	9.5E-03
rs17192725	A	G	0.899	-0.038	0.028	1.8E-01	2.9E-01
rs2182833	G	A	0.800	-0.077	0.022	4.6E-04	1.3E-03
rs2479409	G	A	0.655	-0.048	0.018	7.7E-03	1.5E-02
rs11591147	T	G	0.985	0.326	0.070	3.4E-06	1.7E-05
rs11583680	T	C	0.855	0.120	0.024	8.8E-07	1.5E-05
rs499718	T	C	0.814	0.087	0.022	7.7E-05	2.5E-04
rs28385708	T	C	0.931	-0.023	0.034	5.1E-01	6.0E-01
rs41294821	T	C	0.990	0.053	0.086	5.4E-01	6.0E-01
rs7552841	T	C	0.601	-0.050	0.017	4.2E-03	9.5E-03
rs58255540	G	A	0.949	0.027	0.038	4.9E-01	6.0E-01
rs634272	T	C	0.740	0.089	0.019	4.0E-06	1.7E-05
rs11808052	T	C	0.949	0.031	0.038	4.2E-01	5.8E-01
rs540796	A	G	0.837	0.110	0.023	1.8E-06	1.5E-05
rs562556	G	A	0.837	0.110	0.023	1.7E-06	1.5E-05
rs114162366	A	G	0.980	-0.053	0.062	4.0E-01	5.7E-01
rs631220	A	G	0.837	0.108	0.023	2.5E-06	1.6E-05
rs505151	G	A	0.968	-0.063	0.049	2.1E-01	3.1E-01
rs41294827	T	G	0.973	0.023	0.054	6.7E-01	7.2E-01
rs77011887	T	C	0.979	-0.042	0.060	4.8E-01	6.0E-01
rs77868073	C	T	0.974	0.021	0.054	7.0E-01	7.3E-01
rs487230	A	G	0.783	0.083	0.021	7.3E-05	2.5E-04
rs114527615	A	G	0.980	0.120	0.061	5.1E-02	9.5E-02
rs17111584	C	T	0.968	0.002	0.049	9.7E-01	9.7E-01

Table S10. Association between *PCSK9* polymorphisms and circulating PCSK9 at visit 4 (n=897).

id	A1	A2	freqA2	beta	sd	p	BH
rs2479394	G	A	0.702	-0.016	0.018	3.94E-01	5.12E-01
rs11588151	G	A	0.778	0.079	0.021	1.28E-04	3.70E-04
rs11206510	C	T	0.795	0.101	0.021	1.62E-06	1.05E-05
rs17192725	A	G	0.900	-0.031	0.028	2.68E-01	3.69E-01
rs2182833	G	A	0.800	-0.052	0.022	1.59E-02	2.96E-02
rs2479409	G	A	0.655	-0.065	0.018	2.63E-04	6.84E-04
rs11591147	T	G	0.985	0.429	0.068	5.46E-10	1.42E-08
rs11583680	T	C	0.856	0.143	0.024	3.75E-09	4.88E-08
rs499718	T	C	0.815	0.084	0.022	1.13E-04	3.67E-04
rs28385708	T	C	0.931	0.024	0.033	4.67E-01	5.78E-01
rs41294821	T	C	0.990	0.094	0.085	2.70E-01	3.69E-01
rs7552841	T	C	0.599	-0.053	0.017	2.23E-03	5.26E-03
rs58255540	G	A	0.949	0.091	0.038	1.78E-02	3.08E-02
rs634272	T	C	0.741	0.096	0.019	5.09E-07	4.41E-06
rs11808052	T	C	0.949	0.090	0.038	2.00E-02	3.25E-02
rs540796	A	G	0.838	0.103	0.023	6.34E-06	2.75E-05
rs562556	G	A	0.838	0.105	0.023	3.93E-06	2.04E-05
rs114162366	A	G	0.980	0.022	0.062	7.26E-01	7.55E-01
rs631220	A	G	0.839	0.102	0.023	7.68E-06	2.85E-05
rs505151	G	A	0.968	-0.139	0.049	4.51E-03	9.76E-03
rs41294827	T	G	0.973	0.031	0.053	5.52E-01	6.24E-01
rs77011887	T	C	0.979	0.015	0.059	7.98E-01	7.98E-01
rs77868073	C	T	0.974	0.035	0.053	5.16E-01	6.09E-01
rs487230	A	G	0.784	0.058	0.021	5.23E-03	1.05E-02
rs114527615	A	G	0.980	0.068	0.061	2.63E-01	3.69E-01
rs17111584	C	T	0.968	0.023	0.048	6.35E-01	6.88E-01

Table S11. Partial correlation coefficients.

Variable	Partial correlation	P-value
PCSK9 levels at V1		
Age at V1	-5.2%	0.12
Smoking at V1	-0.1%	0.77
LDLc at V1	15.0%	<0.001
LDLr at V1	37.6%	<0.001
rs562556	16.0%	<0.001
PCSK9 levels at V4		
Age at V4	-2.3%	0.49
SBP at V4	-1.5%	0.65
Statin at V4	30.0%	<0.001
LDLr at V4	36.5%	<0.001
rs562556	16.5%	<0.001

Figure S1. Distribution of the Stanislas cohort population according to age.
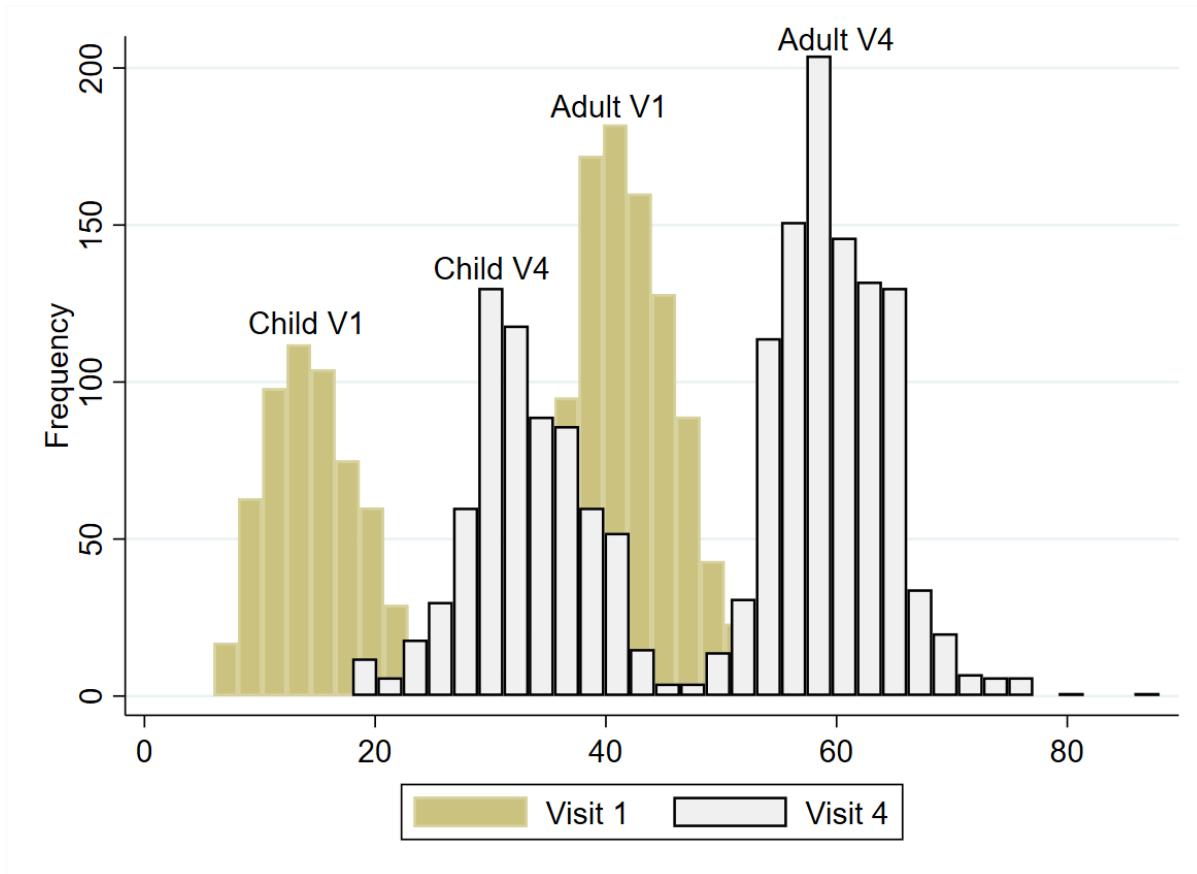
Figure S2. Matrix of linkage disequilibrium of the 26 SNPs for the gene *PCSK9*.

Column labels (left to right):
rs2479394, rs11588151, rs11206510, rs17192725, rs2182833, exm-rs2479409, rs11591147, exm62590, rs499718, GSA-rs28385708, rs41294821, rs7552841, rs58255540, rs634272, GSA-rs11808052, rs540796, GSA-rs562556, GSA-rs114162366, GSA-rs631220, exm62717, rs41294827, GSA-rs77011887, GSA-rs77868073, exm62737, GSA-rs114527615, GSA-rs17111584

0.09 0.86 0.02 0.00 0.40 0.01 0.00 0.52 0.03 0.00 0.00 0.04 0.01 0.01 0.01 1.00 0.00 0.01 0.01 0.00 0.00 0.00 0.09 0.08 0.00
0.08 0.02 0.02 0.00 0.00 0.09 0.00 0.00 0.03 0.00 0.02 0.25 0.98 0.35 0.01 0.01 0.98 0.00 0.00 0.00 0.98 0.01 0.00 0.11
0.22 0.02 0.05 0.01 0.03 0.01 0.00 0.00 0.00 0.19 0.01 0.03 0.01 0.35 0.00 0.99 0.01 0.00 0.00 0.00 0.10 0.00 0.82
0.07 0.04 0.06 0.01 0.03 0.00 0.00 0.01 0.00 0.01 0.02 0.07 0.01 0.04 0.01 0.01 0.01 0.00 0.01 0.10 0.00 0.00
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