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Supplementary webappendix

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Supplementary material

Cardiovascular event definitions in Finnish cohorts (FINRISK 1992, 1997, 2002, and Health 2000)

1) Myocardial infarction (MI). I21–I22 (ICD-10) or 410 (ICD-9) as A) direct, underlying, or contributing cause of death, or as B) main or side diagnosis at hospital discharge.

2) Coronary heart disease (CHD). A) Any of I20–I25, I46, R96 or R98 (ICD-10) or 410–414 or 798 (ICD-9) as underlying or direct cause of death, or B) Any of I200, I21–I22 (ICD-10) or 410, 4110 (ICD-9) as the main diagnosis at hospital discharge, or C) coronary bypass surgery or coronary angioplasty at hospital discharge or identified from the specific country-wide register of invasive cardiac procedures. The definition of CHD includes all MI cases.

3) Stroke (excluding subarachnoid hemorrhage): Any of I61, I63, I64 except I63.6 (ICD-10) or 431, 4330A, 4331A, 4339A, 4340A, 4341A, 4349A, 436 (ICD-9) as A) the underlying or direct cause of death, or as B) the main or side diagnosis at hospital discharge.

4) Cardiovascular disease (CVD): Either MI, CHD or stroke.

An non-fatal event prior to or at the clinical examination date was considered as prevalent. An event during the follow-up in persons with no history of prior events was considered as incident.

Cardiovascular event definitions in COROGENE

CVD was defined in the FINRISK controls as above with the following exceptions.

1) Also subarachnoid haemorrhage (SAH) was considered as a stroke; I60 (ICD-10) or 430 (ICD-9). In ICD-9, 432 (other / unspecified intracranial haemorrhage) was also taken as a stroke. All stroke codes were accepted as any diagnosis at hospital discharge or as any cause of death.

2) Self-reported prevalent MI or stroke (date unknown) was also considered in case there was no events in follow-up. The persons in question were not eligible as controls.

Cardiovascular event definitions in MDC-CC and MPP

Prevalent and incident cardiovascular events in MDC-CC and MPP were ascertained through record linkage of the 10-digit personal identification number of each Swedish citizen with three registries – the Swedish Hospital Discharge Register, the Swedish Cause of Death Register, and the Stroke Register of Malmö.[1] Cardiovascular events included myocardial infarction, ischemic stroke, and death due to coronary heart disease. Myocardial infarction was defined on the basis of ICD 9th and 10th Revisions (ICD-9 and ICD-10) codes 410 and I21, respectively. Stroke was defined on the basis of codes 434 or 436 (ICD-9) and I63 or I64 (ICD-10). Before inclusion, ischemic stroke events in the Swedish Hospital Discharge Register were validated using the Stroke Register of Malmö where original medical records including imaging studies, when available, were examined. Death due to coronary heart disease was defined on the basis of codes 412 and 414 (ICD9) or I22–I23 and I25 (ICD10) in the Swedish Cause of Death Register. Follow-up extended to December 31, 2006. The MDC-CC and MPP study protocols were approved by the ethics committee of Lund University. All participants provided written informed consent.

Supplementary Table 1. Association between Single-Nucleotide Polymorphisms (SNPs) and prevalent coronary heart disease (CHD), cardiovascular disease (CVD), and myocardial infarction (MI).*

						Coronary heart disease		Cardiovascular disease		Myocardial infarction	
SNP	**Region**	**Candidate Gene(s)**	**Risk allele**	**Risk allele freq.**	**Other allele**	**Pooled OR (95% CI)†**	**P value**	**Pooled OR (95% CI)†**	**P value**	**Pooled OR (95% CI)†**	**P value**
rs17465637	1q41	MIA3	C	0·75	A	1·30 (1·08 , 1·56)	**0·006**	1·13 (1·05 , 1·22)	**0·001**	1·16 (1·07 , 1·24)	**$1·4\times10^{-5}$**
rs11206510	1p32	PCSK9	T	0·84	C	0·94 (0·77 , 1·16)	0·575	0·97 (0·89 , 1·06)	0·510	0·95 (0·89 , 1·02)	0·197
rs646776	1p13	CELSR2–PSRC1–SORT1	T	0·79	C	1·15 (0·95 , 1·40)	0·148	1·05 (0·97 , 1·14)	0·238	1·00 (0·94 , 1·07)	0·928
rs6725887	2q33	WDR12	C	0·11	T	1·13 (0·90 , 1·43)	0·294	1·04 (0·95 , 1·15)	0·376	1·07 (0·99 , 1·16)	0·086
rs9818870	3q22	MRAS	T	0·10	C	1·03 (0·80 , 1·32)	0·831	1·00 (0·91 , 1·10)	0·952	1·01 (0·93 , 1·09)	0·846
rs3798220	6q26	LPA	C	0·01	T	0·84 (0·36 , 1·95)	0·676	1·20 (0·90 , 1·59)	0·212	1·10 (0·83 , 1·48)	0·499
rs9349379	6p24	PHACTR1	C	0·44	T	1·15 (0·99 , 1·33)	0·074	1·00 (0·93 , 1·07)	0·969	1·00 (0·94 , 1·06)	0·981
rs4977574	9p21	CDKN2A–CDKN2B	G	0·43	A	1·22 (1·05 , 1·42)	**0·011**	1·21 (1·13 , 1·29)	**$1·4\times10^{-9}$**	1·19 (1·13 , 1·26)	**$5·0\times10^{-11}$**
rs1746048	10q11	CXCL12	C	0·84	T	0·92 (0·75 , 1·12)	0·405	1·01 (0·92 , 1·11)	0·851	1·04 (0·96 , 1·12)	0·304
rs2259816	12q24	HNF1A	T	0·36	G	1·10 (0·94 , 1·28)	0·241	1·01 (0·95 , 1·08)	0·731	1·01 (0·95 , 1·06)	0·824
rs3184504	12q24	SH2B3	T	0·40	C	1·00 (0·85 , 1·16)	0·965	1·04 (0·97 , 1·11)	0·266	1·04 (0·99 , 1·10)	0·131
rs1122608	19p13	LDLR	G	0·79	T	1·31 (1·07 , 1·60)	**0·008**	1·09 (1·01 , 1·18)	0·031	1·01 (0·95 , 1·08)	0·719
rs9982601	21q22	SLC5A3–MRPS6–KCNE2	T	0·14	C	1·58 (1·11 , 2·25)	**0·011**	1·20 (1·08 , 1·34)	**0·001**	1·11 (1·03 , 1·2)	**0·007**

* Association tested with logistic regression adjusted for age and sex. Corogene data with matched case-control design was analyzed using conditional logistic regression.
† The results from FINRISK 92, FINRISK 97, FINRISK 02, Health 2000, Malmö Diet and Cancer Cardiovascular cohort, Malmö Preventive Project, and COROGENE were combined using fixed effects meta-analysis. [2]
Abbreviations: OR, odds ratio; CI, confidence interval

Supplementary Table 2. Age and sex adjusted associations between the genotype score and incident coronary heart disease (CHD), cardiovascular disease (CVD), and myocardial infarction (MI).*

		Genotype score quintile					
	Cohort	**1 (ref.)**	**2**	**3**	**4**	**5**	**P for trend**
HR (95% CI) CHD	FR -92	1·00	1·00 (0·68 , 1·47)	1·03 (0·7 , 1·51)	1·38 (0·96 , 1·98)	1·56 (1·09 , 2·24)	0·003
	FR -97	1·00	1·04 (0·74 , 1·46)	1·30 (0·95 , 1·79)	1·41 (1·03 , 1·94)	1·85 (1·36 , 2·52)	$1·1\times10^{-6}$
	FR -02	1·00	1·02 (0·56 , 1·87)	1·19 (0·66 , 2·12)	1·51 (0·86 , 2·65)	1·81 (1·05 , 3·11)	0·01
	Health 2000	1·00	0·99 (0·55 , 1·79)	1·40 (0·81 , 2·43)	1·19 (0·66 , 2·14)	1·61 (0·93 , 2·76)	0·06
	Pooled†	**1·00**	**1·02 (0·82 , 1·27)**	**1·21 (0·99 , 1·50)**	**1·38 (1·13 , 1·7)**	**1·72 (1·41 , 2·10)**	**$7·3\times10^{-11}$**
HR (95% CI) CVD	FR -92	1·00	1·07 (0·78 , 1·47)	1·05 (0·76 , 1·44)	1·20 (0·88 , 1·63)	1·54 (1·14 , 2·08)	0·004
	FR -97	1·00	0·86 (0·65 , 1·12)	1·16 (0·90 , 1·49)	1·16 (0·90 , 1·51)	1·49 (1·16 , 1·91)	$1·5\times10^{-5}$
	FR -02	1·00	1·13 (0·68 , 1·89)	1·44 (0·89 , 2·33)	1·36 (0·82 , 2·23)	1·96 (1·23 , 3·12)	0·003
	Health 2000	1·00	1·06 (0·65 , 1·73)	1·29 (0·81 , 2·07)	1·34 (0·83 , 2·15)	1·75 (1·12 , 2·73)	0·006
	MDC-CC	1·00	1·01 (0·75 , 1·38)	1·04 (0·77 , 1·41)	0·91 (0·67 , 1·25)	1·31 (0·98 , 1·75)	0·067
	Pooled†	**1·00**	**0·99 (0·85 , 1·15)**	**1·14 (0·98 , 1·32)**	**1·14 (0·98 , 1·32)**	**1·52 (1·32 , 1·75)**	**$1·1\times10^{-10}$**
HR (95% CI) MI	FR -92	1·00	1·04 (0·62 , 1·74)	0·96 (0·56 , 1·65)	1·32 (0·80 , 2·17)	1·40 (0·85 , 2·30)	0·103
	FR -97	1·00	1·02 (0·65 , 1·63)	1·50 (0·99 , 2·28)	1·35 (0·87 , 2·10)	1·90 (1·25 , 2·88)	0·001
	FR -02	1·00	1·11 (0·49 , 2·53)	0·81 (0·34 , 1·96)	1·16 (0·51 , 2·64)	1·93 (0·92 , 4·04)	0·08
	Health 2000	1·00	0·96 (0·47 , 1·94)	1·66 (0·88 , 3·12)	1·10 (0·54 , 2·23)	1·46 (0·76 , 2·80)	0·227
	MDC-CC	1·00	1·11 (0·74 , 1·67)	1·01 (0·66 , 1·53)	1·11 (0·74 , 1·68)	1·34 (0·91 , 1·98)	0·17
	Pooled†	**1·00**	**1·05 (0·83 , 1·34)**	**1·19 (0·94 , 1·50)**	**1·22 (0·97 , 1·54)**	**1·55 (1·24 , 1·94)**	**$3·3\times10^{-6}$**

* Association tested with Wald test using a Cox-proportional hazards model adjusted for sex. Age was used as the time scale.
† The results were combined using fixed effects meta-analysis. [2]
Abbreviations: FR, Finrisk; MDC-CC, The Malmö Diet and Cancer Cardiovascular cohort; MPP, The Malmö Preventive Project; HR, hazard ratio; CI, confidence interval

Supplementary Table 3. Multivariable analysis of the association between genetic risk score and incident events in FINRISK 92, FINRISK 97 and FINRISK 02.*

	HR (95% CI)		
	Incident CHD	**Incident CVD**	**Incident MI**
Sex (1=M, 2=F)	0·43 (0·36 , 0·51)	0·54 (0·47 , 0·62)	0·45 (0·36 , 0·57)
Blood pressure treatment	1·34 (1·13 , 1·58)	1·24 (1·08 , 1·44)	1·27 (1·00 , 1·61)
Systolic blood pressure – mm Hg	1·01 (1·01 , 1·02)	1·01 (1·01 , 1·02)	1·01 (1·00 , 1·02)
Diastolic blood pressure – mm Hg	0·99 (0·98 , 1·00)	1·00 (0·99 , 1·00)	0·99 (0·98 , 1·00)
Body-mass index – weight(kg) / (height(m))2	1·03 (1·01 , 1·04)	1·02 (1·01 , 1·04)	1·04 (1·02 , 1·06)
Diabetes mellitus	2·01 (1·64 , 2·47)	1·93 (1·62 , 2·30)	1·78 (1·33 , 2·38)
LDL cholesterol – mmol/l	1·32 (1·23 , 1·42)	1·17 (1·10 , 1·24)	1·34 (1·21 , 1·48)
HDL cholesterol – mmol/l	0·42 (0·33 , 0·54)	0·49 (0·40 , 0·59)	0·46 (0·33 , 0·65)
Current smoking	1·89 (1·61 , 2·22)	1·86 (1·62 , 2·13)	2·32 (1·86 , 2·89)
Family history of MI	1·40 (1·20 , 1·64)	1·27 (1·12 , 1·45)	1·25 (1·01 , 1·55)
Genetic score 2†	1·01 (0·79 , 1·29)	0·98 (0·80 , 1·19)	1·04 (0·74 , 1·45)
Genetic score 3	1·13 (0·89 , 1·43)	1·15 (0·95 , 1·40)	1·16 (0·84 , 1·61)
Genetic score 4	1·42 (1·13 , 1·78)	1·26 (1·04 , 1·53)	1·38 (1·00 , 1·91)
Genetic score 5	1·67 (1·33 , 2·08)	1·60 (1·33 , 1·92)	1·72 (1·27 , 2·34)

* Association tested with Wald test using a Cox-proportional hazards model and the results were combined using fixed effects meta-analysis. [2]
† The genetic risk score divided into quintiles (each class contains 20% of participants).
Abbreviations: HR, hazard ratio; CI, confidence interval; CHD, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Supplementary Table 4. Pooled associations between the genotype score and incident cardiovascular disease (CVD), coronary heart disease (CHD) and myocardial infarction (MI) with and without the family history (FH) in FINRISK 92, FINRISK 97 and FINRISK 02.*

		Genotype score quintile					
	Model	**1 (ref.)**	**2**	**3**	**4**	**5**	**P for trend**
HR (95% CI) CHD	Pooled	1·00	1·01 (0·79 , 1·28)	1·13 (0·90 , 1·44)	1·43 (1·14 , 1·80)	1·69 (1·35 , 2·11)	$2{\cdot}8\times10^{-9}$
	Pooled with FH	1·00	1·01 (0·79 , 1·29)	1·13 (0·89 , 1·43)	1·42 (1·13 , 1·78)	1·67 (1·33 , 2·08)	$6{\cdot}4\times10^{-9}$
HR (95% CI) CVD	Pooled	1·00	0·97 (0·80 , 1·19)	1·15 (0·95 , 1·40)	1·27 (1·05 , 1·54)	1·60 (1·33 , 1·93)	$7{\cdot}8\times10^{-10}$
	Pooled with FH	1·00	0·98 (0·80 , 1·19)	1·15 (0·95 , 1·40)	1·26 (1·04 , 1·53)	1·60 (1·33 , 1·92)	$1{\cdot}5\times10^{-9}$
HR (95% CI) MI	Pooled	1·00	1·04 (0·74 , 1·45)	1·17 (0·84 , 1·62)	1·39 (1·01 , 1·92)	1·73 (1·28 , 2·36)	$5{\cdot}1\times10^{-6}$
	Pooled with FH	1·00	1·04 (0·74 , 1·45)	1·16 (0·84 , 1·61)	1·38 (1·00 , 1·91)	1·72 (1·27 , 2·34)	$6{\cdot}6\times10^{-6}$

* Associations tested with Wald test using a Cox-proportional hazards model adjusted traditional risk factors and with and without family history of MI. Results were combined using fixed effects meta-analysis. [2]
Abbreviations: HR, hazard ratio; CI, confidence interval

Supplementary Table 5. Pooled associations between the genotype score and incident cardiovascular disease (CVD), coronary heart disease (CHD) and myocardial infarction (MI) with and without the 9p21 locus.*

		Genotype score quintile					
	Model	**1 (ref.)**	**2**	**3**	**4**	**5**	**P for trend**
HR (95% CI) CHD	Pooled	1·00	1·00 (0·80 , 1·25)	1·17 (0·94 , 1·46)	1·39 (1·12 , 1·72)	1·66 (1·35 , 2·04)	$7{\cdot}3\times10^{-10}$
	Pooled with 9p21	1·00	0·95 (0·75 , 1·21)	1·12 (0·88 , 1·41)	1·31 (1·04 , 1·66)	1·51 (1·19 , 1·91)	$1{\cdot}4\times10^{-6}$
HR (95% CI) CVD	Pooled	1·00	0·95 (0·80 , 1·12)	1·10 (0·93 , 1·29)	1·16 (0·99 , 1·36)	1·50 (1·29 , 1·75)	$1{\cdot}9\times10^{-10}$
	Pooled with 9p21	1·00	0·92 (0·77 , 1·10)	1·03 (0·87 , 1·22)	1·09 (0·92 , 1·31)	1·40 (1·18 , 1·67)	$6{\cdot}9\times10^{-7}$
HR (95% CI) MI	Pooled	1·00	0·99 (0·76 , 1·27)	1·11 (0·87 , 1·43)	1·19 (0·93 , 1·53)	1·46 (1·15 , 1·86)	$2{\cdot}9\times10^{-5}$
	Pooled with 9p21	1·00	0·93 (0·71 , 1·22)	1·02 (0·78 , 1·33)	1·13 (0·86 , 1·48)	1·30 (1·00 , 1·71)	0·013

* Associations tested with Wald test using a Cox-proportional hazards model adjusted traditional risk factors and with and without 9p21 locus, rs4977574. Results from FINRISK 92, FINRISK 97, FINRISK 02, Health 2000, and Malmö Diet and Cancer Cardiovascular cohort were combined using fixed effects meta-analysis. [2]
Abbreviations: HR, hazard ratio; CI, confidence interval

References

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