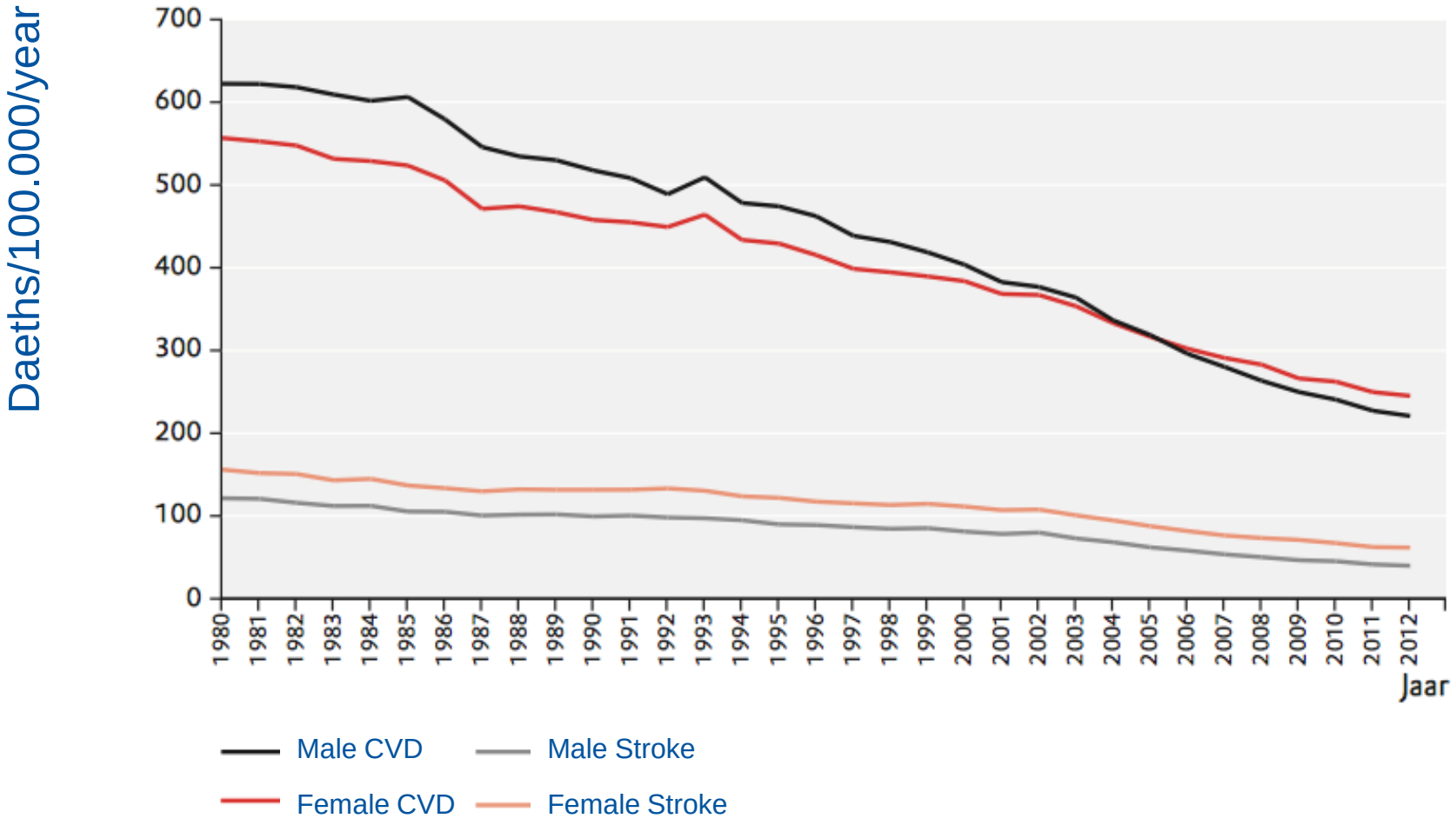
Athero-Express

G.Pasterkamp
UMCU

University Medical Center
Utrecht

Age corrected death rate cardiovascular disease in the Netherlands



Atherosclerosis: current concept

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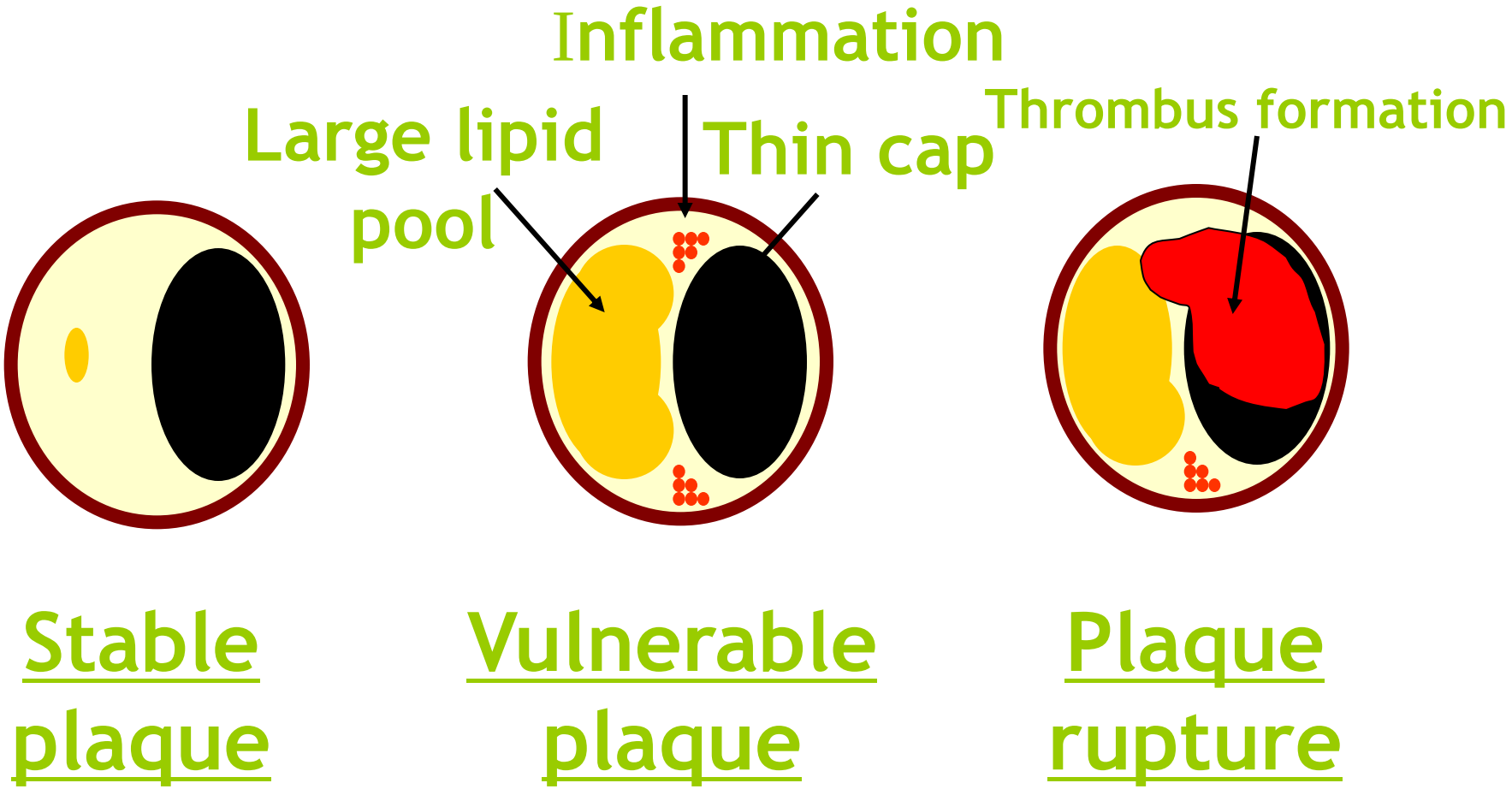
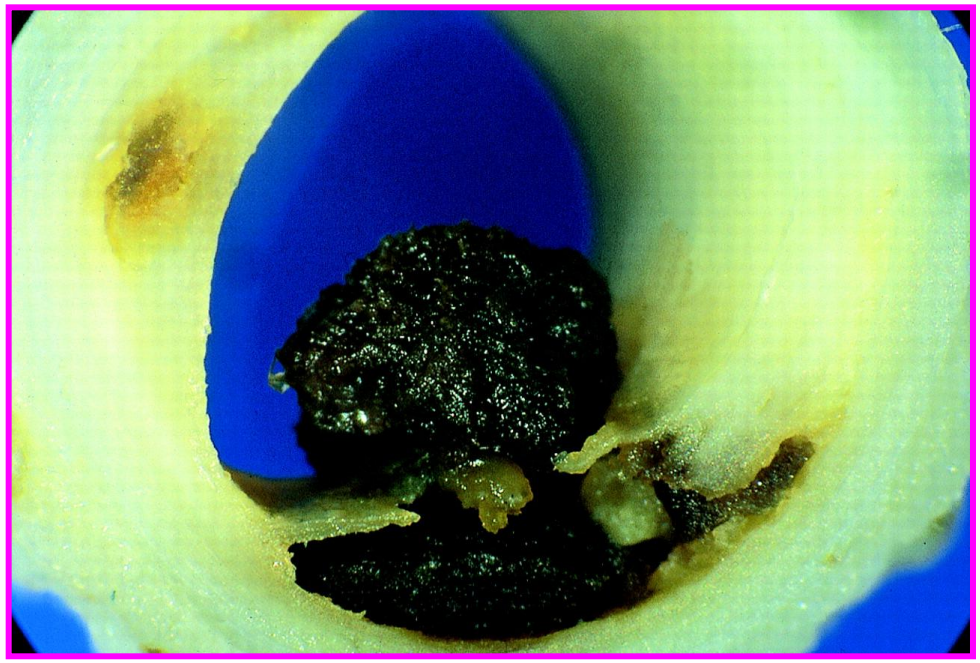
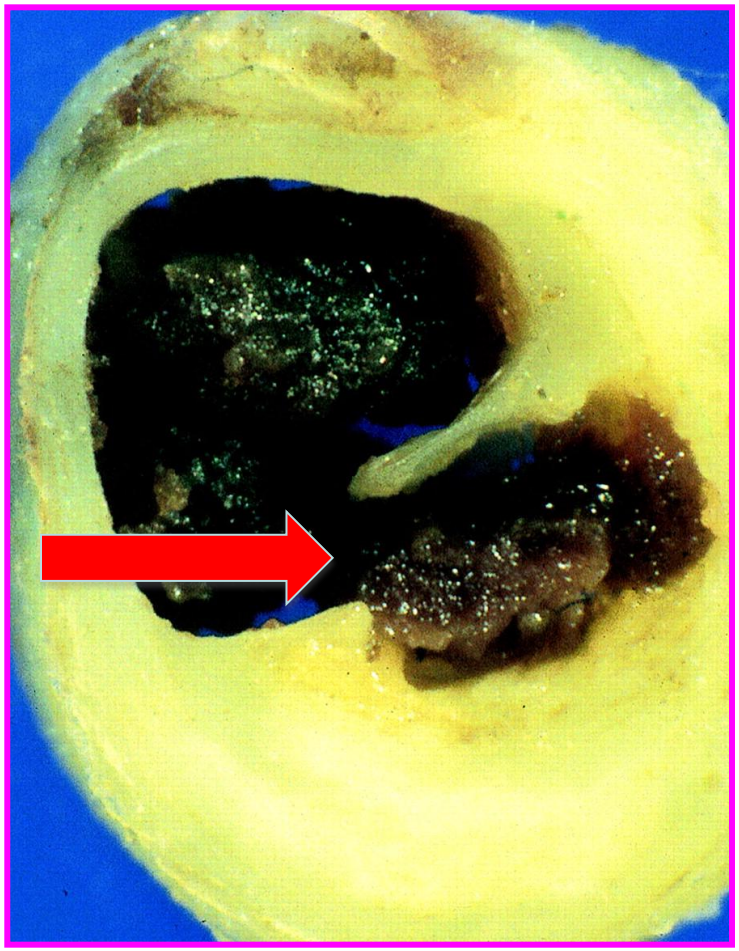
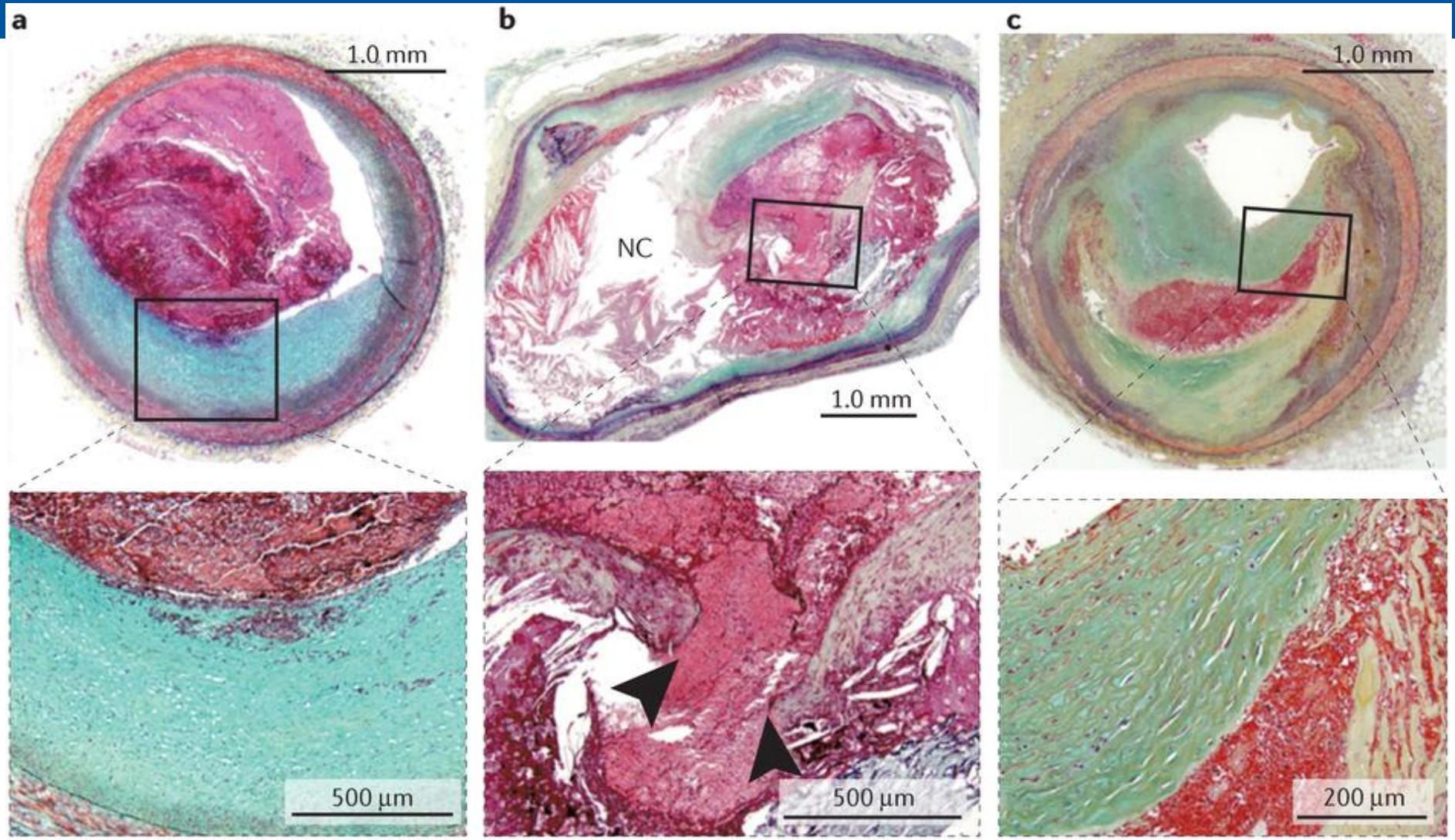
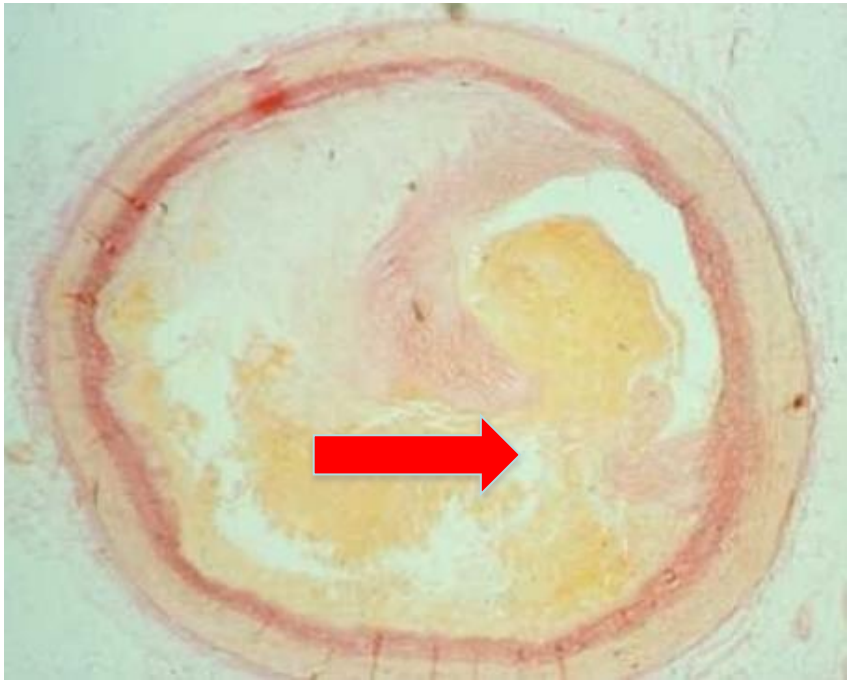


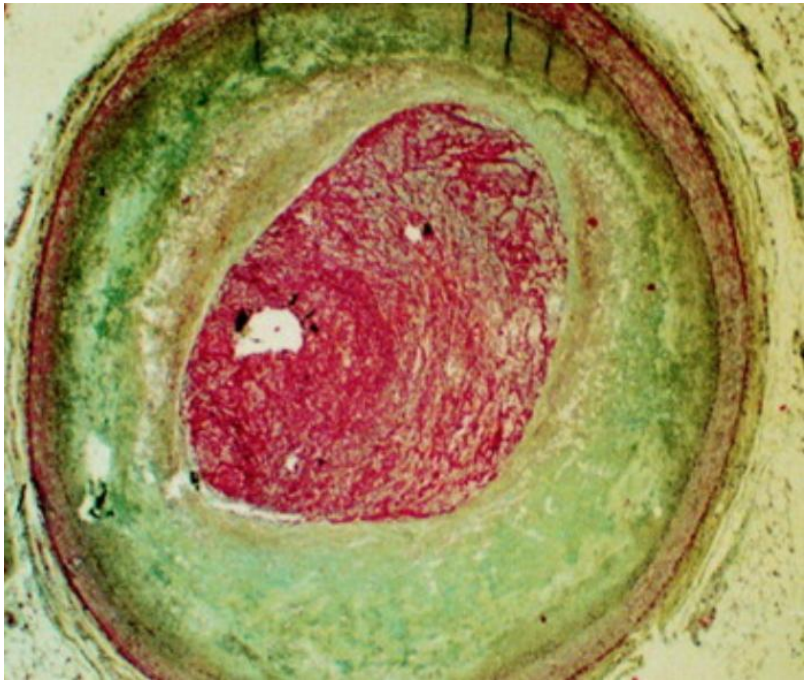




Davies et al.


a
1.0 mm
500 µm
b
NC
1.0 mm
500 µm
c
1.0 mm
200 µm





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J Am Coll Cardiol. 2015 Mar 3;65(8):846-55. doi: 10.1016/j.jacc.2014.11.041. Epub 2015 Jan 16.

The myth of the "vulnerable plaque": transitioning from a focus on individual lesions to atherosclerotic disease burden for coronary artery disease risk assessment.

Arbab-Zadeh A[1], Fuster V[2].

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2 Mount Sinai Medical Center, Icahn School of Medicine, New York, New York.

Abstract

The cardiovascular science community has pursued the quest to identify vulnerable atherosclerotic plaque in patients for decades, hoping to prevent acute coronary events. However, despite major advancements in imaging technology that allow visualization of rupture-prone plaques, clinical studies have not demonstrated improved risk prediction compared with traditional approaches. Considering the complex relationship between plaque rupture and acute coronary event risk suggested by pathology studies and confirmed by clinical investigations, these results are not surprising. This review summarizes the evidence supporting a multifaceted hypothesis of the natural history of atherosclerotic plaque rupture. Managing patients at risk of acute coronary events mandates a greater focus on the atherosclerotic disease burden rather than on features of individual plaques.

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The NEW ENGLAND JOURNAL of MEDICINE

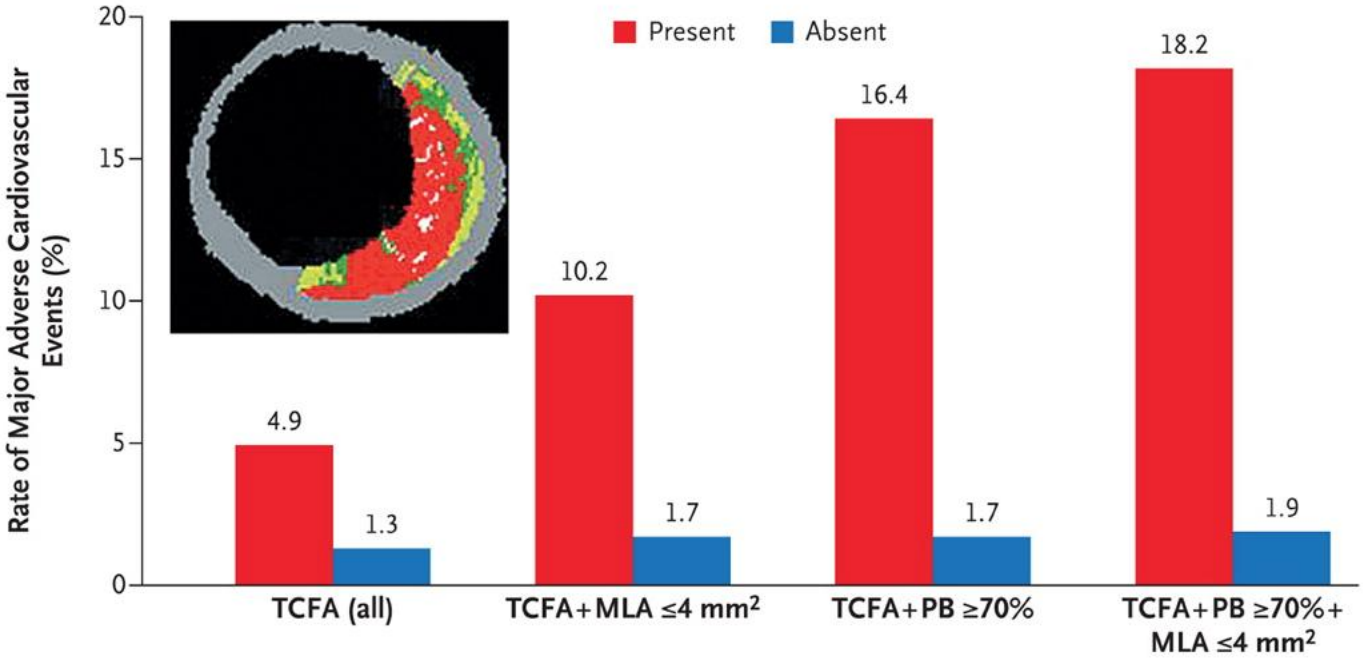
ORIGINAL ARTICLE

A Correction Has Been Published

A Prospective Natural-History Study of Coronary Atherosclerosis

Gregg W. Stone, M.D., Akiko Maehara, M.D., Alexandra J. Lansky, M.D., Bernard de Bruyne, M.D., Ecaterina Cristea, M.D., Gary S. Mintz, M.D., Roxana Mehran, M.D., John McPherson, M.D., Naim Farhat, M.D., Steven P. Marso, M.D., Helen Parise, Sc.D., Barry Templin, M.B.A., Roseann White, M.A., Zhen Zhang, Ph.D., and Patrick W. Serruys, M.D., Ph.D., for the PROSPECT Investigators*

N Engl J Med 2011; 364:226-235 | January 20, 2011 | DOI: 10.1056/NEJMoa1002358



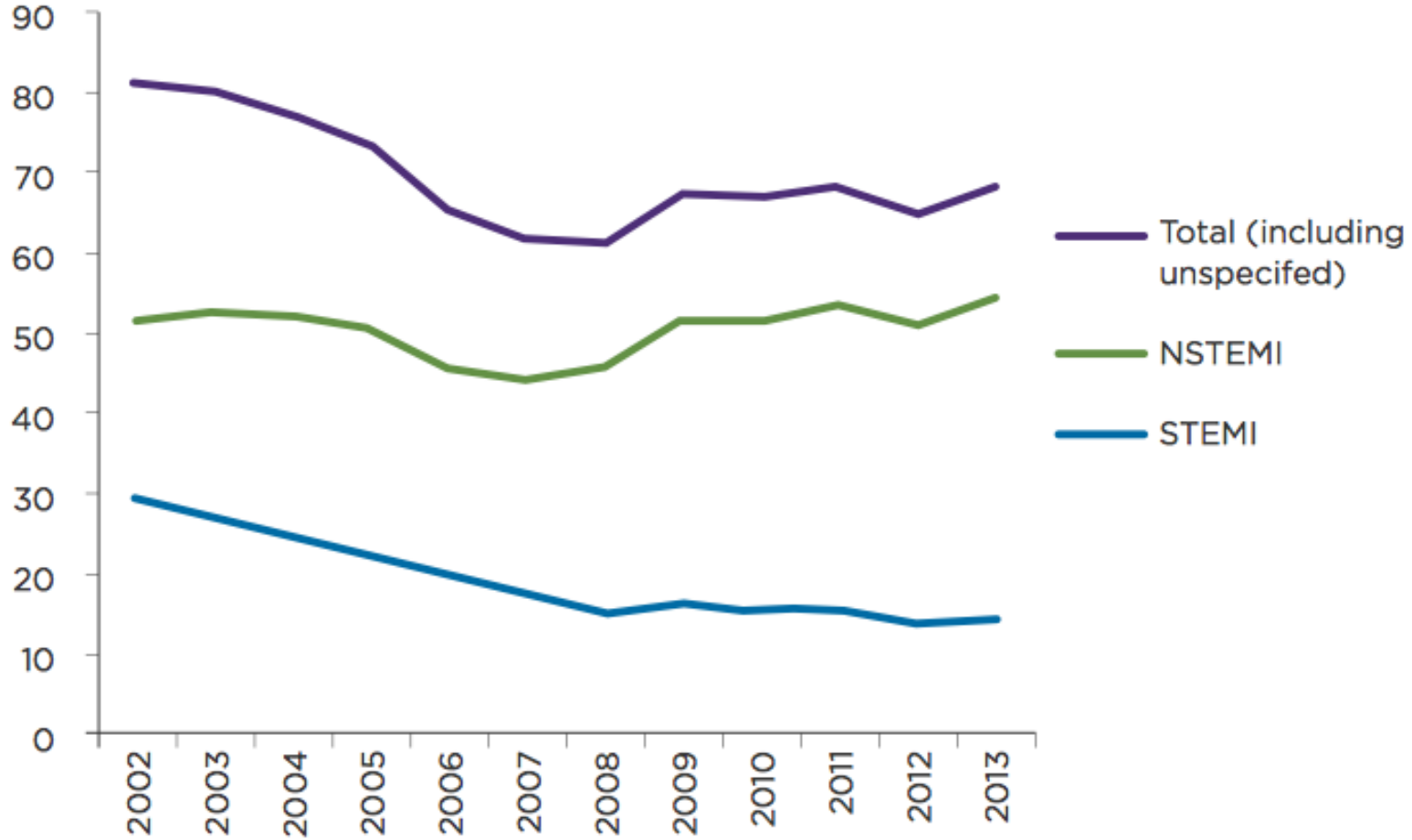
Lesion hazard ratio (95% CI)	3.90 (2.25–6.76)	6.55 (3.43–12.51)	10.83 (5.55–21.10)	11.05 (4.39–27.82)
P value	<0.001	<0.001	<0.001	<0.001
Prevalence (%)	46.7	15.9	10.1	4.2

- Identified were 596 thin-cap fibroatheromas
- Major adverse cardiovascular events, 26 (51.0%) were thin-cap fibroatheromas

Trends in Acute Myocardial Infarction Incidence, Detection, and Treatment

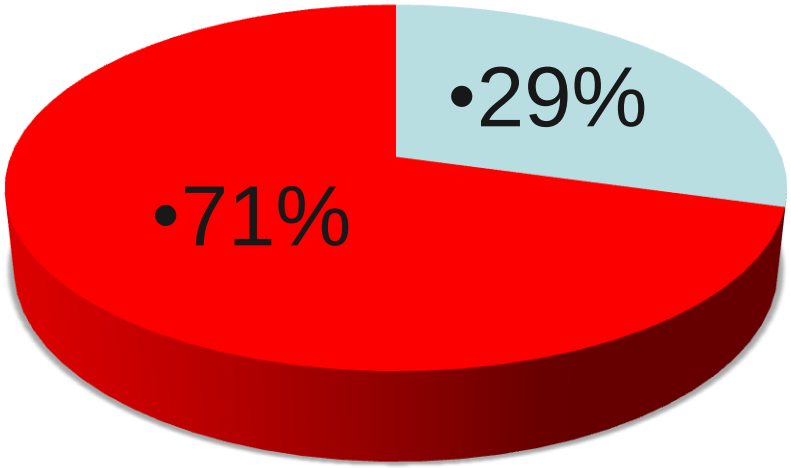
Based on the 2015 50 Top Cardiovascular Hospitals Study

Figure 1: AMI Rate per 10,000 Aged Medicare Part A Beneficiaries

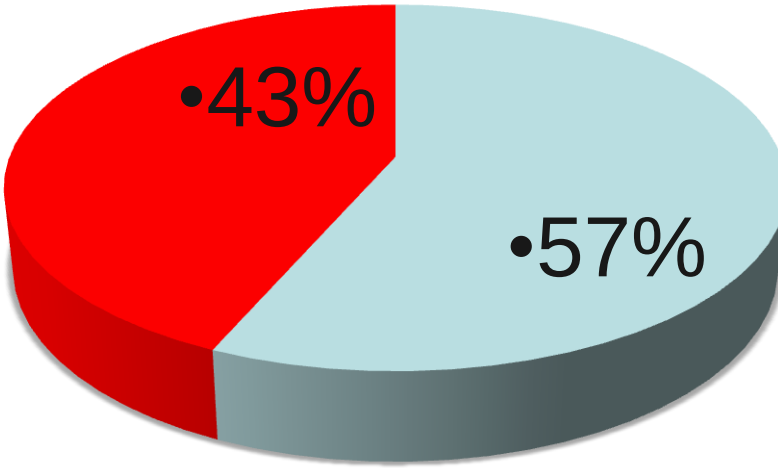


Merged data from OCT and pathology studies

•STEMI



•NSTEMI



rupture

erosion

G Pasterkamp, H den Ruijter, P Libby. Nature reviews Cardiology 2016

•1970 •1990 •2010

•Antihypertensive
•medication

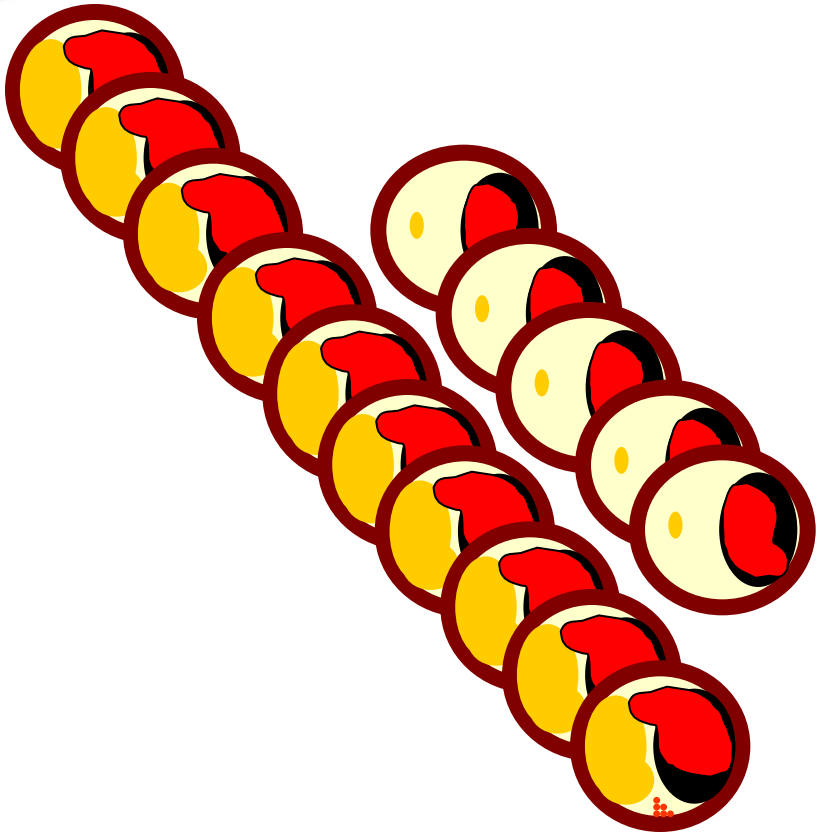
•Lipid lowering
•therapy

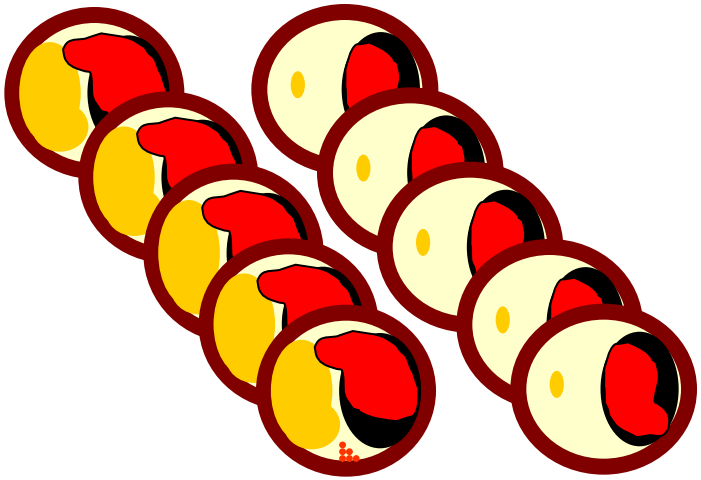
•Smoking policy
•Risk factor treatment

•STEMI
•NSTEMI

•Total burden of ACS

•STEMI
•NSTEMI





. Nature reviews Cardiology 2016

Death rate following stroke, the Netherlands

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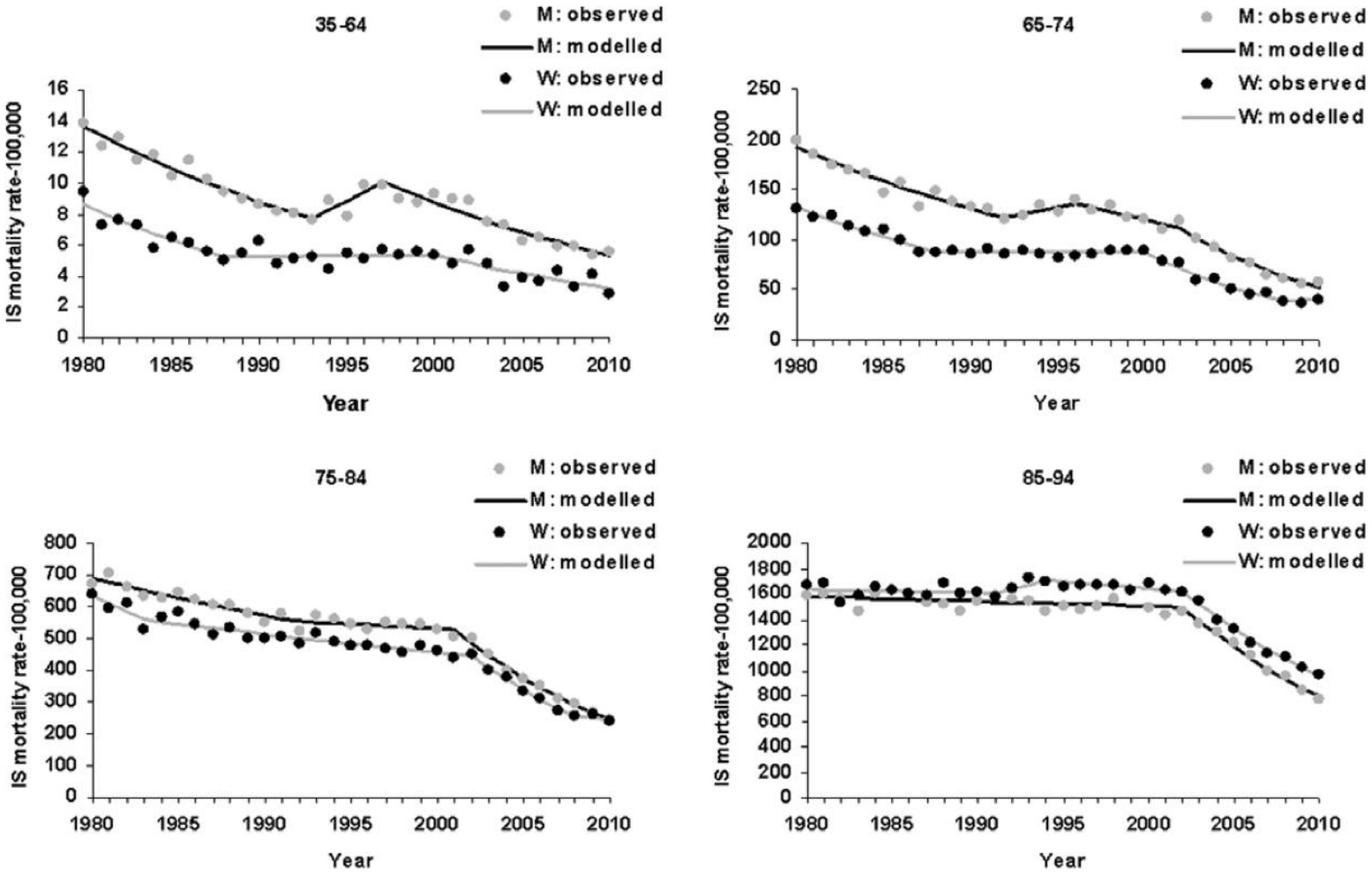

Vaartjes et al. Stroke 2013

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- Collecting endarteriectomy specimen (carotid, femoral and AAA) and blood (start 2002)
- Now >4000 patients included.
- GWAS data available of 1800 patients, whole genome methylation of 700 plaques.

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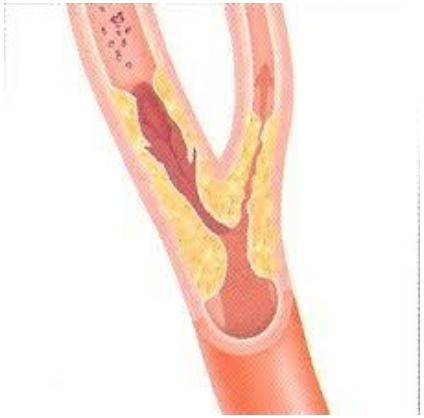
- Femoral+ iliac



- carotid

- AAA

- N= 1000
- N= 2400
- N= 600

Time-Dependent Changes in Atherosclerotic Plaque Composition in Patients Undergoing Carotid Surgery

Guus W. van Lammeren, MD, PhD*; Hester M. den Ruijter, PhD*; Joyce E.P. Vrijenhoek, MD; Sander W. van der Laan, MSc; Evelyn Velema, MSc; Jean-Paul P.M. de Vries, MD, PhD; Dominique P.V. de Kleijn, PhD; Aryan Vink, MD, PhD; Gert Jan de Borst, MD, PhD; Frans L. Moll, MD, PhD; Michiel L. Bots, MD, PhD; Gerard Pasterkamp, MD, PhD

Background—Time-dependent trends in the incidence of cardiovascular disease have been reported in high-income countries. Because atherosclerosis underlies the majority of cardiovascular diseases, we investigated temporal changes in the composition of atherosclerotic plaques removed from patients undergoing carotid endarterectomy.

Methods and Results—The Athero-Express study is an ongoing, longitudinal, vascular biobank study that includes the collection of atherosclerotic plaques of patients undergoing primary carotid endarterectomy in the province of Utrecht from 2002 to 2011. Histopathologic features of plaques of 1583 patients were analyzed in intervals of 2 years. The analysis included quantification of collagen, calcifications, lipid cores, plaque thrombosis, macrophages, smooth muscle cells, and microvessels. Large atheroma, plaque thrombosis, macrophages, and calcifications were less frequently observed over time, with adjusted odds ratios of 0.72 (95% confidence interval, 0.650-0.789), 0.62 (95% confidence interval, 0.569-0.679), 0.87 (95% confidence interval, 0.800-0.940), and 0.75 (95% confidence interval, 0.692-0.816) per 2-year increase in time, respectively. These changes in plaque characteristics were consistently observed in patient subgroups presenting with stroke, transient ischemic attack, ocular symptoms, and asymptomatic patients. Concomitantly, risk factor management and secondary prevention strategies among vascular patients scheduled for carotid endarterectomy significantly improved over the past decade.

Conclusions—In conclusion, over the past decade, atherosclerotic plaques harvested during carotid endarterectomy show a time-dependent change in plaque composition characterized by a decrease in features currently believed to be causal for plaque instability. This appears to go hand in hand with improvements in risk factor management. (***Circulation*.2014;129:2269-2276.**)

Key Words: endarterectomy, carotid ■ histology ■ plaque, atherosclerotic ■ primary prevention

Reproduced in femoral artery plaques

Plaque composition	2002-2003 n=250	2004-2005 n=408	2006-2007 n=352	2008-2009 n=332	2010-2010 n=271
> 40% lipid (%)	33	36	27	21	14*
Intra plaque bleeding (%)	74	75	62	49	37*
Vessel density (AU)	6.7	8.5	7.7	7.3	6.3

Intra plaque bleeding over time

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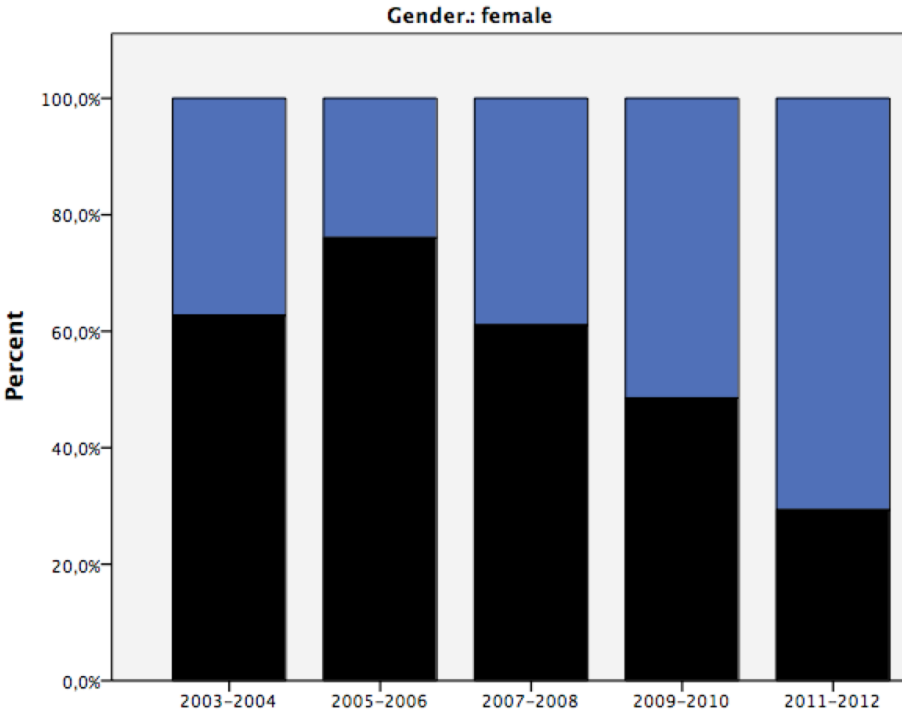

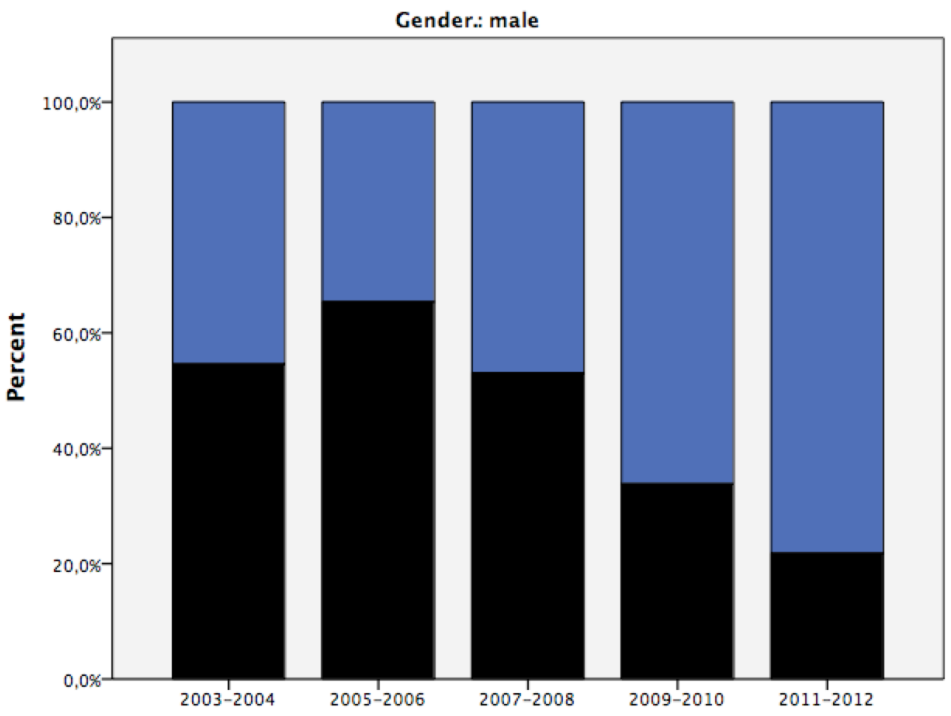

Calcification over time

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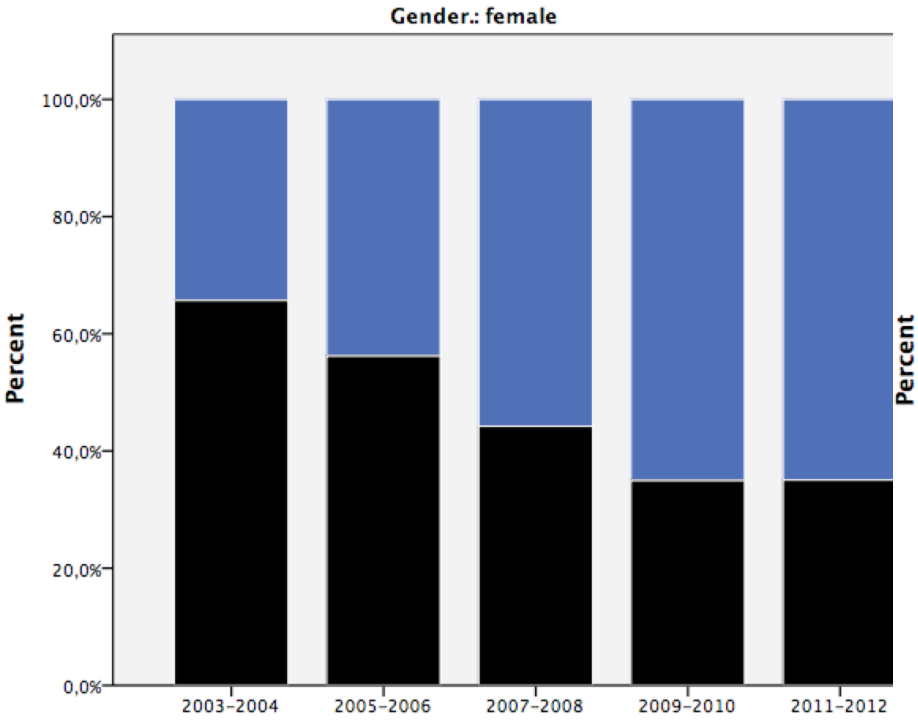

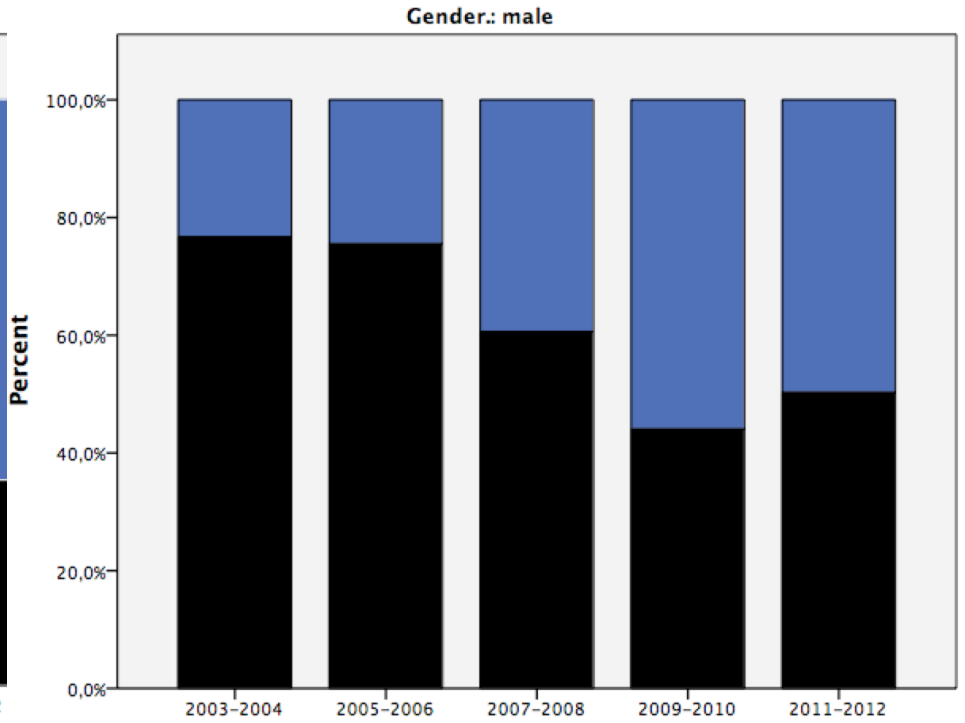

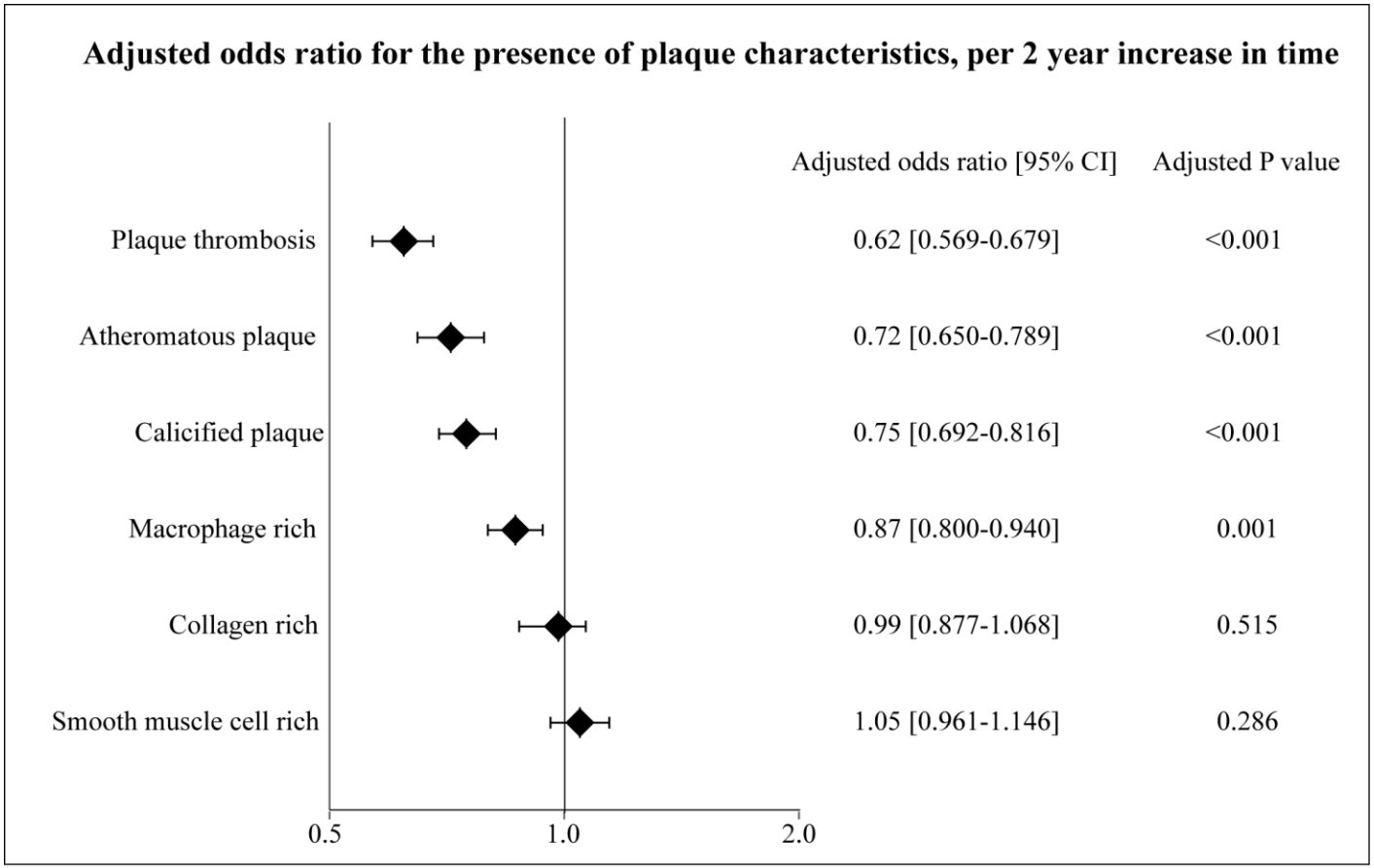

Lammeren et al. Circulation 2014

Femoral artery plaques (% of plaques)

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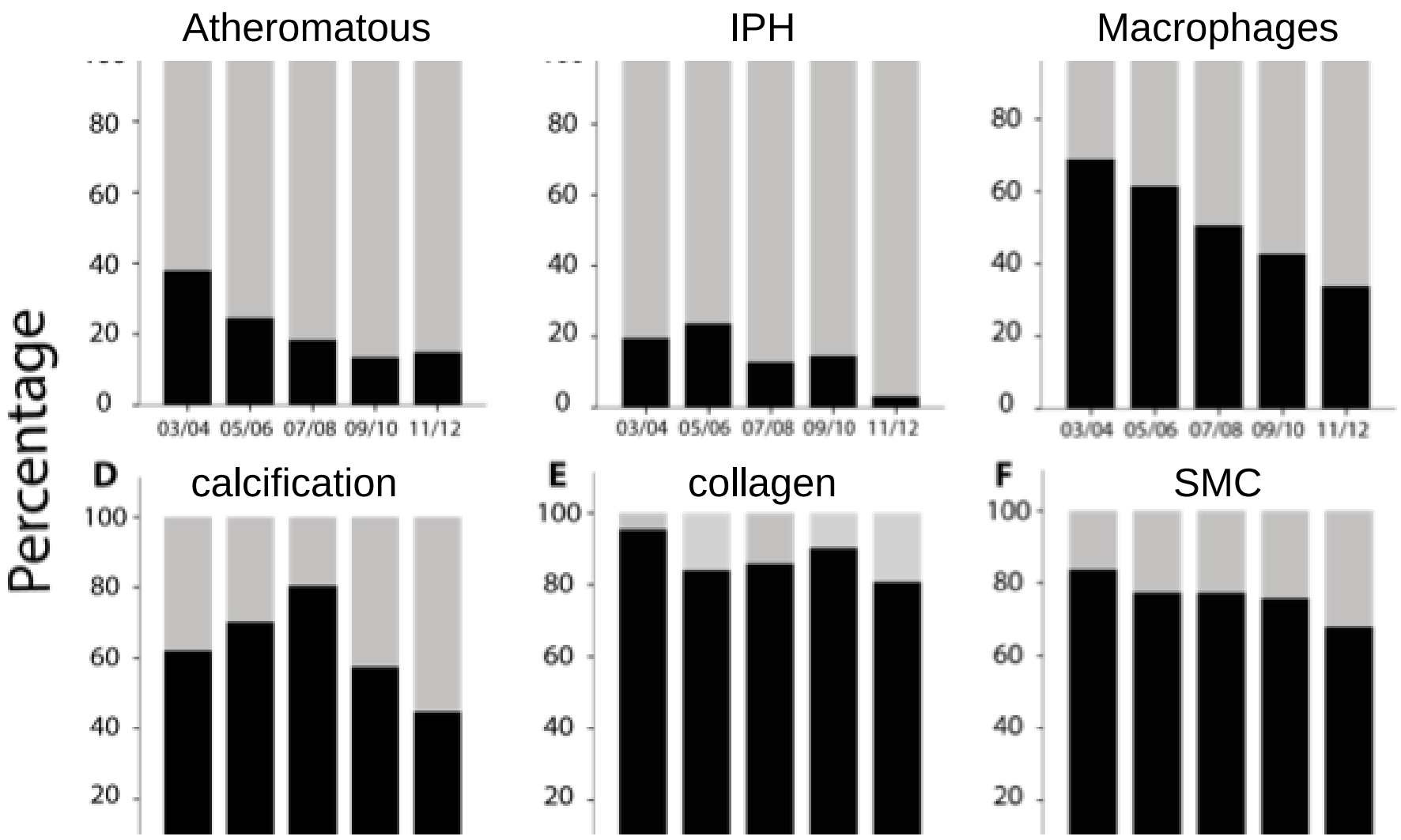

If underlying pathology is shifting: implications

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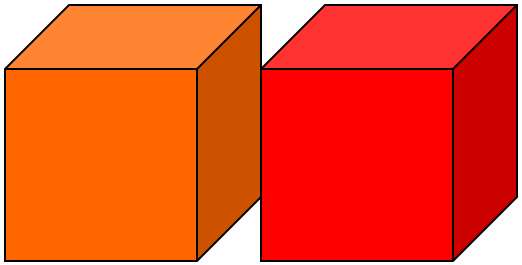
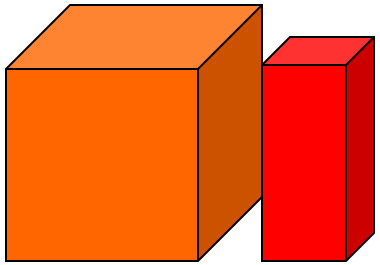


Stable lesion

Vulnerable lesion



- In the presence of (a)symptomatic disease: much more stable lesions are observed.
- For increasing number of patients: Are we still chasing the right target, e.g. the “vulnerable plaque”?
- What does this imply for tissue and plasma biobanks (biomarkers): Do data and samples obtained before 2000 still represent current patient population?

Patients undergoing carotid endarterectomy

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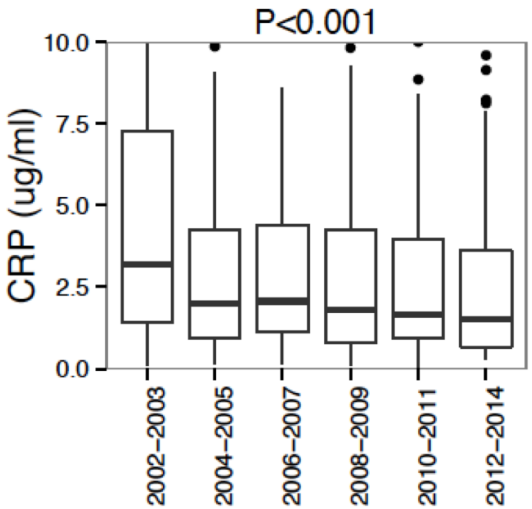
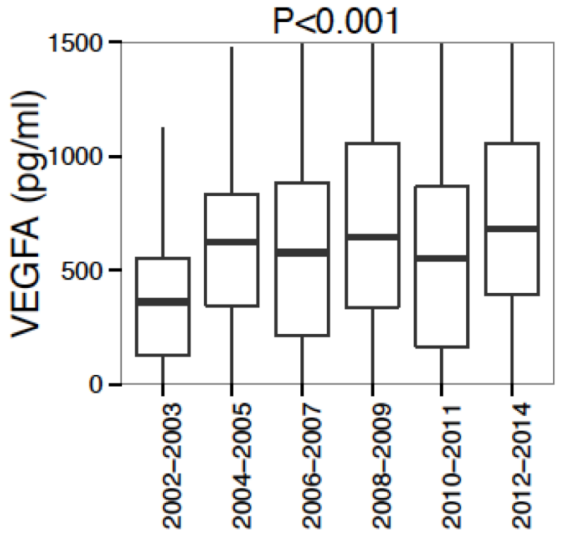
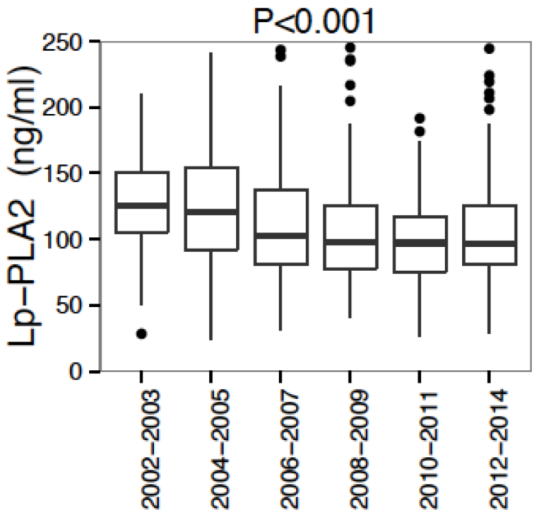
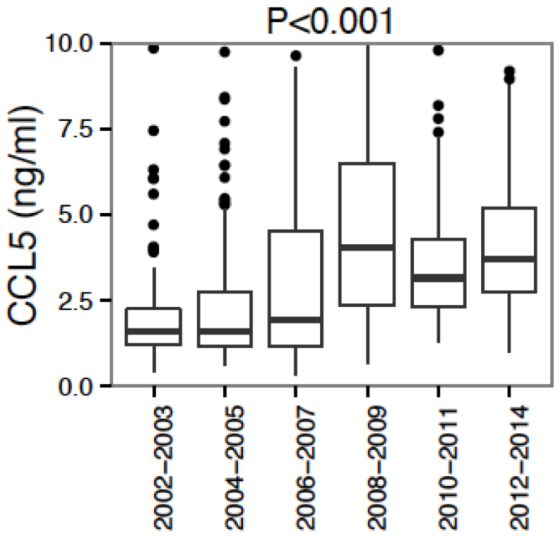




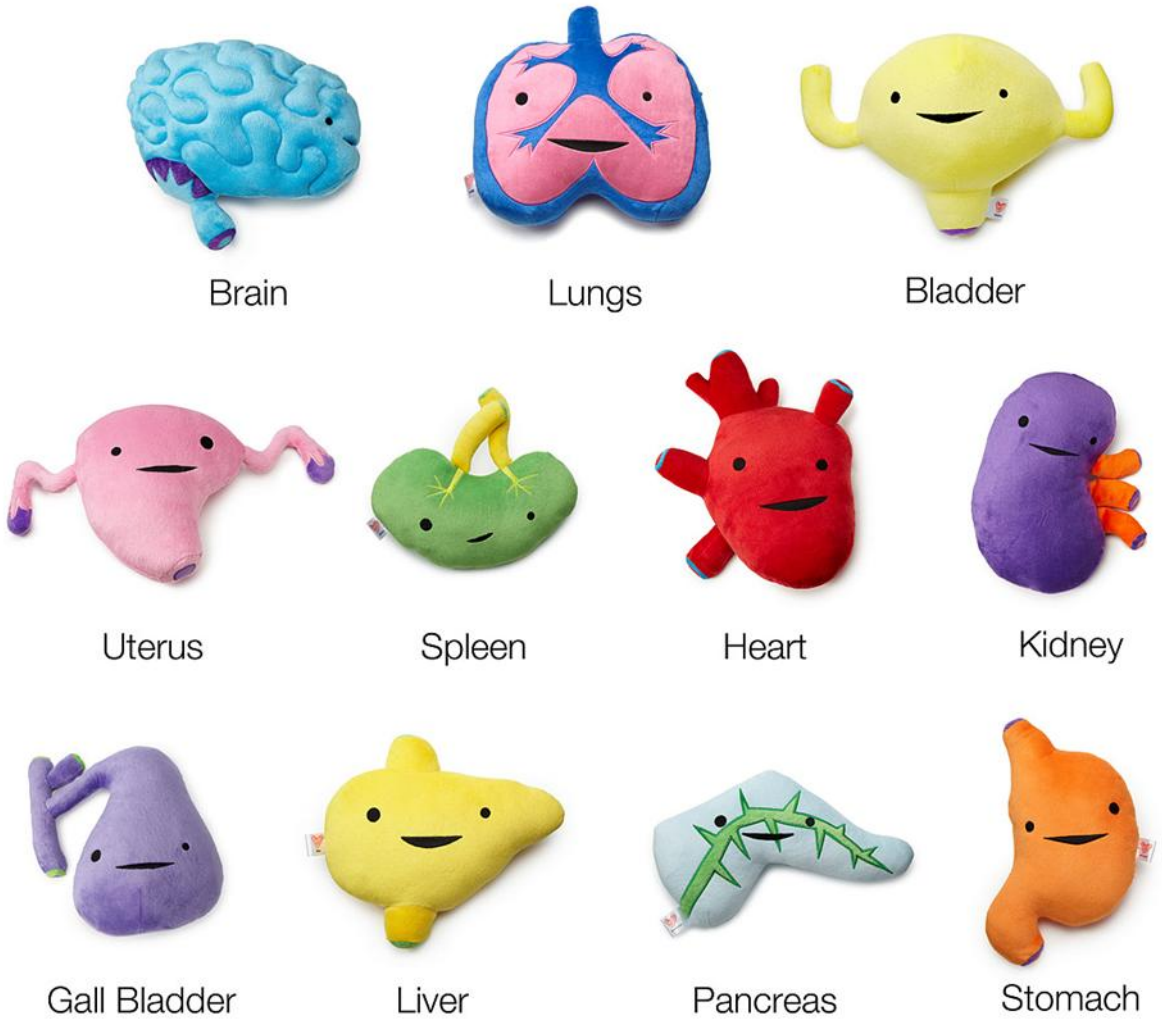




Governmental policy in the Netherlands: smoking banned from public areas since 2004.

All organs and cells share the same DNA

But how the genetic information is used differs for each organ



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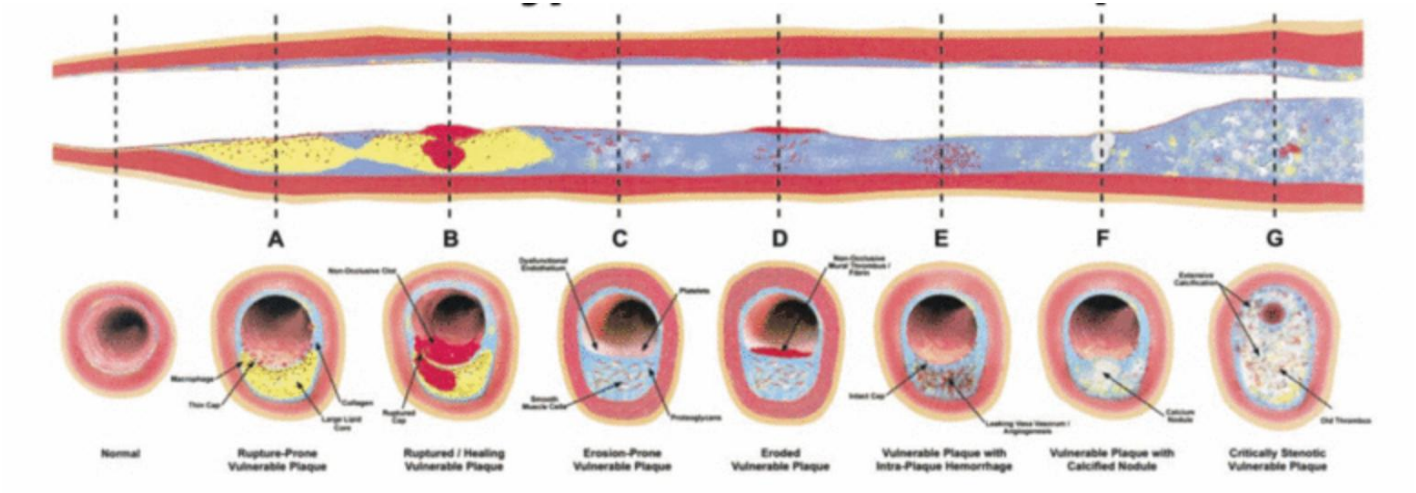
A
B
C
D
E
F
G
Normal
Rupture-Prone Vulnerable Plaque
Ruptured / Healing Vulnerable Plaque
Erosion-Prone Vulnerable Plaque
Eroded Vulnerable Plaque
Vulnerable Plaque with Intra-Plaque Hemorrhage
Vulnerable Plaque with Calcified Nodule
Critically Stenotic Vulnerable Plaque

Athero-Express

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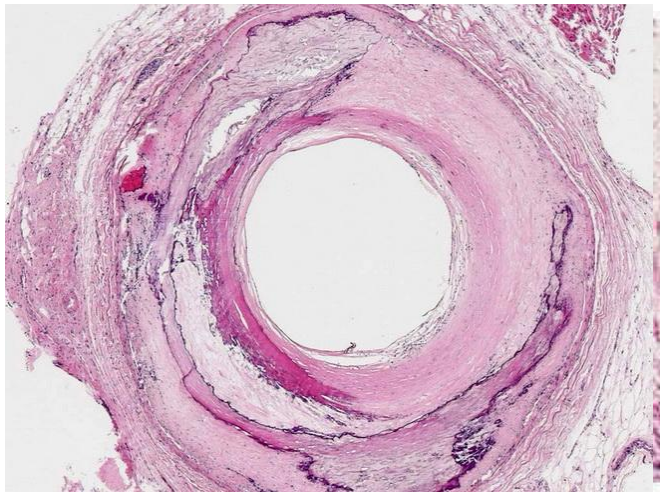
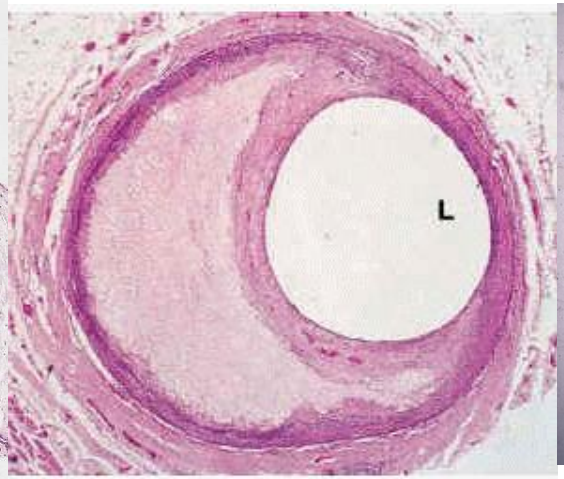
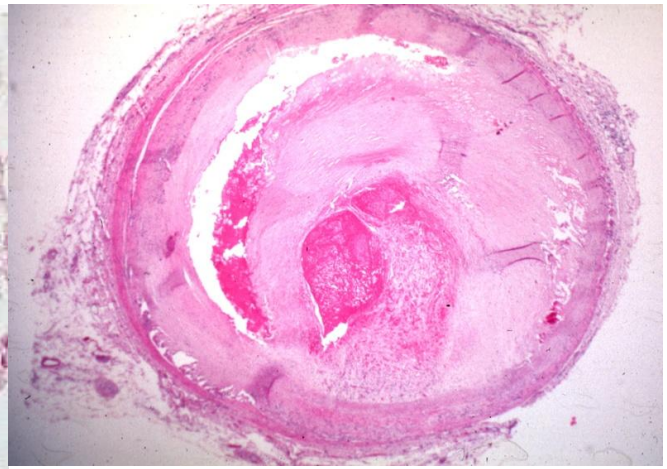
Are plaque characteristics determined by genetic architecture?



•kalk



•vet



•bloedingen

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•Van der Laan S.W., *et al.* **In preparation.**

Associations of 57 Cardiovascular Risk Loci with atherosclerotic plaque traits

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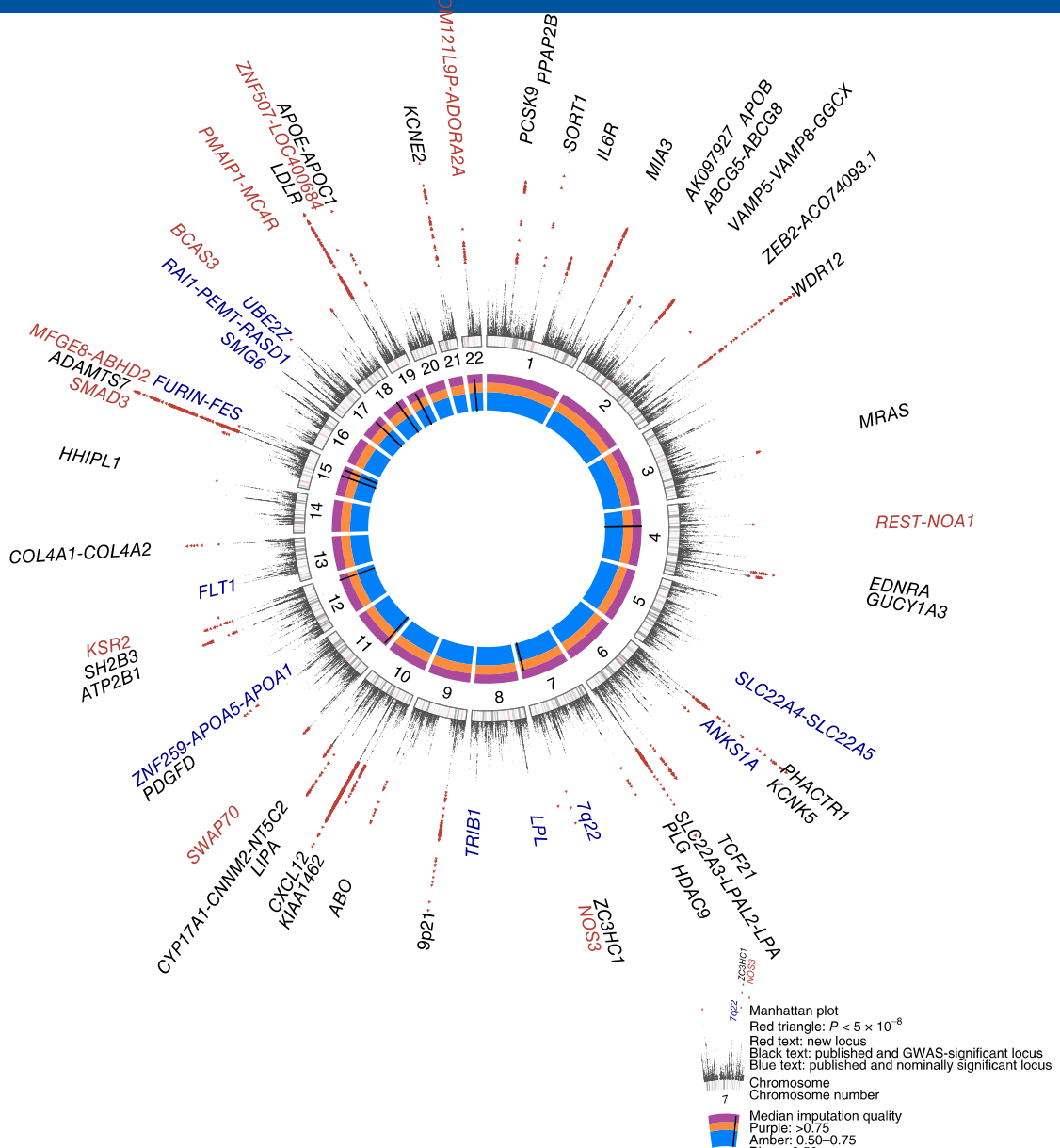
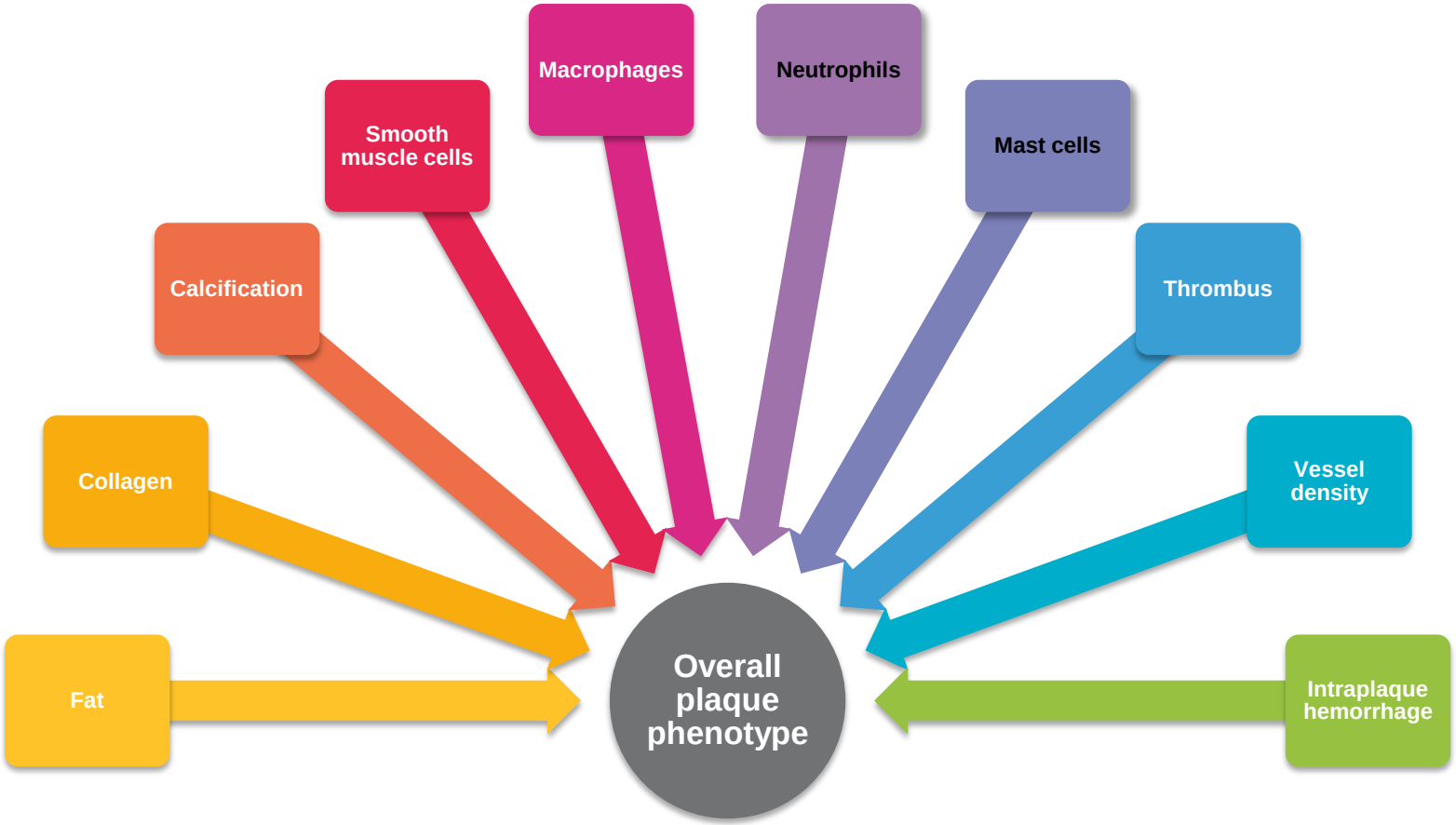


Questions

- To what extent do the 57 known CAD susceptibility loci correlate with (vulnerable) plaque characteristics?



•Van der Laan S.W., *et al.* **In preparation.**

19 out of 57 CAD risk variants associate with a plaque characteristic
a ~6.5-fold enrichment, p = 3.8x10^{-11}

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Phenotype	Locus	OR [95% CI]	P	Disease	GWAS dir.
Calcification	*WDR12*	0.74 [0.58 – 0.94]	0.012	CAD	+
Calcification	*ZNF259-APOA5-APOA1*	1.26 [1.01 – 1.58]	0.043	CAD	+
Calcification	*LDLR*	1.59 [1.21 – 2.07]	6.29x10^{-4}	CAD	-
Calcification	*KCNE2 (gene desert)*	0.71 [0.55 – 0.91]	7.92x10^{-3}	CAD	-
Collagen	*NOS3*	1.73 [1.03 – 2.90]	0.031	CAD	-
Collagen	*SMG6*	0.78 [0.64 – 0.95]	0.012	CAD	-
Fat	*MIA3*	1.27 [1.02 – 1.56]	0.029	CAD	+
Fat	*ZEB2-ACO74093.1*	1.38 [1.00 – 1.92]	0.049	CAD	-
Fat	*7q22*	0.63 [0.51 – 0.77]	5.09x10^{-6}	CAD	-
Fat	*NOS3*	1.73 [1.03 – 2.90]	0.031	CAD	-
Fat	*TRIB1*	0.77 [0.65 – 0.92]	3.54x10^{-3}	CAD	-
Fat	*ABO*	1.27 [1.02 – 1.59]	0.034	CAD	-
IPH	*LIPA*	1.27 [1.07 – 1.52]	6.33x10^{-3}	CAD	-

Phenotype	Locus	β [s.e.m.]	P	Disease	GWAS dir.
Macrophages	*BCAS3*	-0.137 [0.054]	0.011	CAD	-
SMCs	*LIPA*	0.083 [0.040]	0.036	CAD	-
SMCs	*COL4A1/A2*	0.103 [0.042]	0.015	CAD	-
Vessels	*SWAP70*	0.079 [0.040]	0.046	CAD	+
Vessels	*KSR2*	0.109 [0.040]	6.97x10^{-3}	CAD	-
Vessels	*UBE2Z*	-0.080 [0.038]	0.034	CAD	-

•Van der Laan S.W., *et al.* **In preparation.**

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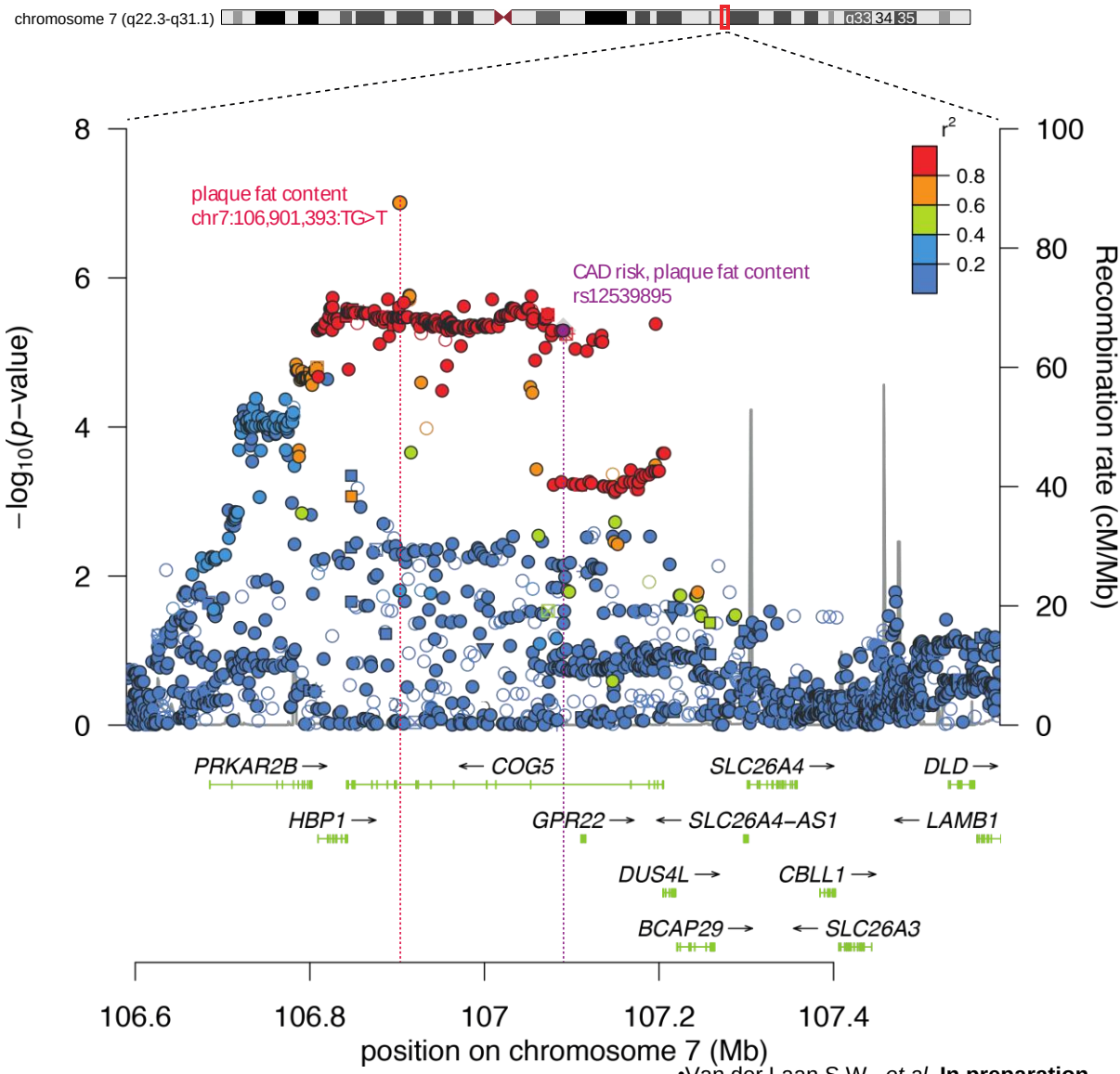
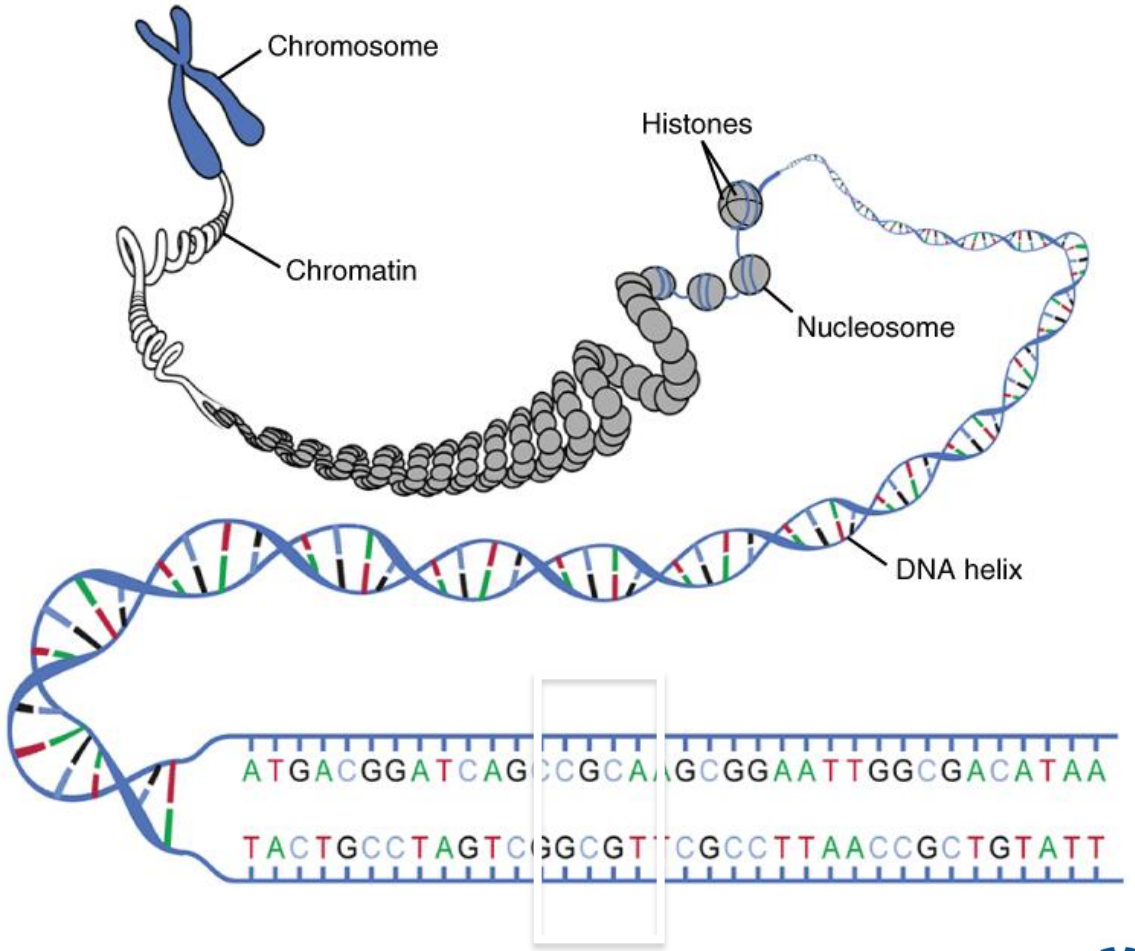
Variant rs12539895 on 7q22 is associated with **less intraplaque fat content** (OR = 0.63, A-allele)

Same allele associated with **decreased susceptibility for CAD** (OR = 0.96)

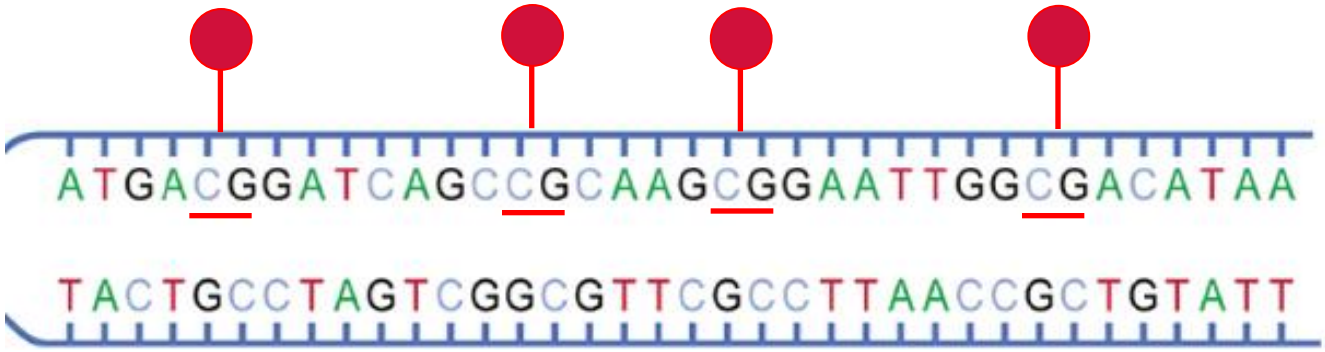
Most significant: chr7:106,901,393:I:D, TG > T in the intron of *COG5* (OR = 0.52 [0.40-0.66 95% CI] per A-allele, p = 2.14×10^{-7}, CAF= 0.17)

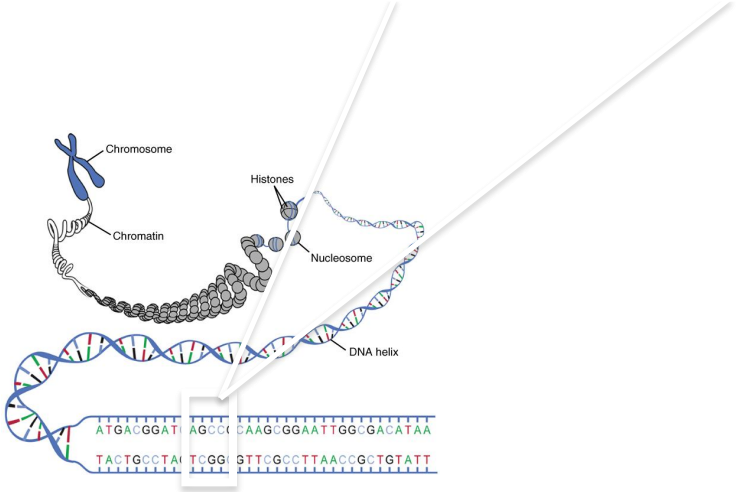


•Van der Laan S.W., *et al.* **In preparation.**


Chromosome
Histones
Chromatin
Nucleosome
DNA helix
ATGACGGATCAG
GCGGAATTGGCGACATAA
TACTGCCTAGTC
CGCCTTAACCGCTGTATT

Methylation: no transcription





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Case: the hunger study

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- Winter 1944-1945
  - 3.5 million people
  - 20.000 deaths

Case: the Hongerwinter studie

Normal birthweight

low birthweight

Case: the Hongerwinter studie

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Later age: obesity +

Normal weight

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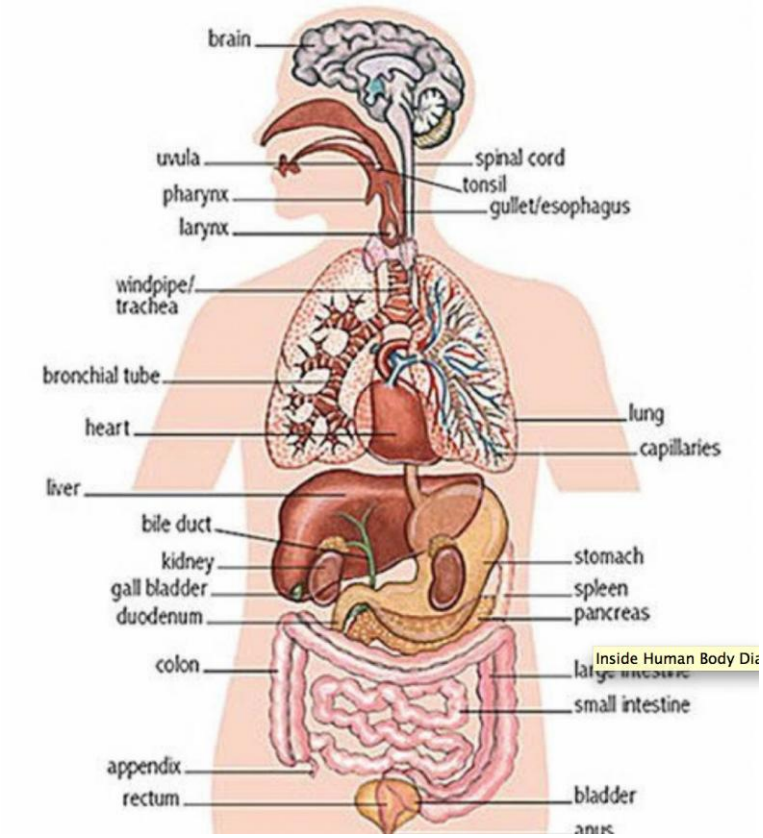
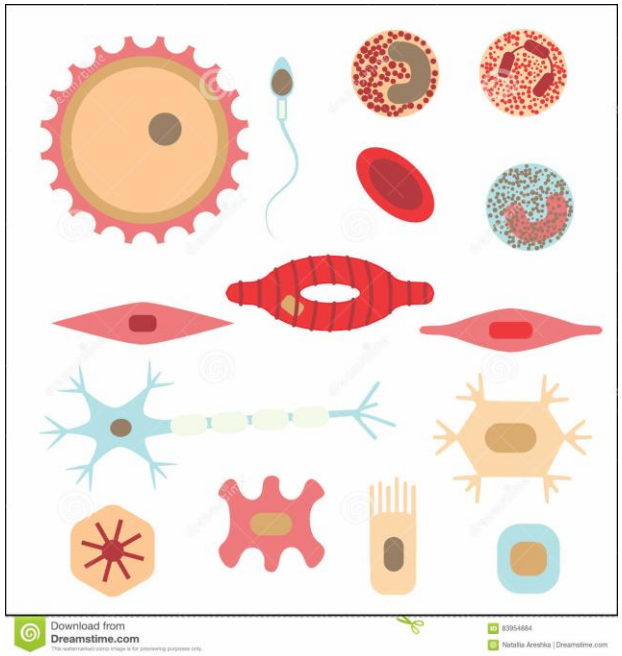
- Genetische code is bij een individu hetzelfde in ieder orgaan
- Maar of de code wordt “afgeschreven”, is niet hetzelfde per orgaan of cel.





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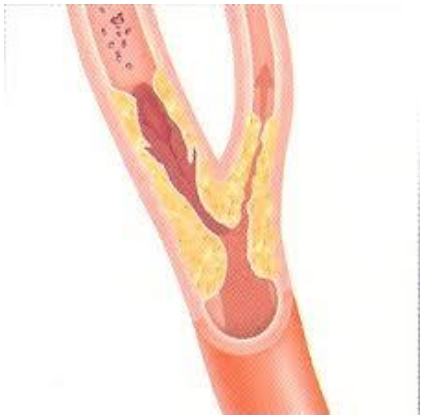
Athero-Express: de grootste verzameling van

- beenvaten



- halsslagader

- aneurysma

- N= 1000
- N= 2300
- N= 600

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DNA methylation: smoking

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DNA methylatian in plaques: smoking

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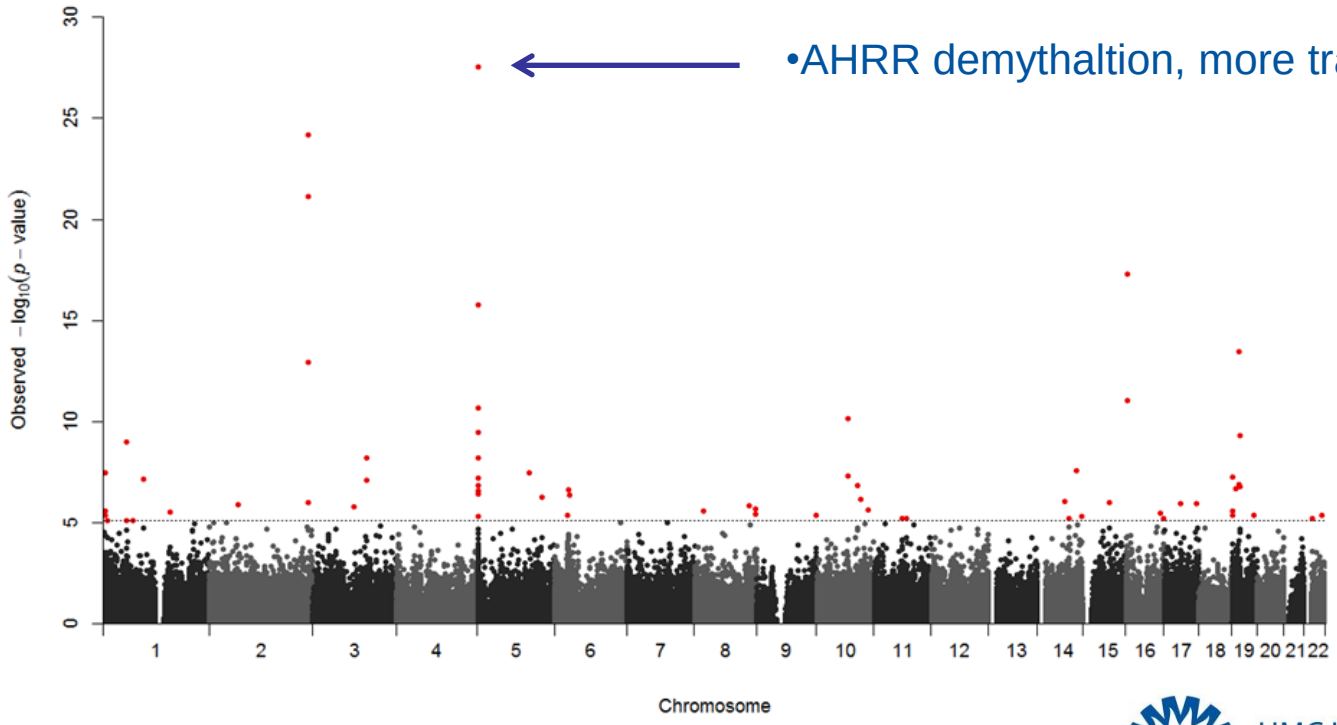

•AHRR demythaltion, more transcription

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Epigenetic gene transcription regulation

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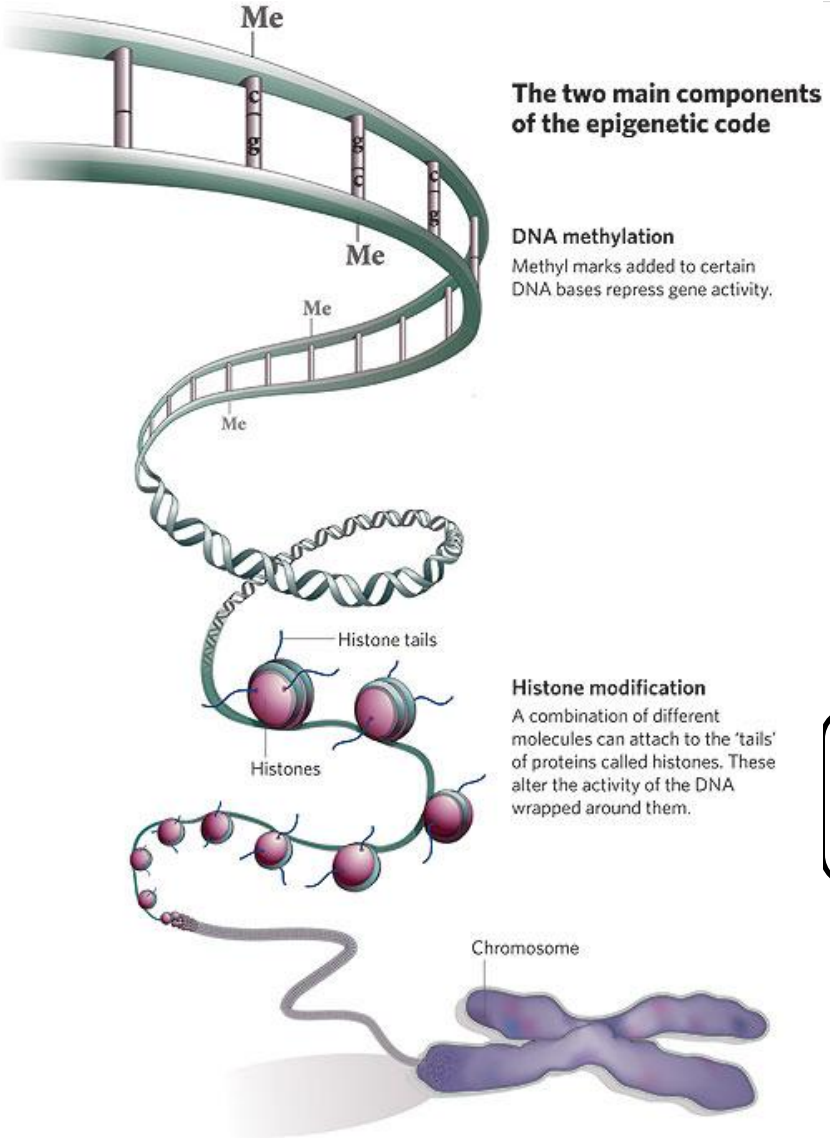
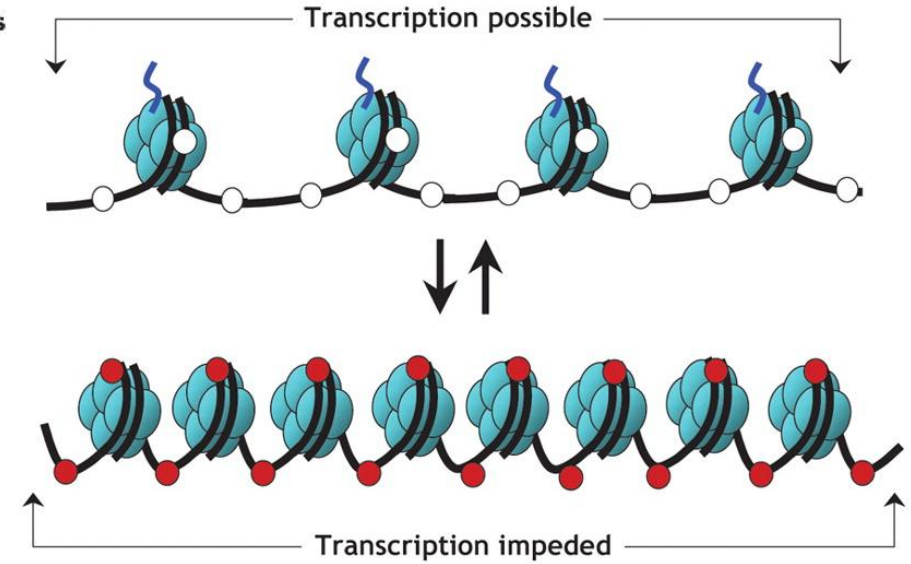


The two main components of the epigenetic code

DNA methylation
Methyl marks added to certain DNA bases repress gene activity.

Histone modification
A combination of different molecules can attach to the 'tails' of proteins called histones. These alter the activity of the DNA wrapped around them.



- DNA-methylation only occurs at Cytosine-Guanine (CpG)

- DNA-methylation is cell type specific

Next step: did methylation of DNA in plaques change in non smokers after banning smokers in public areas?

Acknowledgements