Sex-differences in triglyceridemic genetic risk scores and risk of myocardial infarction

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Introduction

- CVD was at 2023 the underlying cause of death in 37 % of males and 43 % of females (in CZ)

- Triglycerides
  - Believed to be associated with CVD
  - Significant genetic background
  - GWAS → ~ 300 SNPs with effects 0.01 - 0.27 mmol/L
  - Polygenic determination

- Genetic risk score (GRS)
  - an estimate of the cumulative contribution of genetic factors

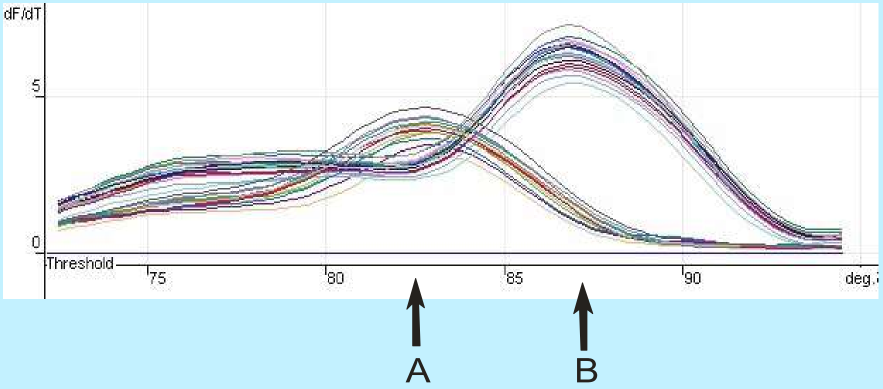
Would TG associated GRS work to predict the risk of developing ACS?

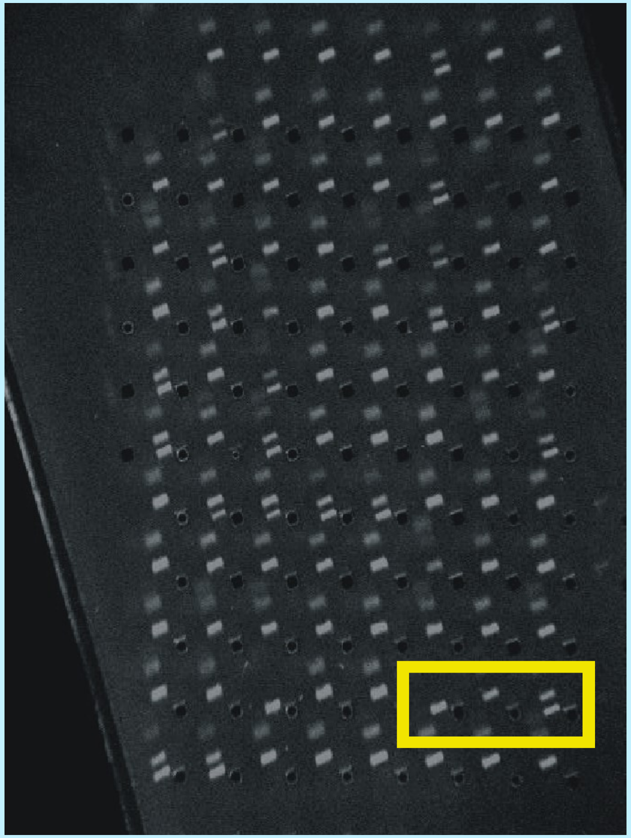
Subjects and methods

- Subjects
  - Patients (ICEM C. unit)
    - Males (N = 913)
    - Females (N = 680)
  - Controls (post-MONICA)
    - Males (N = 890)
    - Females (N = 1,341)

- Complet set of 18 SNPs

  (1.2% controls, 1.7% of patient excluded)





Analysed SNPs/genes

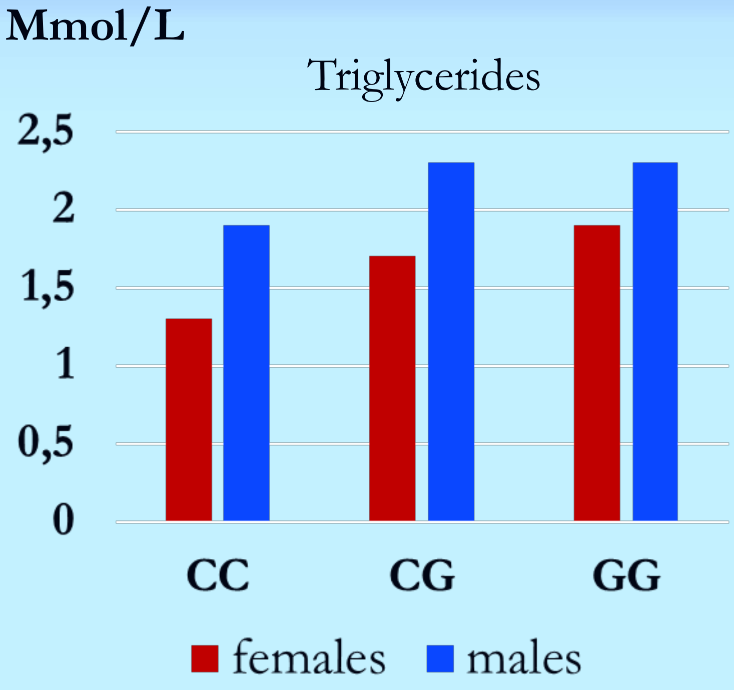
(selected according GWAS; effect replicated on CZ case control study)

	SNP	Gene	function
1	rs1260326	*GCKR*	glukokinase regulator
2	rs439401	*APOE*	binding of lipoproteins to cell-surface receptors
3	rs964184	*APOA5*	stimulation of lypolysis
4	rs2412710	*CAPN3*	calcium transport in muscles
5	rs1495743	*NAT2*	effects n-acetylation
6	rs2929282	*FRMD5*	regulates cytoskeletal remodeling
7	rs13238203	*TYW1B*	hypermodification of guanosine
8	rs12678919	*LPL*	degradation of TG in bloodstream
9	rs2068888	*CYP26A1*	clearing bioactive retinoids
10	rs261342	*LIPC*	degradation of TG in bloodstream
11	rs11613352	*LRP1*	regulation of intracellular signaling
12	rs9686661	*MAP3K1*	regulates cell survival and apoptosis
13	rs11649653	*CTF1*	regulates cancer cell migration and metastasis
14	rs1321257	*GALNT2*	regulates glycosylation
15	rs7205804	*CETP*	transport of CE to LDL particles
16	rs2954029	*TRIB1*	regulator of retinoic acid receptors
17	rs2247056	*HLA*	binding of peptide antigens
18	rs10401969	*SORT1*	facilitates the formation of LDL particles

Hubacek et al. Mol Diag Ther 2019

Results

Example - APOA5



both P = 0.001

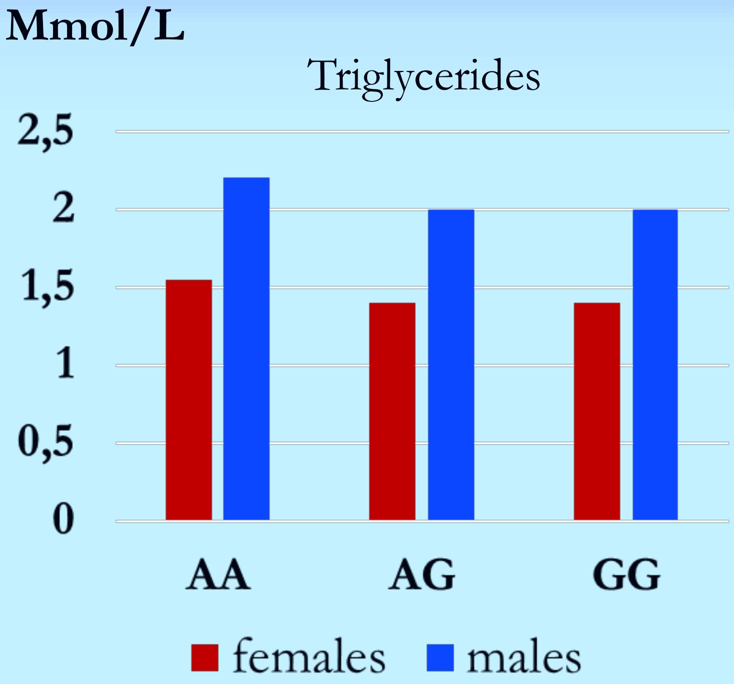
Association with ACS

P = 0.67 OR (95%CI)
1.03 (0.89 – 1.19)

P = 0.23 OR (95%CI)
1.05 (0.85 – 1.29)
♂

P = 0.58 OR (95%CI)
0.99 (0.81 – 1.22)
♀

Example - CYP26A1



both $P < 0.05$

Association with ACS

$P = 0.002$ OR (95%CI)

1.32 (1.11 – 1.59)

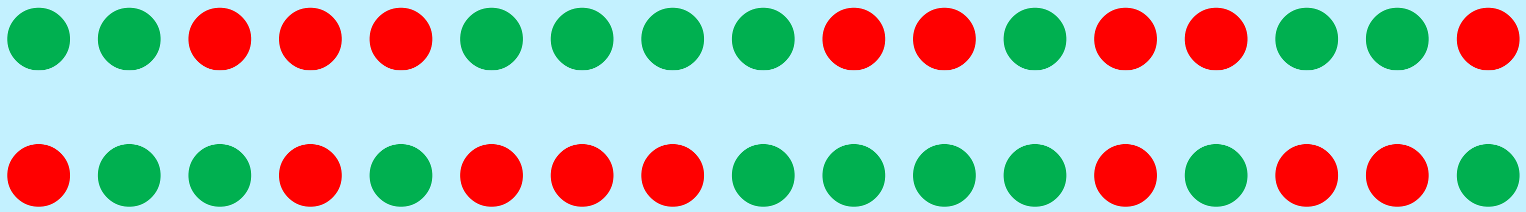
♂ + ♀

!!but!!

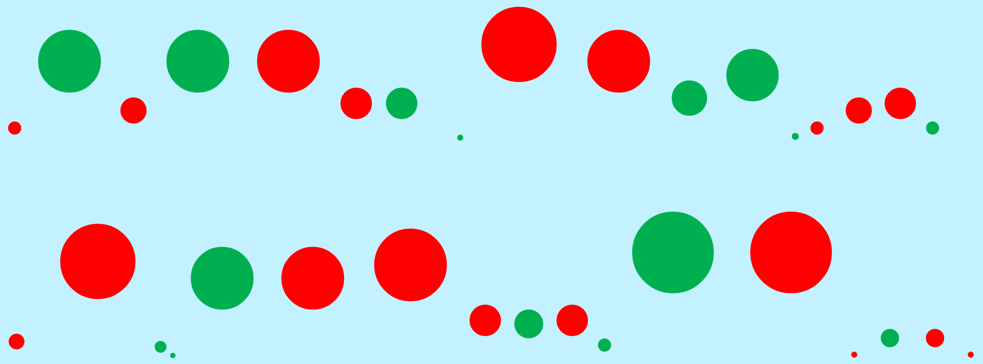
G allele is the risky

Genetic risk score

- cumulative contribution of genetic factors on phenotype
- <u>unweighted</u> – number of risk alleles



- <u>weighted</u> – takes into account the effect size (log OR, log HR, beta c.)



Genetic risk score - uGRS

- Two independent GRS
    - Based on ACS risk
    - Based on association with TG values
- uGRS
    - Normal distribution
    - Relative low number of categories
    - each risk allele +1 (0 1 2)
    - ACS - $P < 0.1$
    - TG - $P < 0.1$ or β at least 0,2 mmol/L
- Categorisation
    - No rules
    - No definitions
        - normal ???
        - risk ???

Genes selected for GRS (ACS effect)

	Gene	MAF/population	Risky in males	Risky in females
1	*TYW1B*	3.0	CC	+ T
2	*NAT2*	22.2	+C	
3	*FRMD5*	5.9	AA	+ T
4	*CAPN3*	1.9	+ A	GG
5	*LPL*	9.4	+ G	AA
6	*APOE*	39.0	TT	
7	*SORT1*	8.0	TT	+ C
8	*CYP26A1*	48.2	AA	

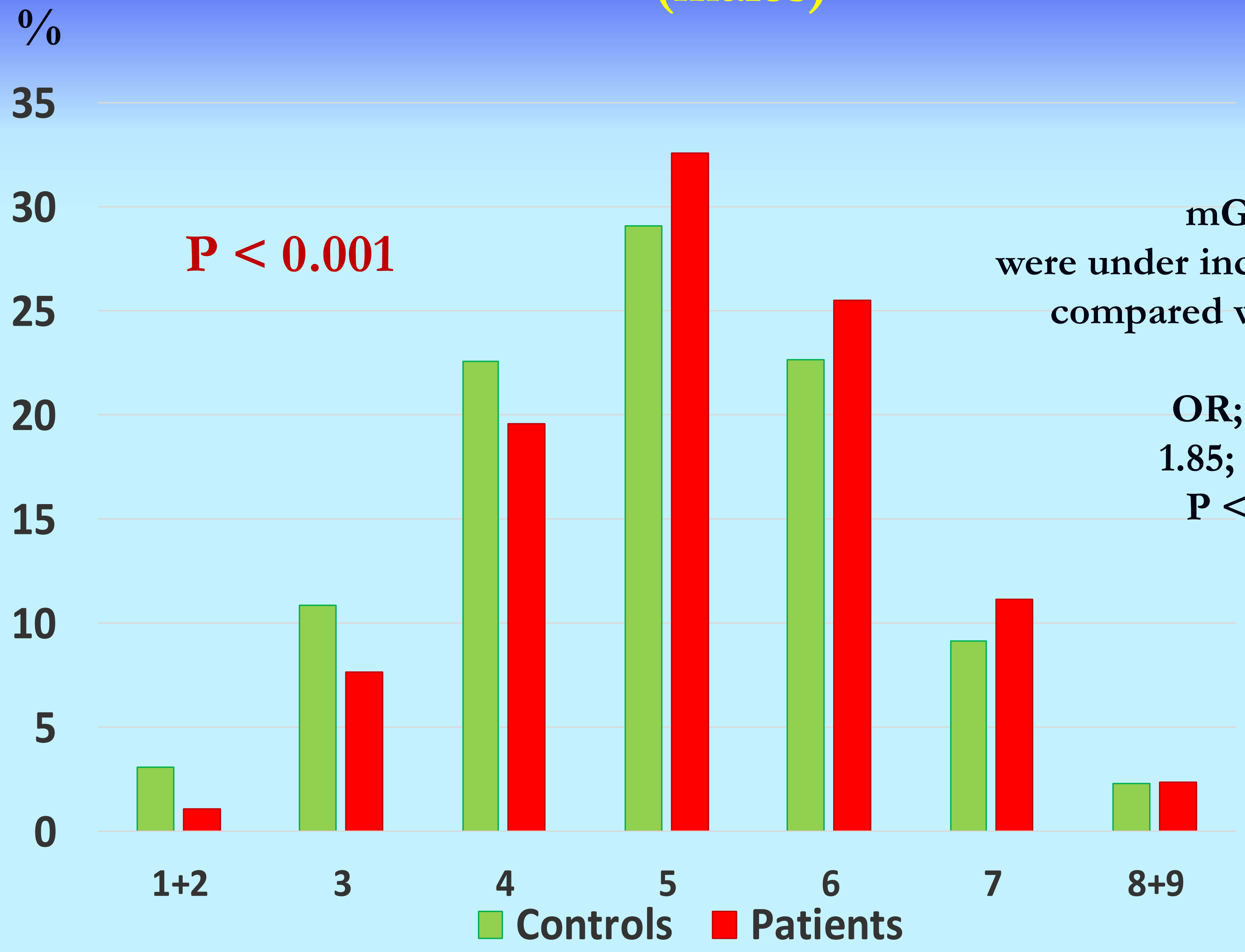
all SPNs with MAF < 10% → sex specific effect

(associated with ACS in males, females or both)

LPL, APOE, SORT1 – mechanism of effect on TG is known

mGRS based on ACS risk

(males)



P < 0.001

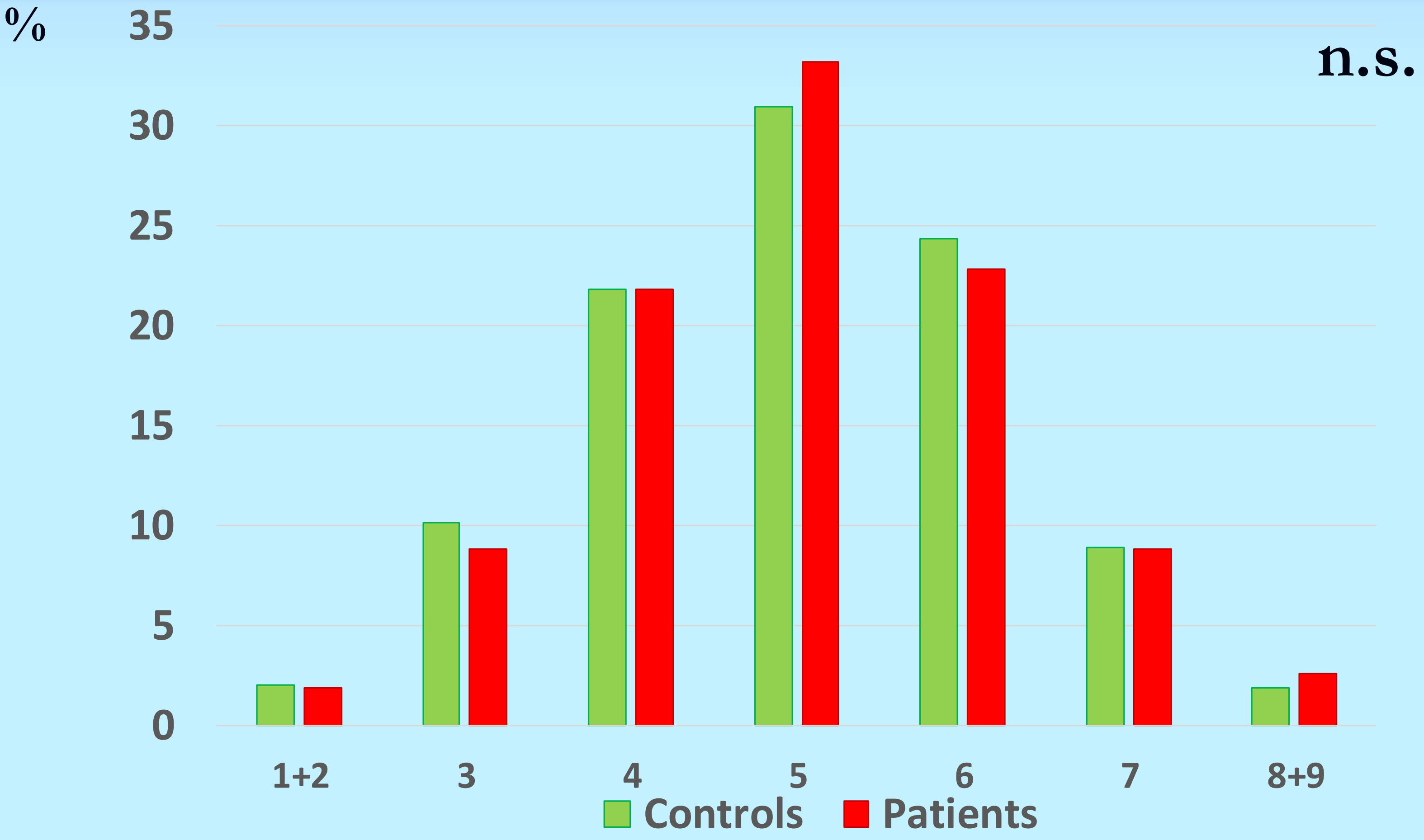
mGRS > 6
were under increased risk of MI
compared with mGRS < 3

OR; 95% CI
1.85; 1.34-2.56
P < 0.0005

2.04 **1.95** **2.11** **1.97** **1.83** **2.22** **2.17** **(TG)**

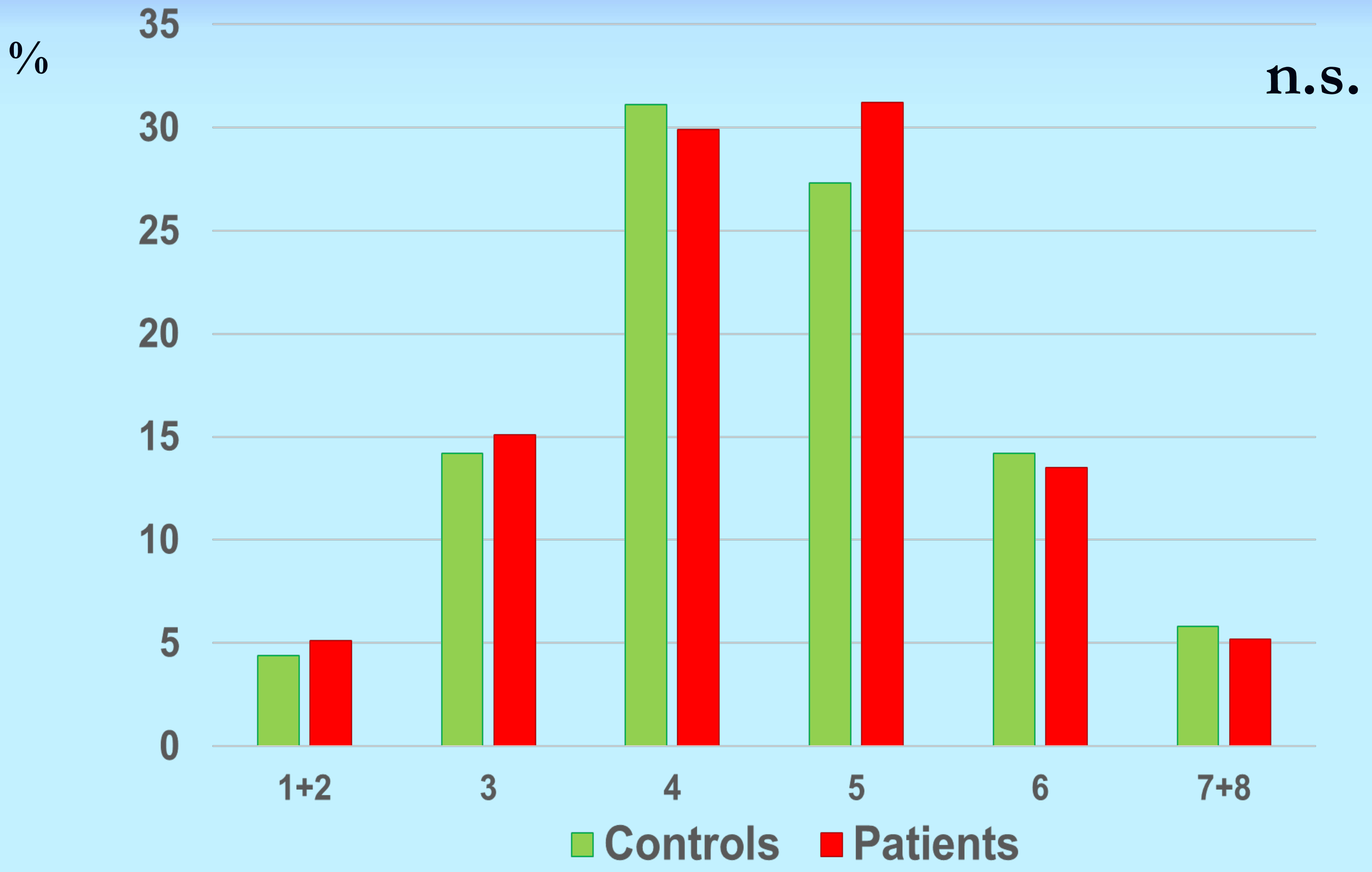
mGRS and ACS risk

(applied on females)



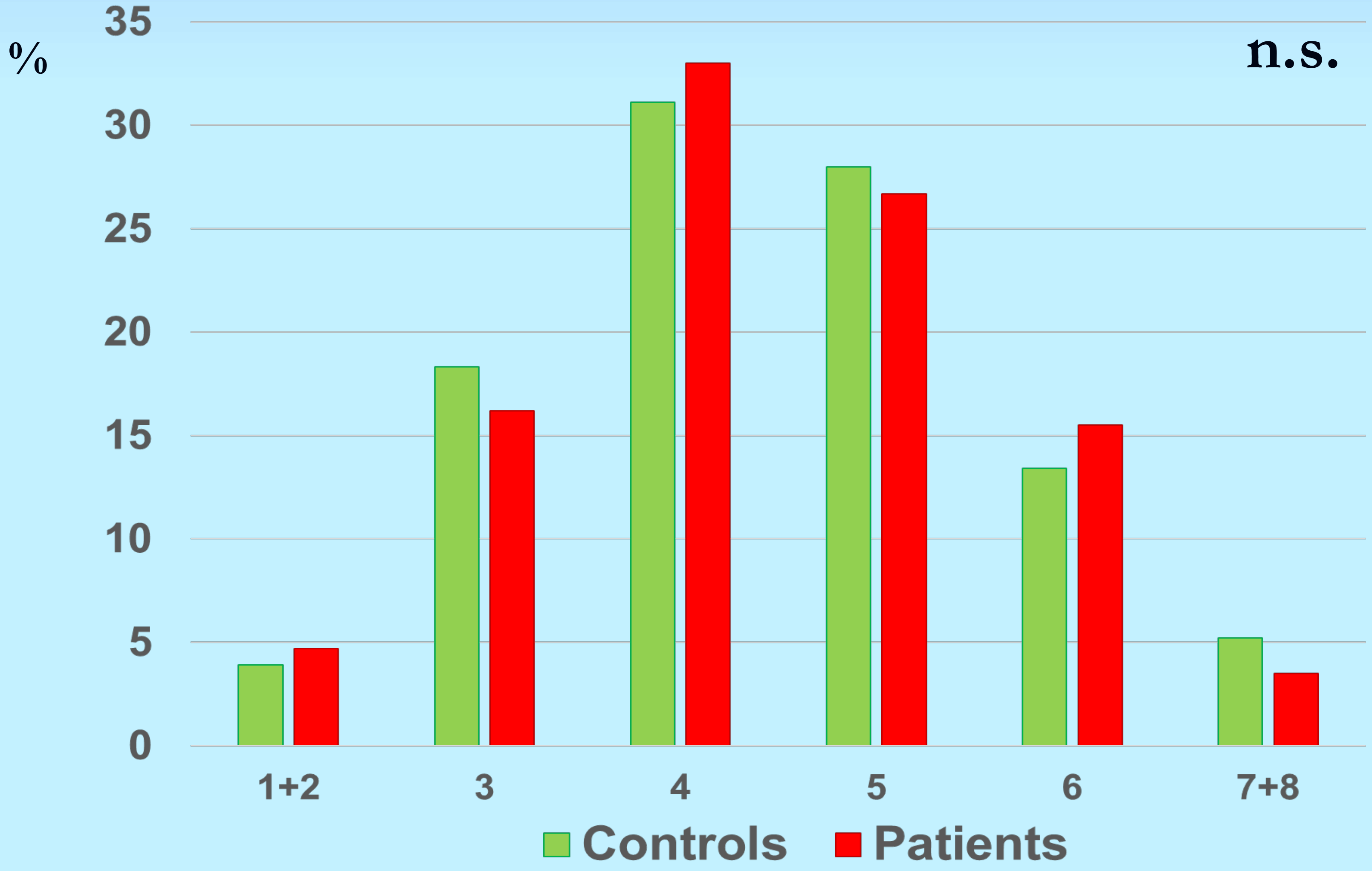
fGRS and ACS

(applied on females)



fGRS and ACS risk

(applied on males)



Genes selected for GRS

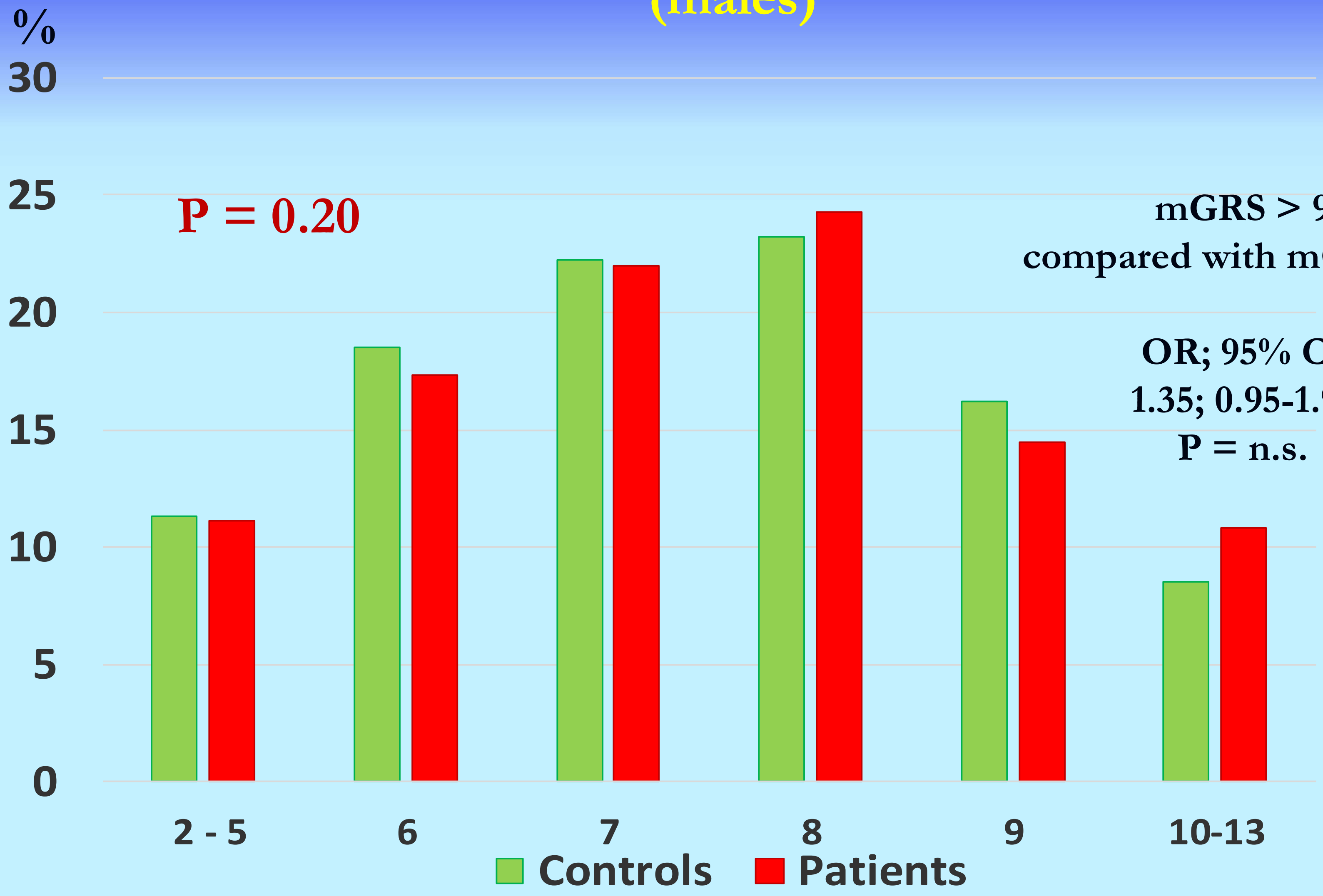
(TG effect males)

	Gene	P	Δ TG
1	*MAP3K1*	0.470	0.32
2	*GCKR*	0.096	0.20
3	*APOA5*	0.001	0.32
4	*CAPN3* *	0.032	0.36
5	*NAT2* *	0.695	0.22
6	*APOE* *	0.151	0.20
7	*SORT1* *	0.007	0.29
8	*TRIB1*	0.150	0.26

***Effect on TG as well as on ACS**

GRS based on TG values

(males)



P = 0.20

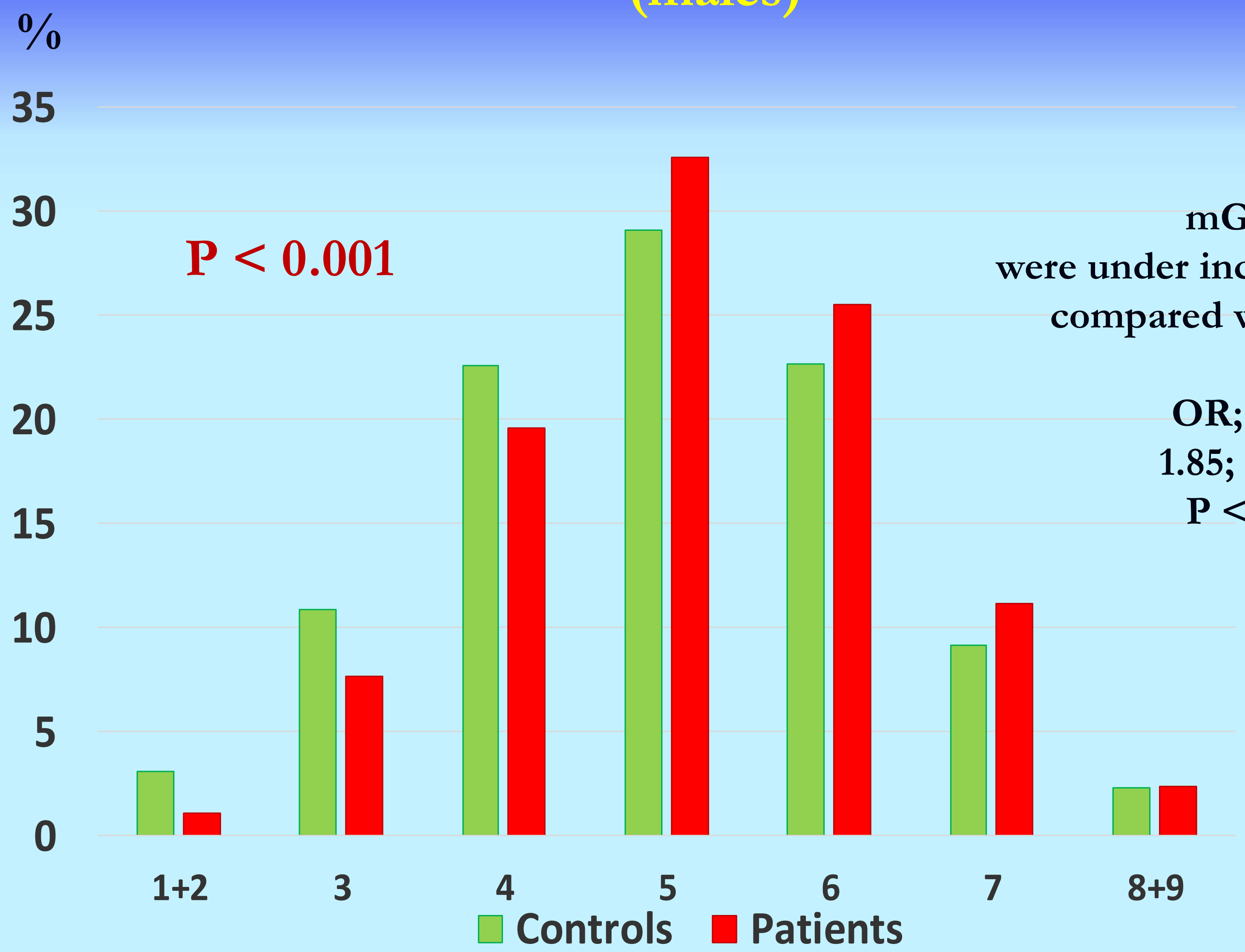
mGRS > 9
compared with mGRS < 7

OR; 95% CI
1.35; 0.95-1.91
P = n.s.

1.66	1.62	2.08	2.20	2.20	2.50	(TG)

GRS based on ACS risk

(males)



P < 0.001

2.04 1.95 2.11 1.97 1.83 2.22 2.17 (TG)

mGRS > 6
were under increased risk of MI
compared with mGRS < 3

OR; 95% CI
1.85; 1.34-2.56
P < 0.0005

Genetic vs „traditional“ RF

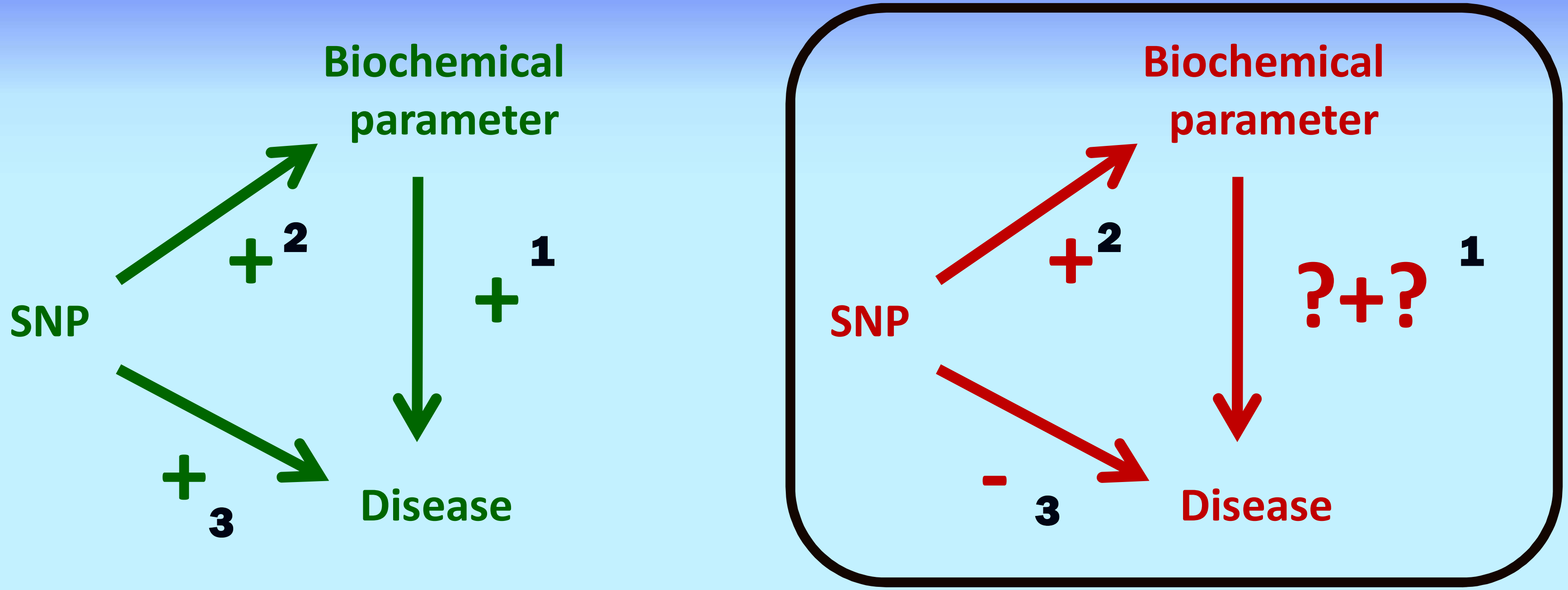
(males only)

OR

■ GRS („TG“) ACS	1.85	
Smoking	3.86	
Diabetes	1.75	
Hypertension	1.41	
Overweight	1.01	
Plasma cholesterol	4.8 ± 1.1	5.7 ± 1.0
Plasma triglycerides	2.1 ± 1.5	2.0 ± 1.3

Mendelian randomisation

TG and ACS risk



MR is a method of studying the causal effects of potential risk factor (TG) on outcome (ACS) using genetic variants associated with the exposure of interest

Conclusions

take home messages

- Sex specific effect of selected SNPs
- MR questions TG (values common in the population) as causative RF for ACS
- Risk associated with analysed SNPs is likely not mediated by the effect on TG
    - Regulatory effects on ???

Thanks for your attention!

…times are getting more and more complicated…
It is easy to substitute genetic information for genetic desinformation

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