Kan förebyggande hälsoinsatser mot kardiometabol sjukdom underlättas genom att utläsa sjukdomsrisk och följsamhet till behandling i blodet?

Olle Melander, MD, PhD,

Professor i Internmedicin, Lunds Universitet, IKVM

Överläkare, specialist Internmedicin, VO Akutsjukvård och Internmedicin, SUS

Precisionsmedicinskt Center Syd

Styrelse PMC:

Jesper Petersson (RS forskningschef)
Stefan Jovinge (SUS forskningschef)
Maria Björkqvist (Dekan, MedFak, LU)
David Gisselsson-Nord (Vice-dekan, MedFak, LU)
Gunilla Bodelsson (Medicinsk Service, VC KlinGen/patologi)
Thoas Fioretos (KlinGen, Director SciLife Lund)
Åsa Petersén (Rare dis)
Helena Elding Larsson (Pediatrik)
Olle Melander + Sophia Zachrisson (adjungerade)

Föreståndare: Olle Melander (Internmedicin)
Bitr Föreståndare: Sophia Zackrisson (Radiologi)

Admin + grant manager (100%)
Projektbidrag

ARBETSGRUPPER
(PROJEKT + IMPLEMENTERING)

PRECISIONSPREVENTION

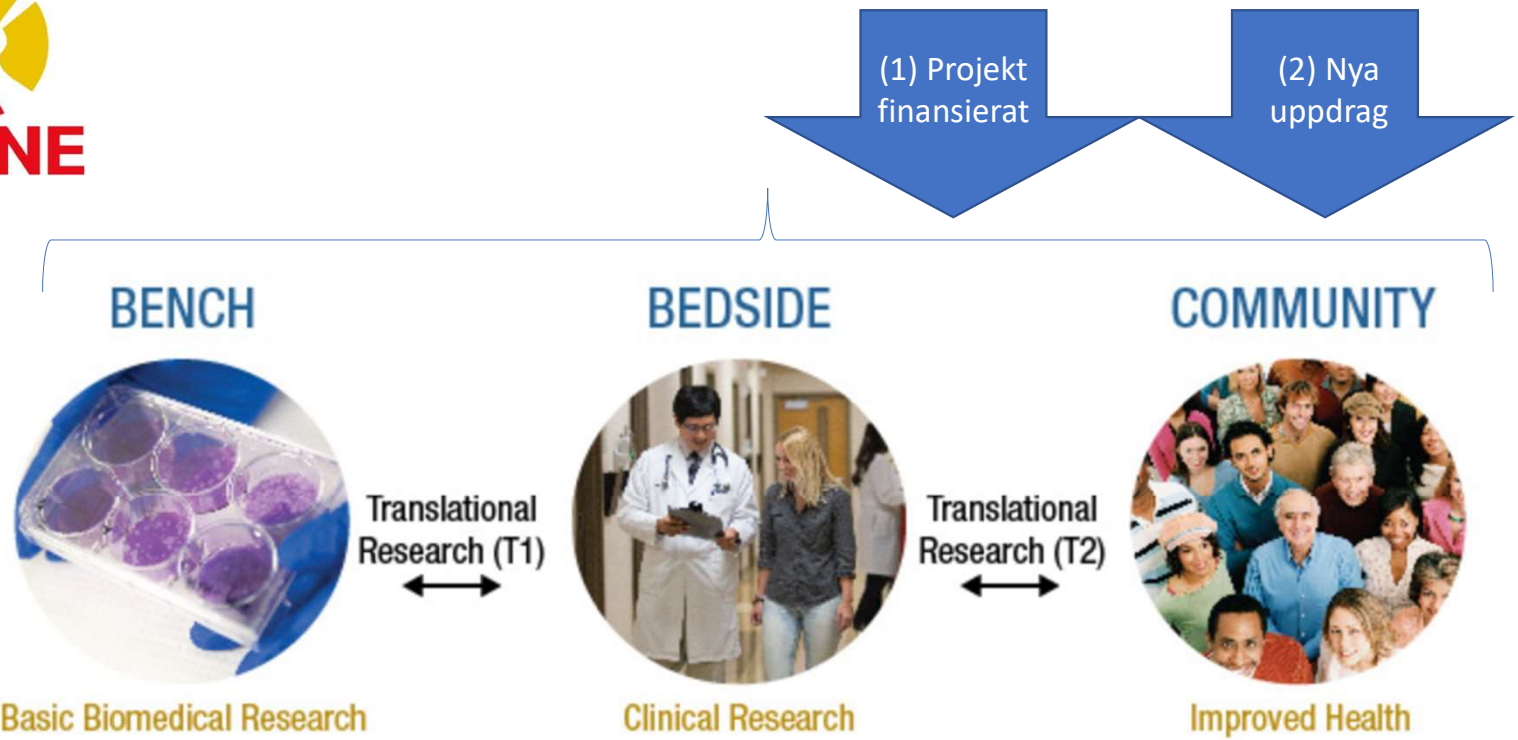
SAMARBETE MED PRIMÄRVÅRDEN / RIKTADE HÄLSOSAMTAL

STÖDFUNKTIONER:

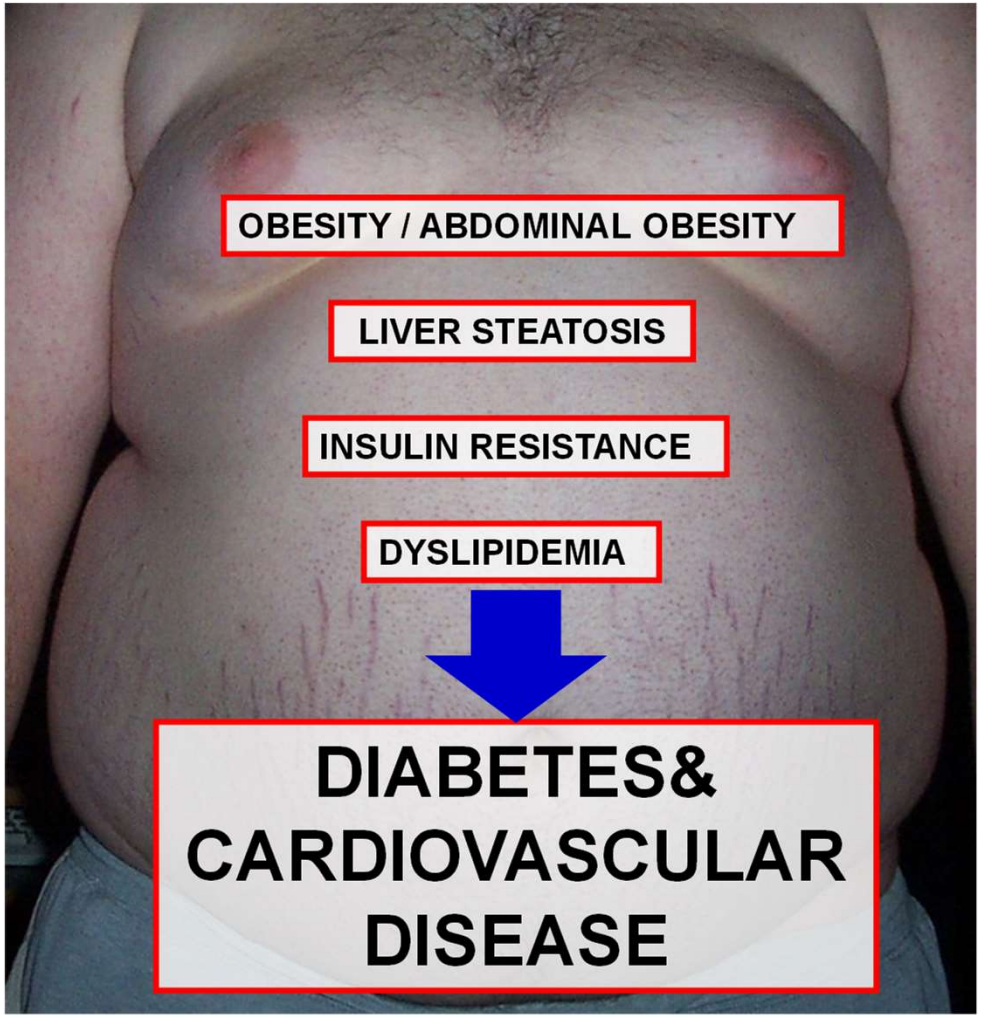
- SciLife
- Health Economy
- Clin Studies Sweden
- Digital health
- ATMP
- Drug repurposing
- Ethics / law

PRECISIONSMEDICINSKT CENTER SYD

<u>Precisionsmedicinskt Center Syds uppgift</u> är att utifrån hälso- och sjukvårdens behov driva:
(1) implementeringsnära PM-projekt (som har stor chans att gå vidare till #2)
(2) implementera PM i hälso- och sjukvården

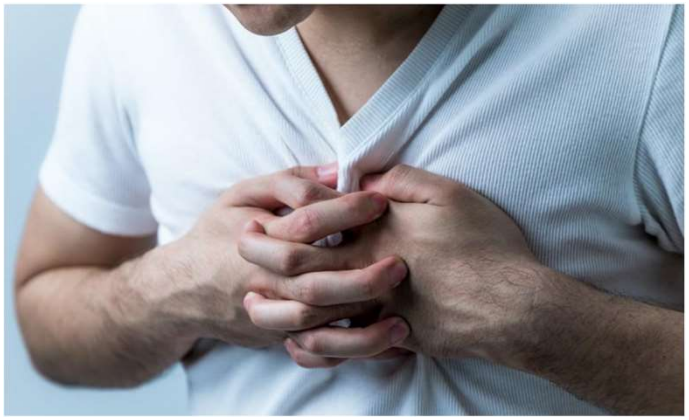


”CARDIOMETABOLIC DISEASE”



To know how to do ≠ To do it

SEKUNDÄRPREVENTION



*En kamp mot symptomen
*Inser allvaret
→motivation-följsamhet

PRIMÄRPREVENTION

*Inga symptom
*Inser inte allvaret
→**<u>sätt att mäta resultat av LIVSSTILS prevention</u>**

VIKTEN AV ATT FÖLJA UPP OCH JUSTERA

GENETIC SUSCEPTIBILITY TO CARDIOMETABOLIC DISEASE

= USED TO BE SURVIVAL GENES

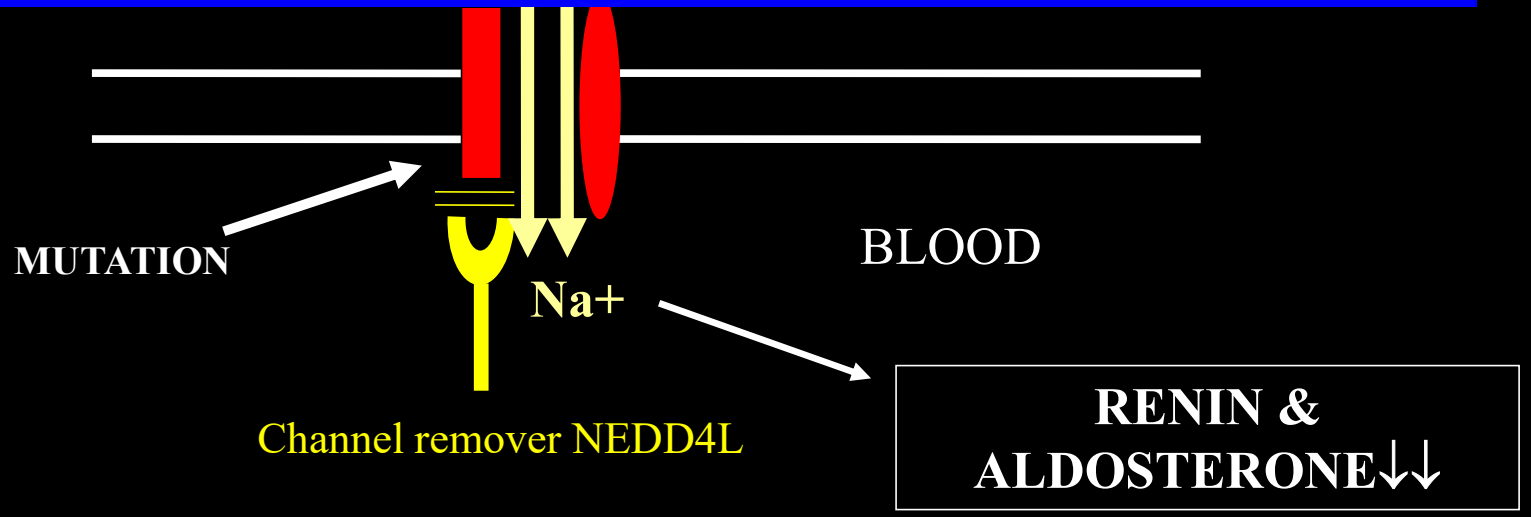
=SENTITIVITY TO CURRENT LIFESTYLE

=CAN BE ELIMINATED WITH LIFESTYLE CHANGE

Severe salt sensitive MONOGENIC hypertension (LIDDLE´S SYNDROM=

(2 familial cases in MDC- pedigree extended 5 cases)

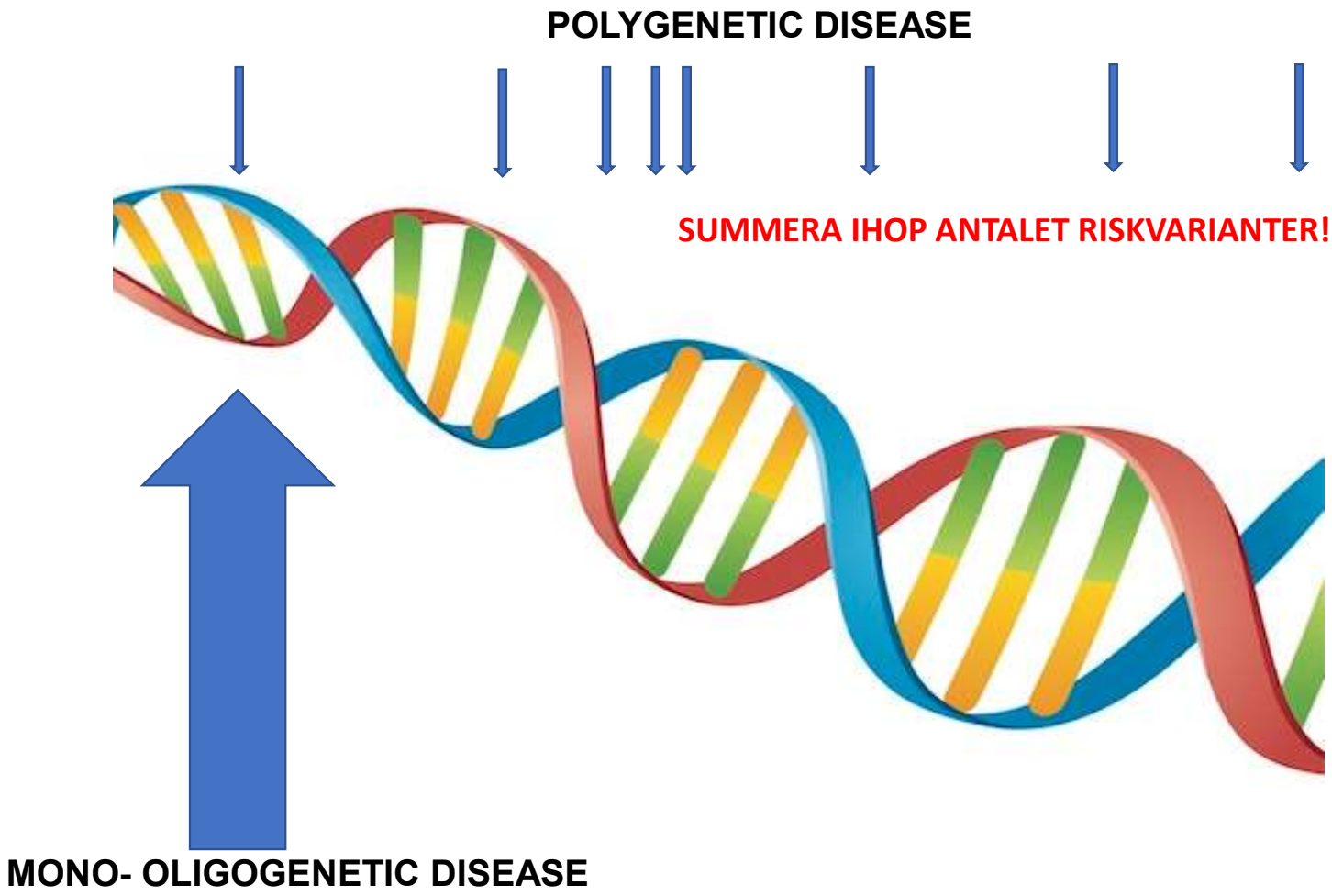
A 100% GENETIC DISEASE CAN BE COMPLETELY PREVENTED WITH A 100% ENVIRONMENTAL ACTION!



Melander et al. Hypertension 1998

GENETIC RISK OF CORONARY ARTERY DISEASE (CAD) IS REVERSIBLE

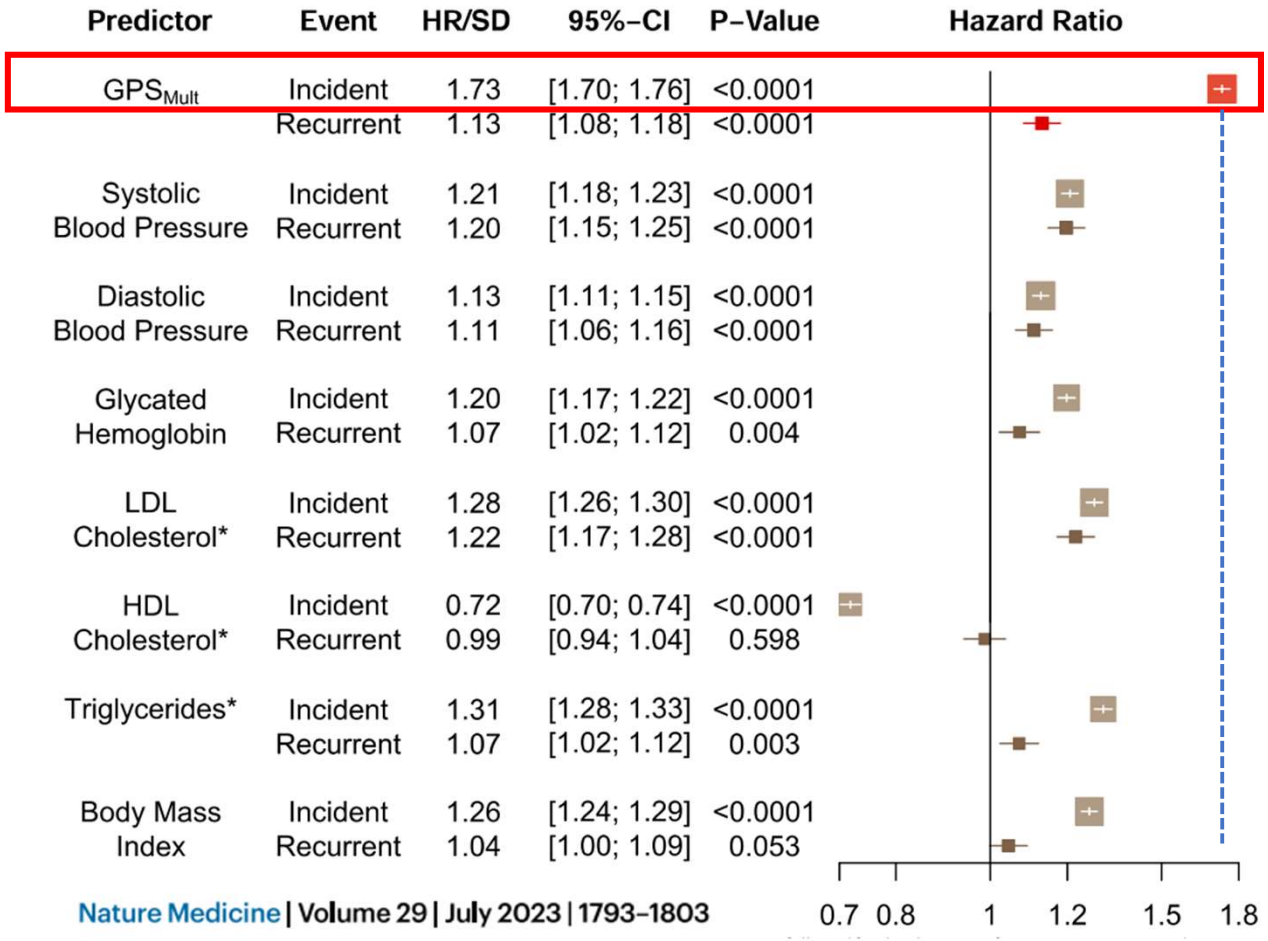
(=HJÄRTINFARKT ELLER REVASKULARISERING)



Polygenetisk risk för CAD är starkare än samtliga traditionella riskfaktorer (TRFs)

Polygenetisk risk för CAD kan inte fångas upp med familjehistoria och mätning av TRFs

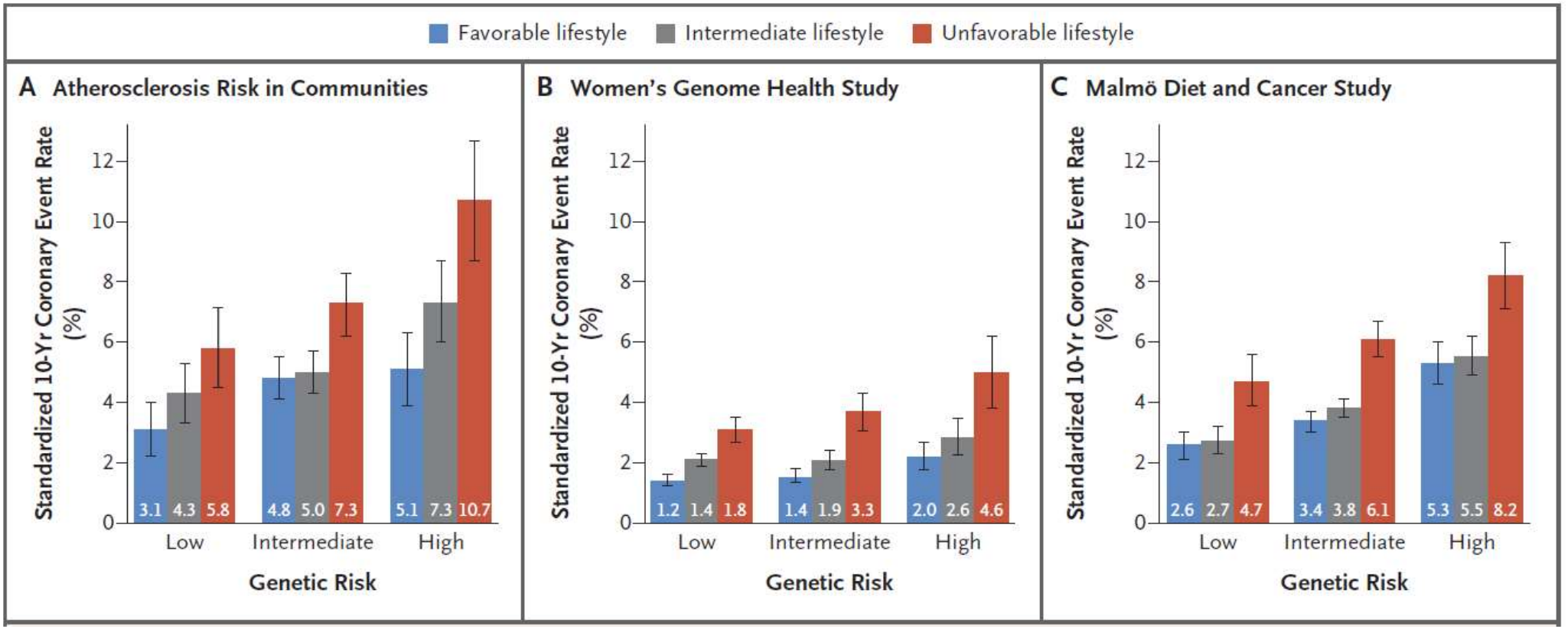
Polygenetisk risk för CAD identifierar ”dolda högriskindivider”



Nature Medicine | Volume 29 | July 2023 | 1793–1803

GENTERAPI??

Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Disease



N Engl J Med (Nov 2016)

Genetic risk, coronary heart disease events, and the clinical benefit of statin therapy: an analysis of primary and secondary prevention trials

Lancet. 2015 Jun 6;385(9984):2264-2271

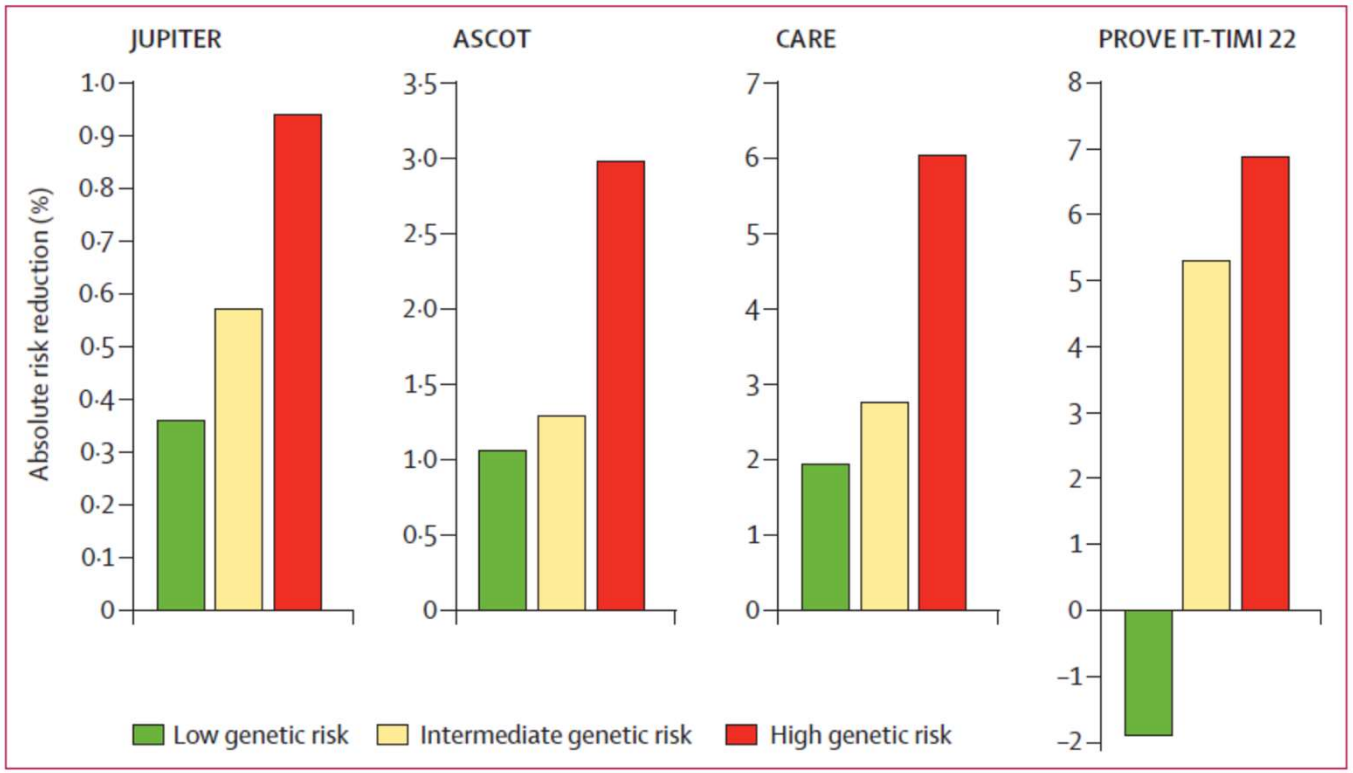


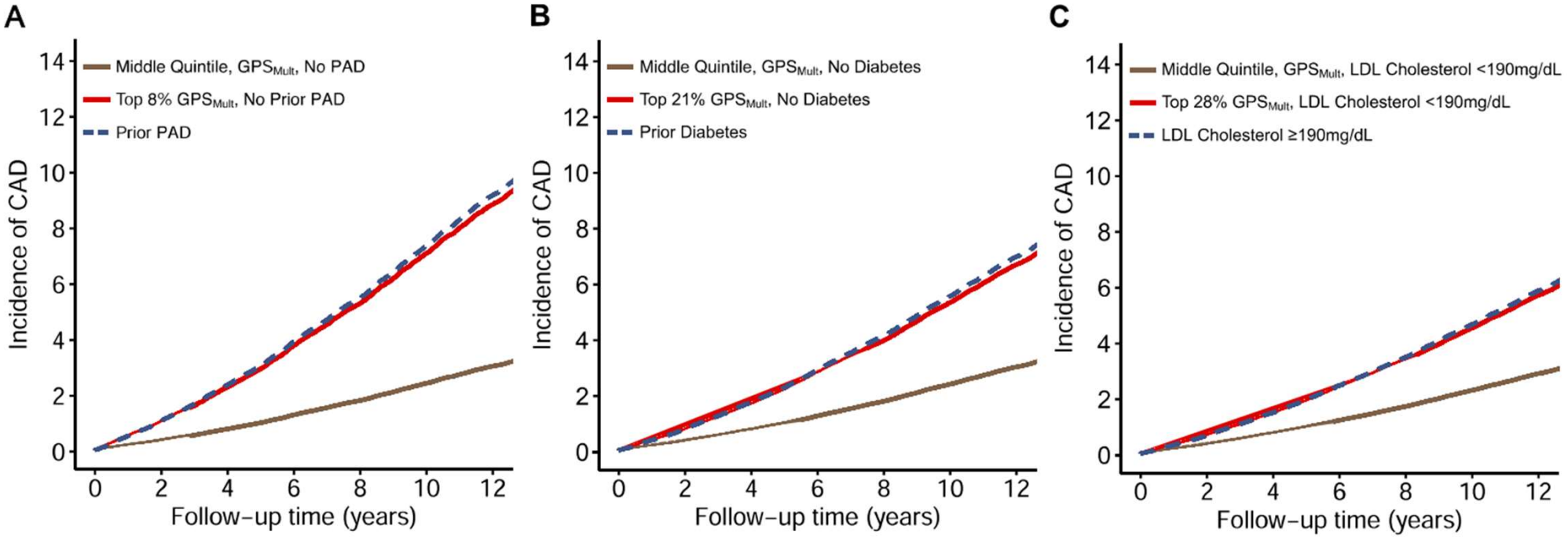
Figure 3: Absolute risk reductions of coronary heart disease events with statin therapy across genetic risk score categories

Mätning av polygenetisk risk för CAD identifierar 20% av befolkningen med ”dold risk” (oavsett ålder)

8% of population has same CAD risk as PAD

21% of population has same risk as type 2 diabetes

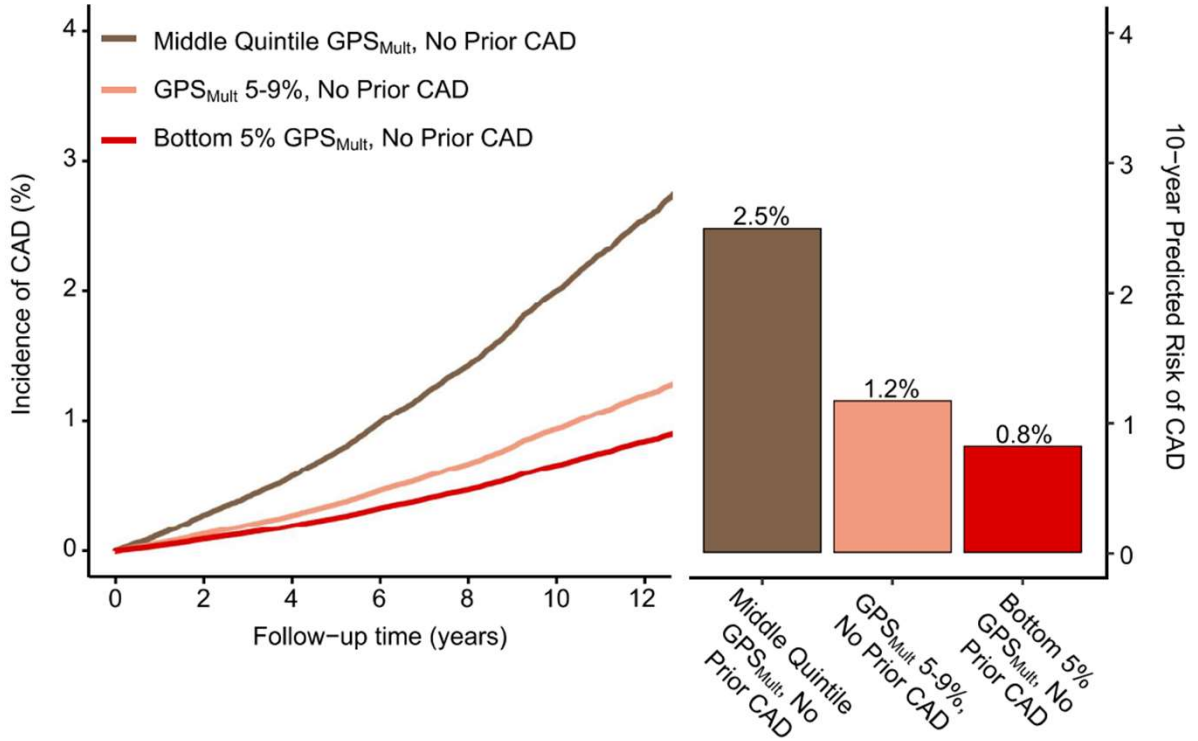
28% of population has same risk as familial hypercholestrolemia



20% OF POPULATION WITH SAME RISK AS TYPE 2 DIABETES: STATIN + INTENSE LIFE STYLE

Nature Medicine | Volume 29 | July 2023 | 1793–1803

Polygenetisk risk mätning identifierar lågriskindivider som inte har nytta av farmakologisk primärprevention (precisionsmedicin)



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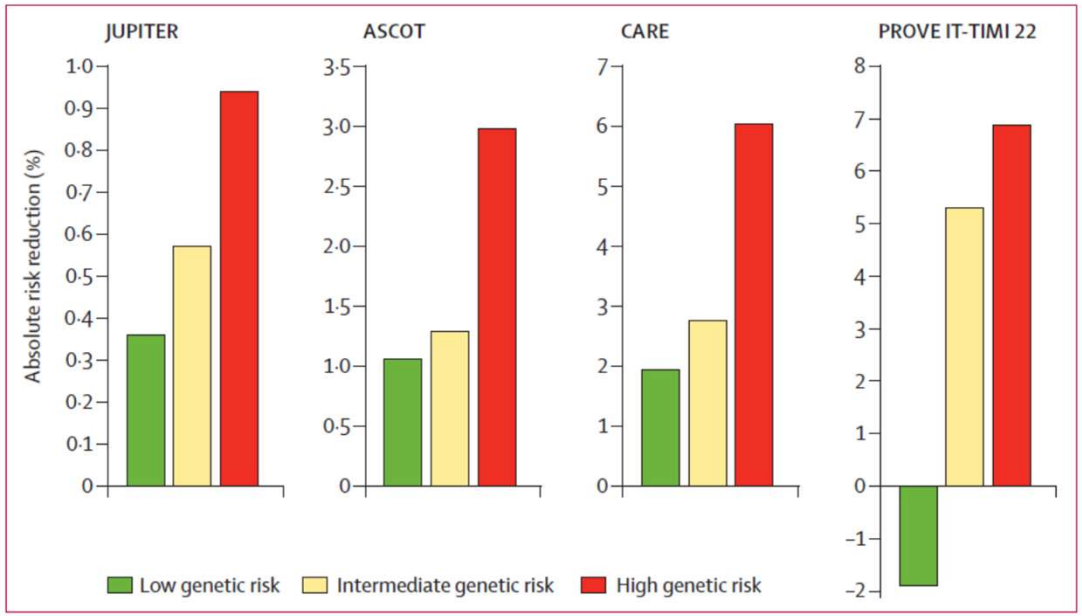


Figure 3: Absolute risk reductions of coronary heart disease events with statin therapy across genetic risk score categories

***Kostnad av test: 250 kr <u>en gång i livet</u>**
***Genetisk högrisk: 20 mg rosuvastatin (3 kr per dygn)**
***Genetisk lågrisk: Avstå behandling (sparar pengar)**

***Hälsoekonomisk analys**
***Juridisk/Etisk analys**
***Infrastruktur för screening**

<u>Circulation</u>

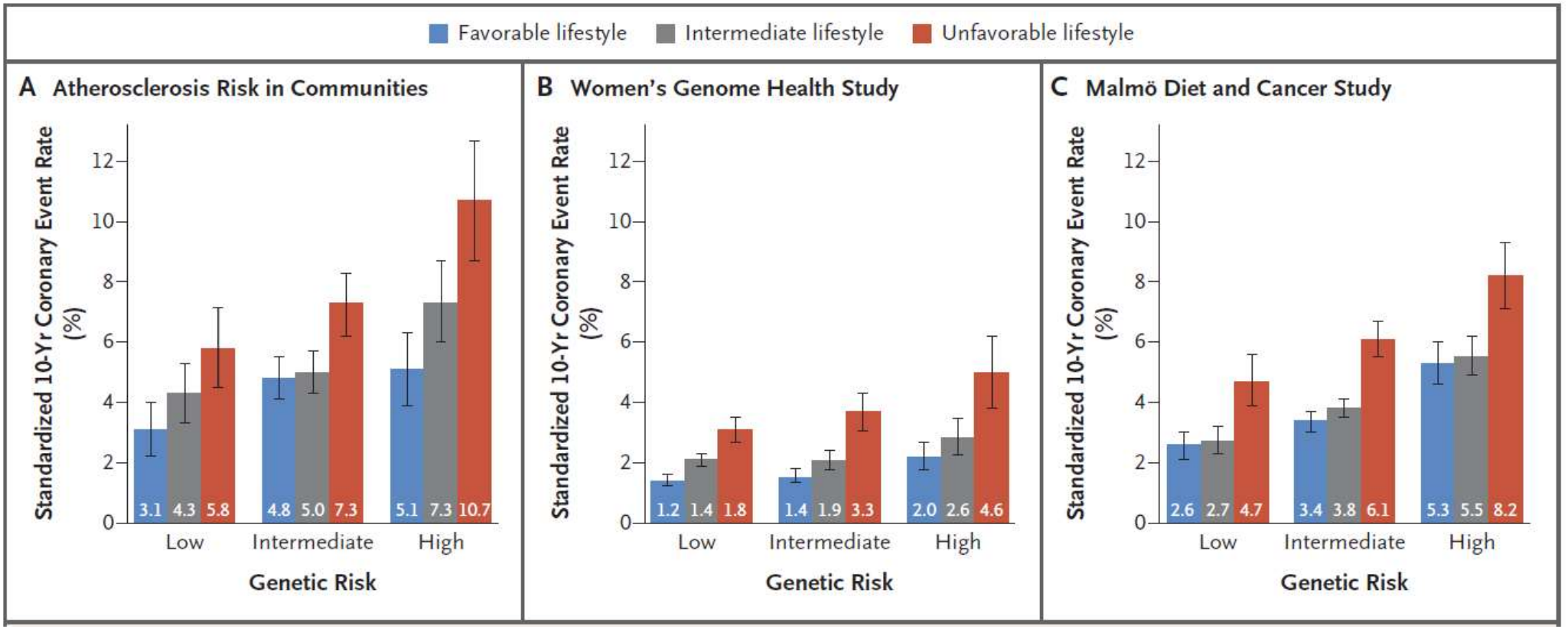
AHA SCIENTIFIC STATEMENT

Polygenic Risk Scores for Cardiovascular Disease: A Scientific Statement From the American Heart Association

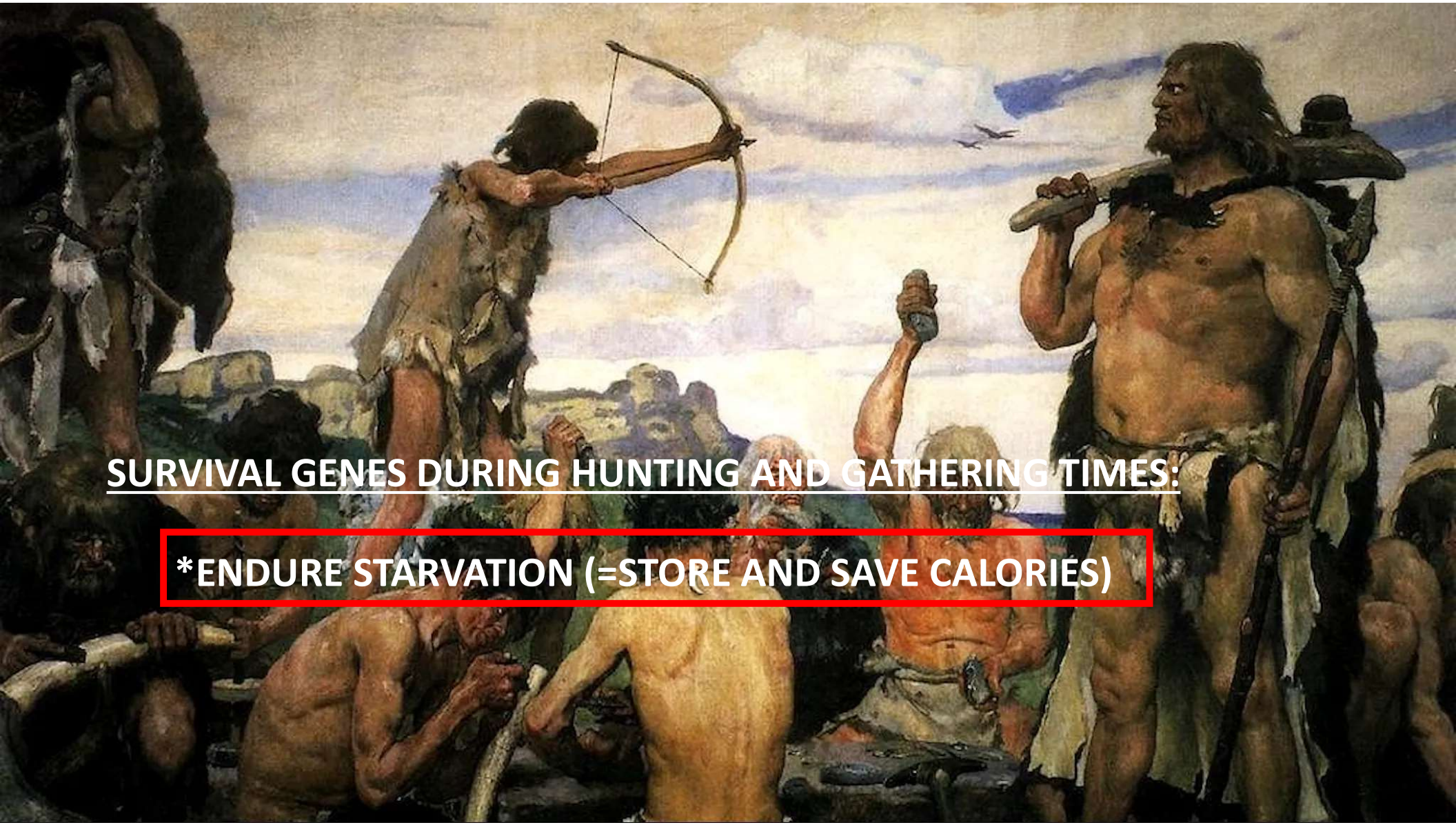
Jack W. O'Sullivan, MBBS, DPhil, Chair; Sridharan Raghavan, MD, PhD; Carla Marquez-Luna, PhD; Jasmine A. Luzum, PharmD, PhD; Scott M. Damrauer, MD, FAHA; Euan A. Ashley, MBChB, DPhil, FAHA; Christopher J. O'Donnell, MD, MPH; Cristen J. Willer, DPhil; Pradeep Natarajan, MD, MMSc, Vice Chair; on behalf of the American Heart Association Council on Genomic and Precision Medicine; Council on Clinical Cardiology; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular Radiology and Intervention; Council on Lifestyle and Cardiometabolic Health; and Council on Peripheral Vascular Disease

Circulation. 2022;146:e93–e118. DOI: 10.1161/CIR.0000000000001077

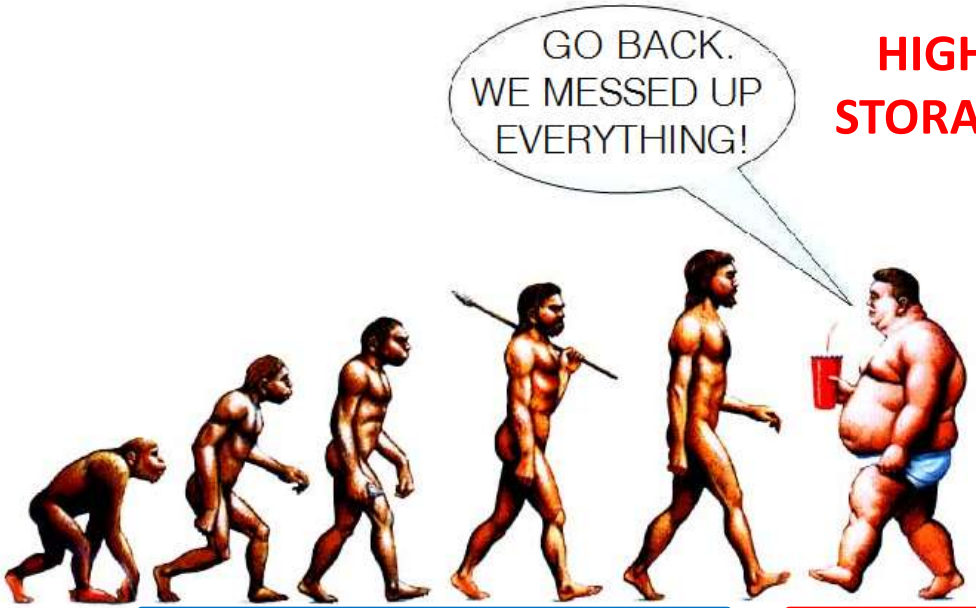
Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Disease



N Engl J Med (Nov 2016)

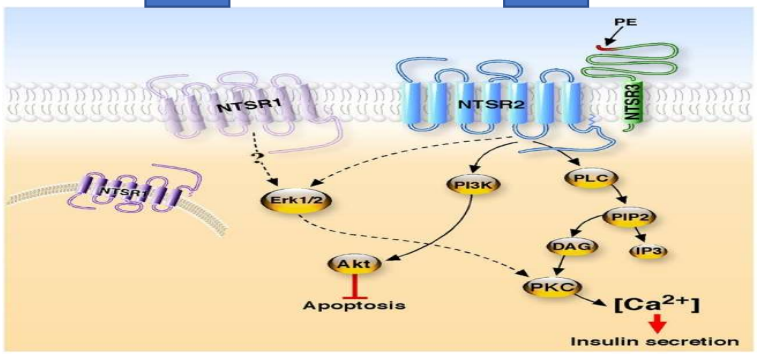

SURVIVAL GENES DURING HUNTING AND GATHERING TIMES:
*ENDURE STARVATION (=STORE AND SAVE CALORIES)

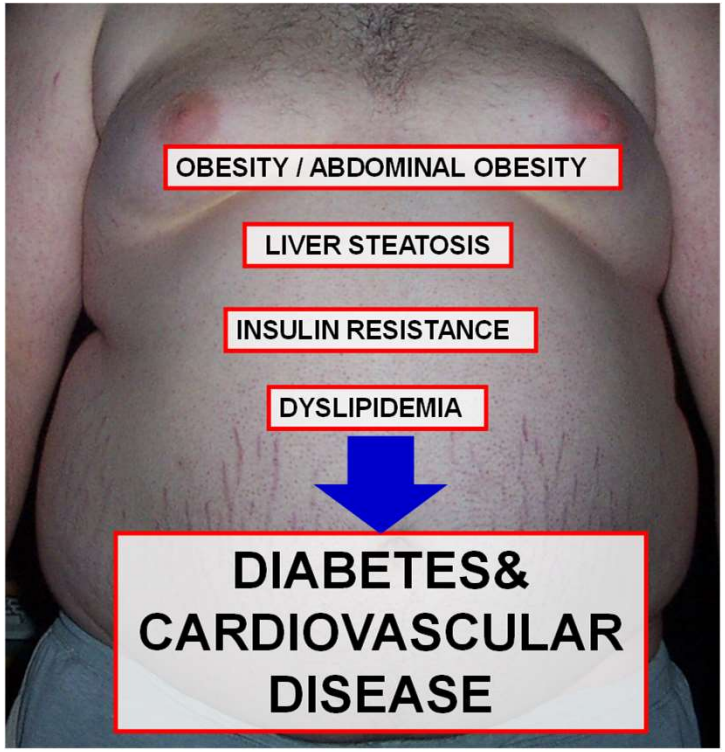
HIGH GUT SECRETION OF NEUROTENSIN LEADS TO STORAGE AND EFFECTIVE SAVING OF FAT IN THE LIVER



HIGH NEUROTENSIN: LIFE SAVER

HIGH NEUROTENSIN: KILLER



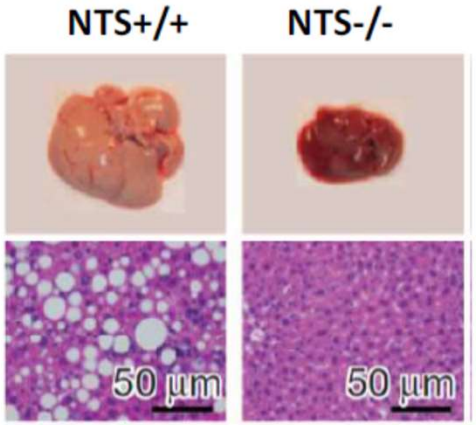


JAMA 2012;308:1469-75

Nature 2016;553:411-15

Neurotensin (NTS) promotes liver fat accumulation and development of diabetes and CVD

Mice lacking NTS do not develop hepatic steatosis

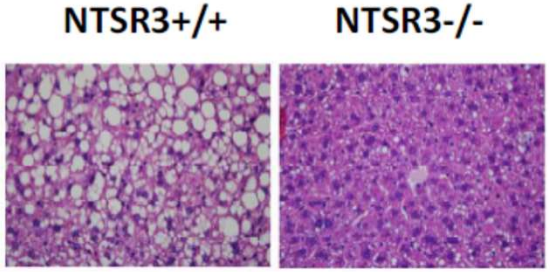


Liver H&E staining

(Nature 2016;553:411-15)

Mice lacking the NTS receptor-3 (NTSR3) do not develop hepatic steatosis

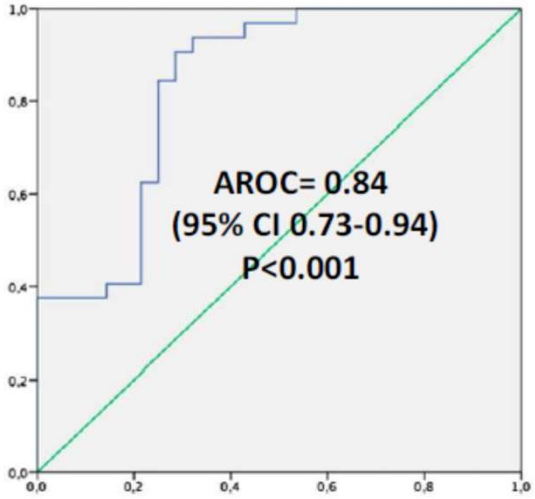
NTSR3 = SORT1



Liver H&E staining

(J Hepatol 2015;62:175-81)

High pro-NTS in humans predicts hepatic steatosis (NAFLD)



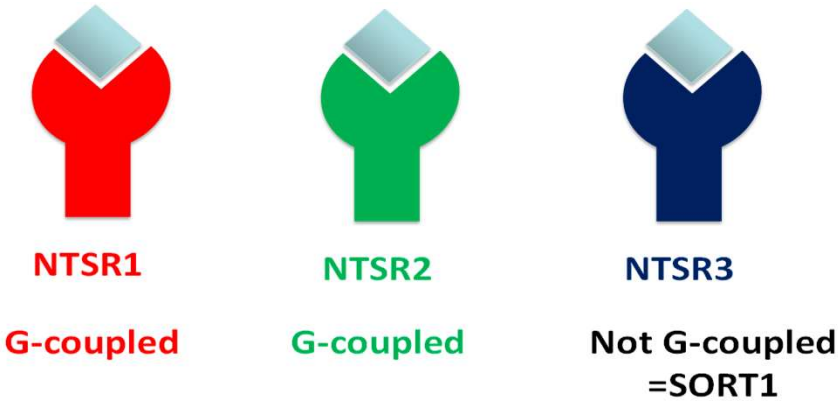
(JCEM 2018;103:2253-60)

NTS>150 pmol/L independently predicts risk for both diabetes and CVD
(JAMA 2012;308:1469-75)
(ATVB 2016;36:1692-97)

ORIGINAL CONTRIBUTION

Association of Plasma Proneurotensin With Incidence of Diabetes, Cardiovascular Disease, Breast Cancer, and Mortality

Olle Melander, MD, PhD
Alan S Maisel, MD
Peter Almgren, MSc
Jonas Manjer, MD, PhD
Mattias Belting, MD, PhD
Bo Hedblad, MD, PhD
Gunnar Engström, MD, PhD
Ute Kilger, PhD
Peter Nilsson, MD, PhD
Andreas Bergmann, PhD
Marju Orho-Melander, PhD



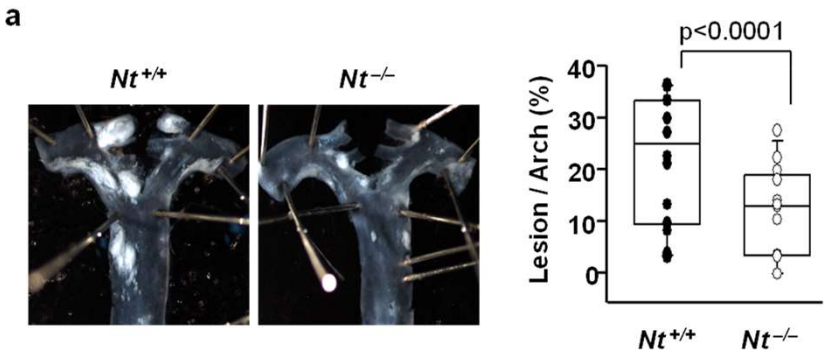
*GUT (N-CELLS) AND BRAIN

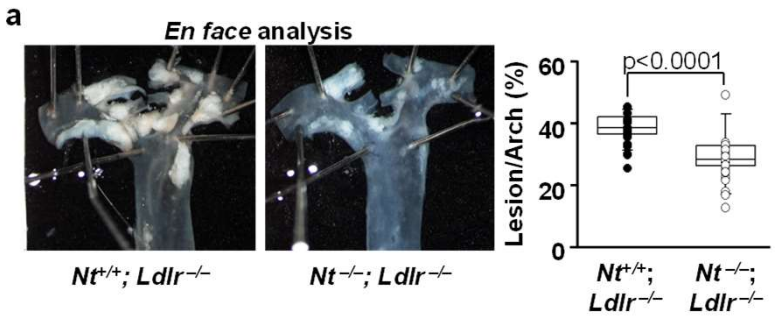
*FAT INTAKE TRIGGERS RELEASE

*CANCER INITIATION / GROWTH

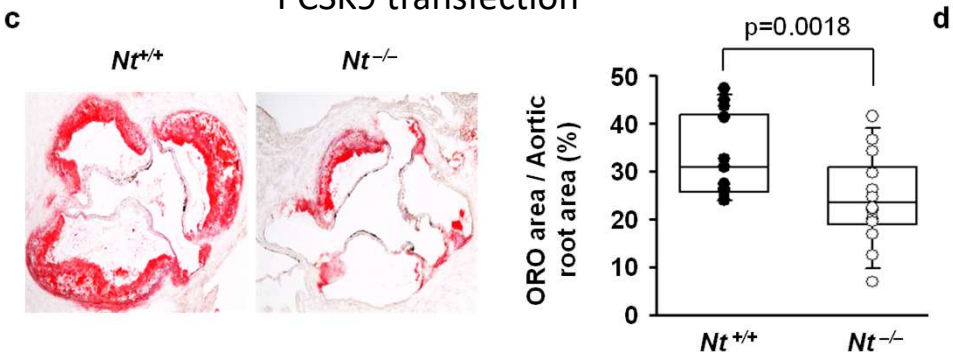
JAMA 2012;308:1469-75

Mice without neurotensin are protected from atherosclerosis in two different athero models and humans with high pro-NT have increased progression of atherosclerosis

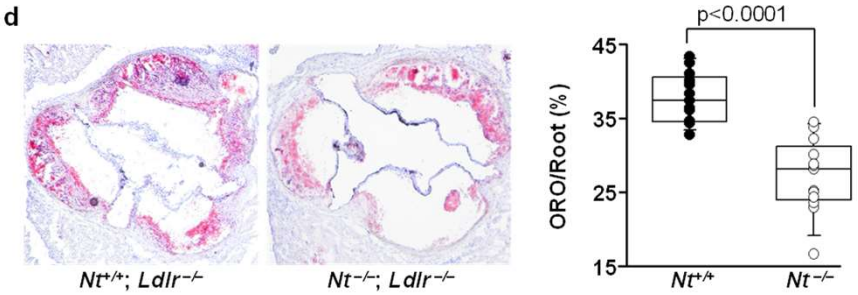




PCSK9 transfection



LDLR knock



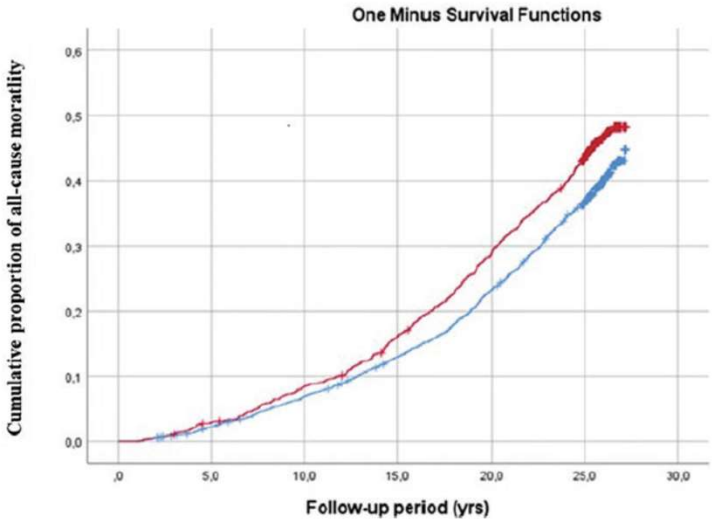
	N	Stand. β**	95% CI**	P-value
IMT-bulb-max progression*	2135	0.055	0.014-0.096	0.009

Atherosclerosis, March 2024

Plasma Proneurotensin and Prediction of Cause-Specific Mortality in a Middle-aged Cohort During Long-term Follow-up

Ayesha Fawad,[1] Andreas Bergmann,[2] Janin Schulte,[2] Zahra A. Butt,[3] Peter M. Nilsson,[1] Louise Bennet,[1] Marju Orho-Melander,[1] and Olle Melander[1]

Pro-NTS >150 pmol/L



		Fully adjusted[a]		
	ll participants	Quartile 1-3	Quartile 4	P
All-cause mortality				
No./events No.	4478/1823	3365/1316	1113/507	
HR (95% CI)			1.20 (1.08-1.33)	.001
Cardiovascular diseases				
No./events No.	4478/562	3365/397	1113/165	
HR (95% CI)			1.30 (1.08-1.56)	.005
Gastrointestinal diseases				
No./events No.	4478/42	3365/24	1113/18	
HR (95% CI)			2.37 (1.28-4.39)	.006
Mental and behavioral diseases				
No./events No.	4478/89	3365/61	1113/28	
HR (95% CI)			1.56 (0.99-2.34)	.057

JCEM 2022;103:1940-47

NEUROTENSIN (NTS) >150 pmol/L- 25% OF THE POPULATION "HYPERCONSERVES" FAT

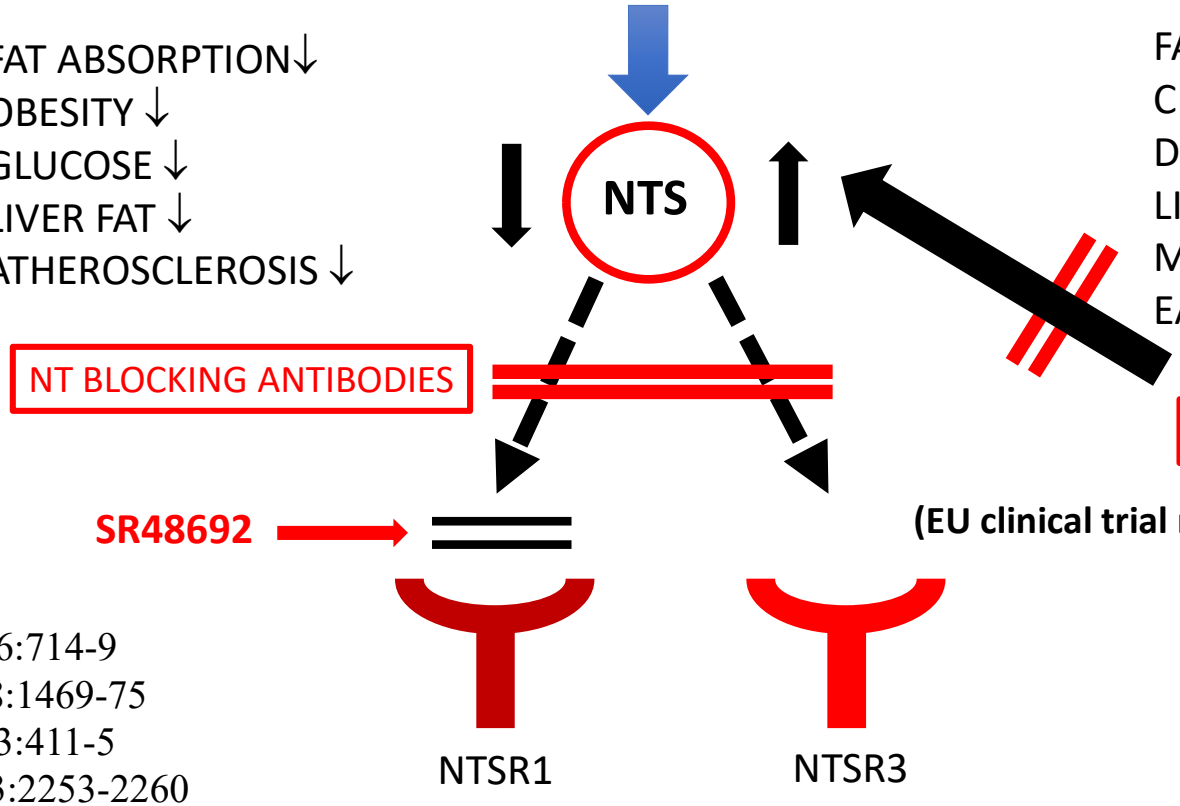
* GENETIC SURVIVAL ADVANTAGE DURING THE STONE AGE = HUGE DISADVANTAGE TODAY

ANIMAL MODELS WITHOUT NTS

FAT ABSORPTION↓
OBESITY ↓
GLUCOSE ↓
LIVER FAT ↓
ATHEROSCLEROSIS ↓

PEOPLE WITH HIGH NTS

FAT ABSORPTION↑
CENTRAL OBESITY ↑
DIABETES ↑
LIVER FAT ↑
MYOCARDIAL INFARCTION↑
EARLY DEATH ↑

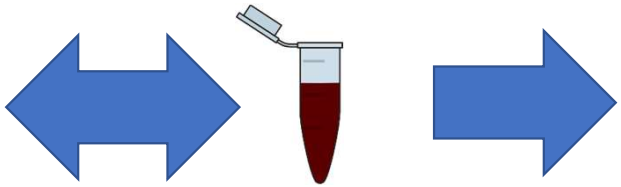


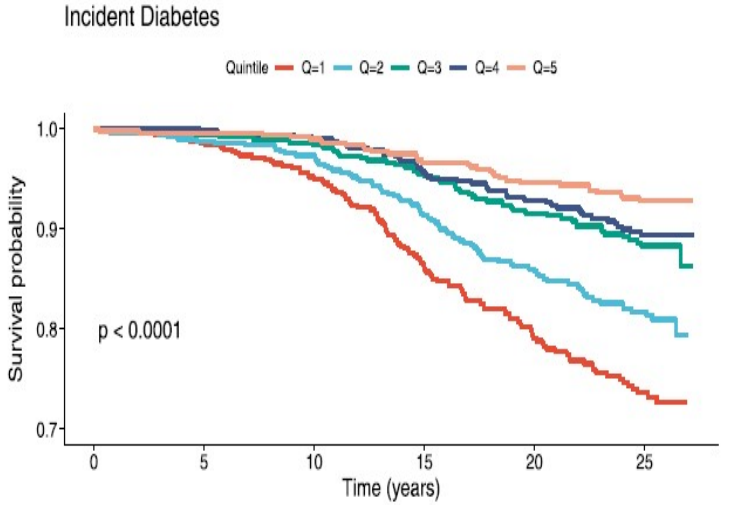
(EU clinical trial number 2022-500366-10-00/IN**).**

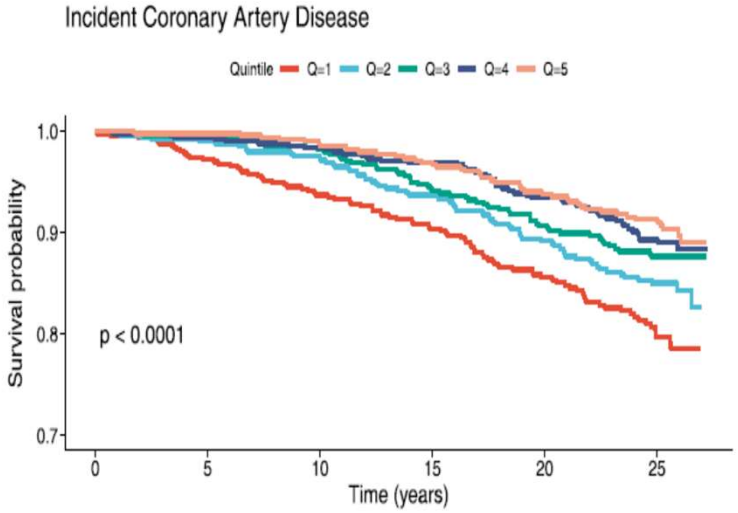
Nature. 2010;466:714-9
JAMA. 2012;308:1469-75
Nature. 2016;533:411-5
JCEM. 2018;103:2253-2260

HEALTHY DIET MEASURED IN BLOOD PREDICTS (LOW) CARDIMETABOLIC RISK (HCFP-BLOOD-FINGERPRINT)

HCFP blood fingerprint







Eur J Nutr. 2019;58:1801-1814
BMC Med. 2022;20:122

CILENTO-MALMÖ COMPARISON: SEARCH FOR PROTECTIVE DIET METABOLITES

Internal and Emergency Medicine
https://doi.org/10.1007/s11739-020-02625-4

IM - ORIGINAL

Check for updates

Comparison of cardiovascular disease and cancer prevalence between Mediterranean and north European middle-aged populations (The Cilento on Ageing Outcomes Study and The Malmö Offspring Study)

Olle Melander[1,2] · Paola Antonini[4] · Filip Ottosson[1] · Louise Brunkwall[1] · Widet Gallo[1] · Peter M. Nilsson[1,2] · Marju Orho-Melander[1] · Gaetano Pacente[4] · Giovanni D'Arena[4,5] · Salvatore Di Somma[3,4]

ENVIRONMENTAL EXCHANGE

N=60 (n=59)

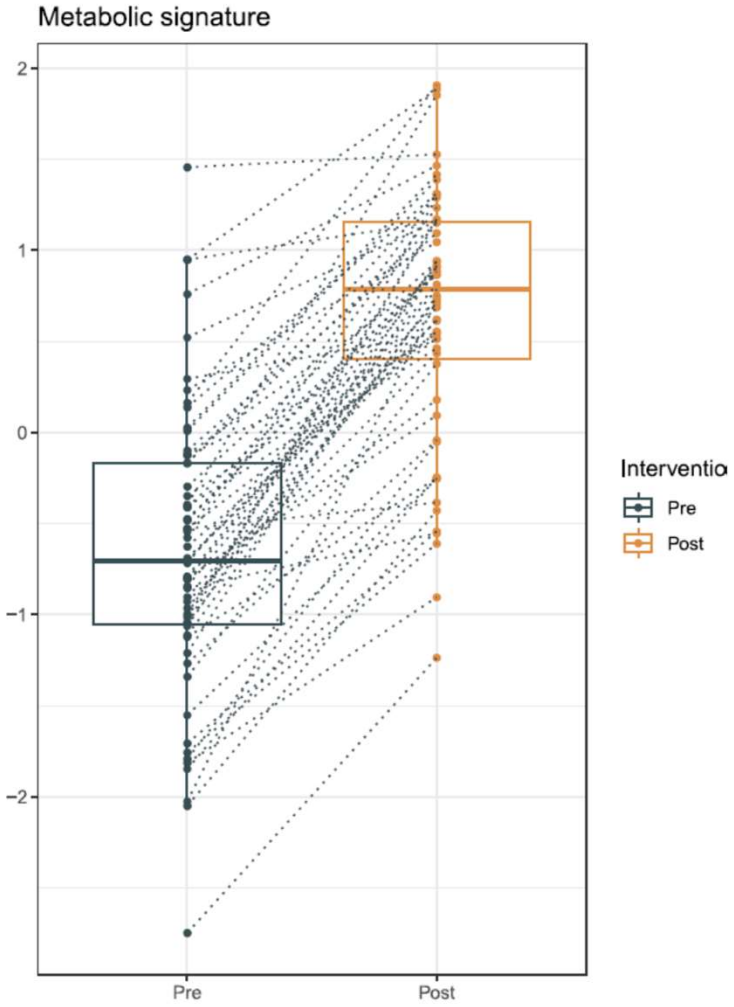
1 week in Cilento

All meals local Cilento food

Malmö, Sweden

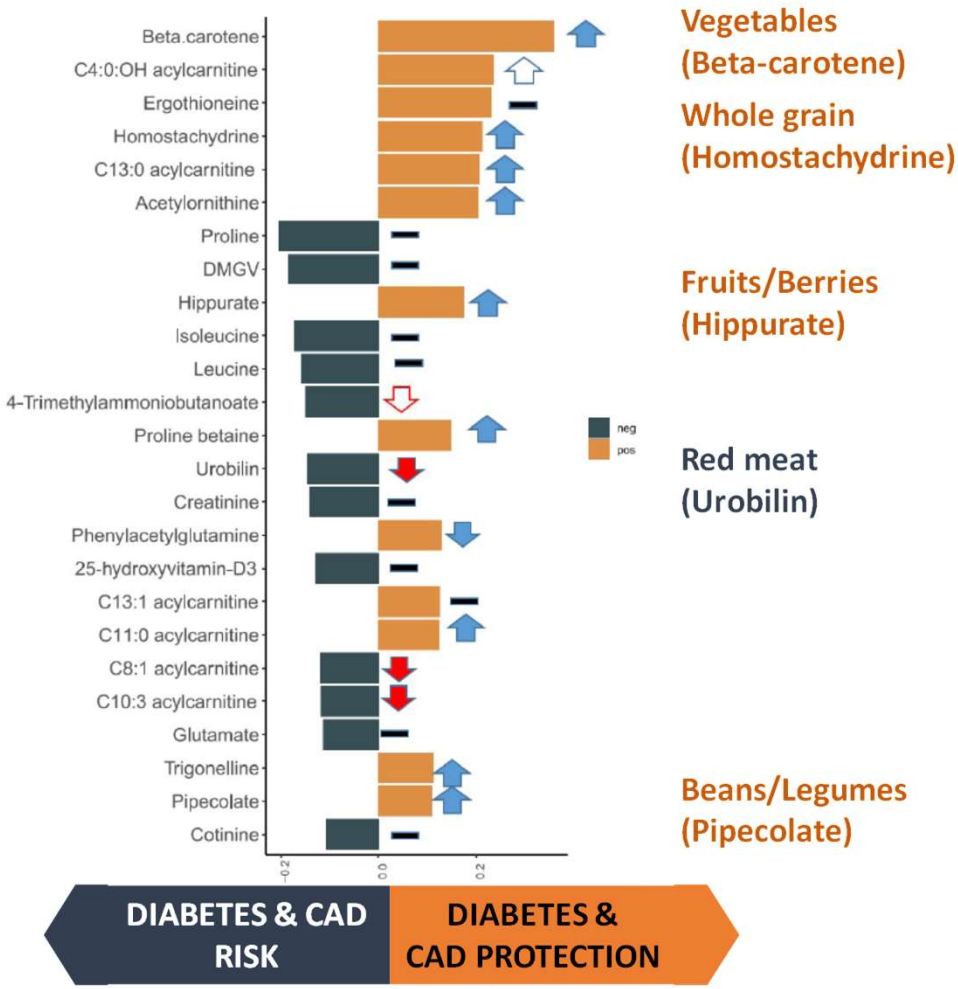
Cilento, Italy

”HCFP blood fingerprint” improves 100% by 1 week Mediterranian diet (P= 2 x 10^{-21})



“Disease protective” metabolites ⬆

“Disease risk” metabolites ⬇



Vegetables (Beta-carotene)

Whole grain (Homostachydrine)

Fruits/Berries (Hippurate)

Red meat (Urobilin)

Beans/Legumes (Pipecolate)

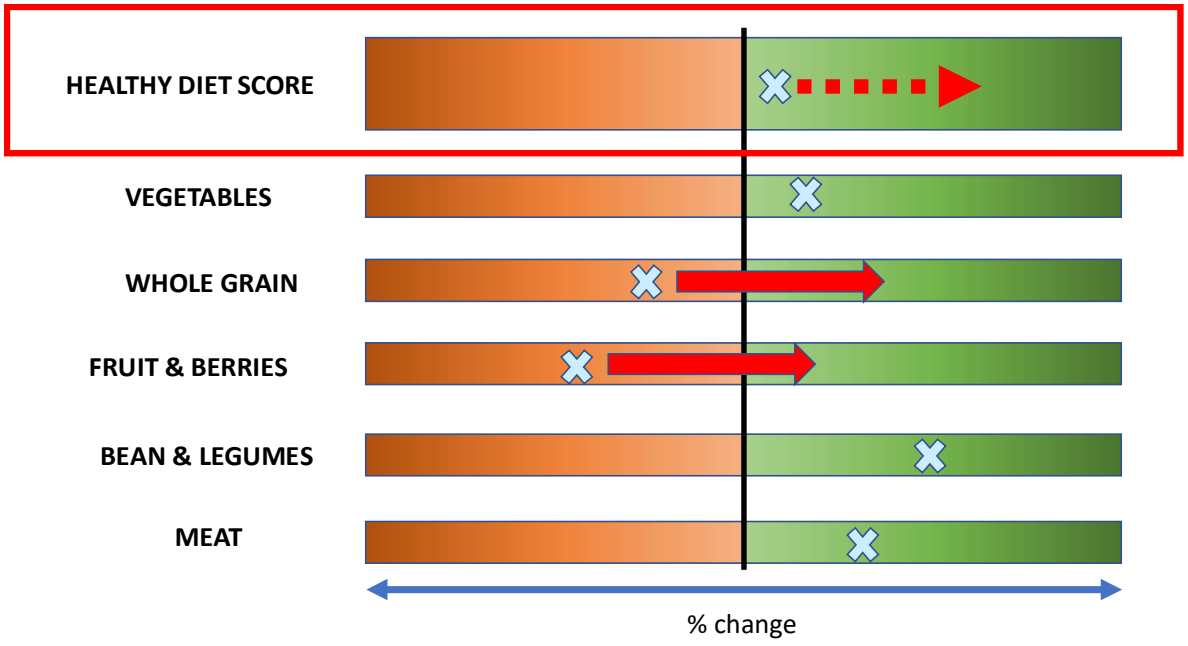
Nationellt vårdprogram levnadsvanor, kortversion

Matvanor

MONITOR "HEALTHY/UNHEALTHY" DIET-METABOLITES IN BLOOD"

Alcohol - PEth

Tobacco - cotinine



Understanding of metabolites that enters blood after specific food components which are to be incresed or decreased according to Nordic Nutrition Guidlines 2023

Fasted sample (t=0) **sample (2h)** **sample (4h)** **sample (6h)**

Specific food item (≈200 kcal)

Visit 1:	**Vegetables**
Visit 2:	**Beans/Legumes**
Visit 3:	**Fruits/Berries**
Visit 4:	**Fish/Seafood**
Visit 5:	**Dairy**
Visit 6:	**Nuts and seeds**
Visit 7:	**Whole grain**
Visit 8:	**Red meat**
Visit 9:	**Processed meat**
Visit 10:	**Veg oils**
	Alcohol / Salt / Sugar

BASLINJE
PROVTAGNING
FASTANDE (n=60)

HÄLSOSAMTAL

(n=60)

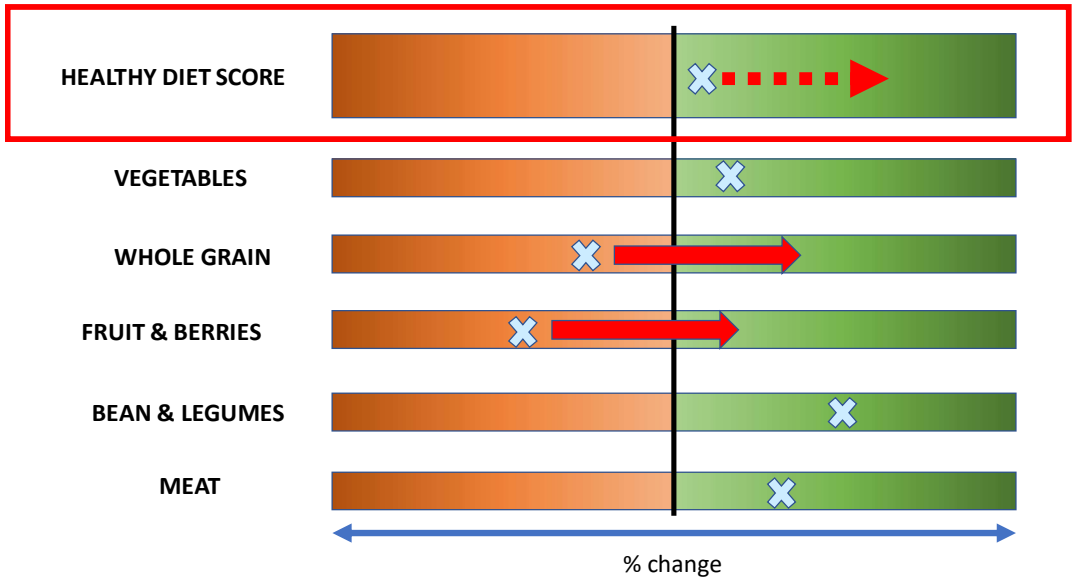
Ca 1 MÅN
PROVTAGNING
(n=60)

FRÅN THD BIOBANK

INFORMERAT
SAMTYCKE

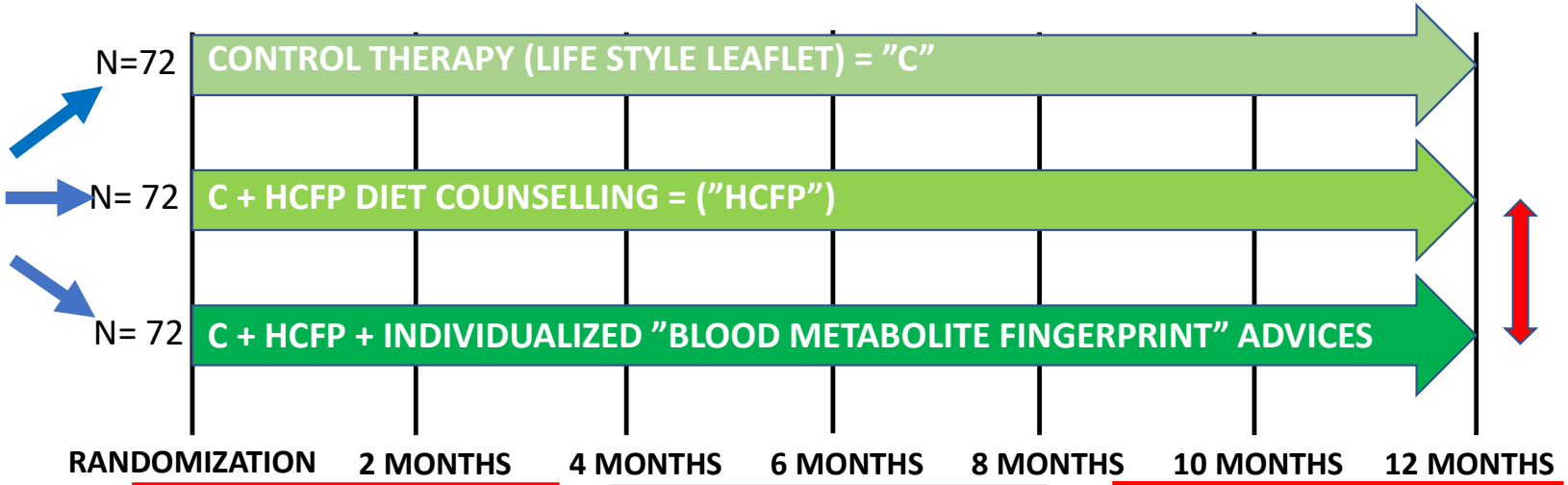
Vilken effekt har RHS på “kostrelaterade blodmetaboliter”?

Pilotstudie Vårdcentralen Granen, Malmö



BLOD-METABOLIT FÖRÄNDRINGAR AV HÄLSOSAMTAL?

Leder mätning av kostrelaterade blodmetaboliter vid riktade hälsosamtal till förbättrad följsamhet till kostråd?



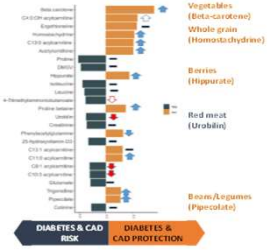
BETWEEN GROUP DIFFERENCE IN 12-MONTH CHANGE IN GLYCEMIA?

SHORT VERSION ”NVPL”

+

DIET COUNSELLING

+



HCFP-BLOOD-FINGERPRINT

PRECISIONS (PRIMÄR) PREVENTION-5 ÅRSVISION

Population: 1,420,000

*Mätning av **<u>polygenetisk risk</u>**:
20% statin + livsstil
10% behöver aldrig statin

*Mätning av **<u>kostrelaterade metaboliter</u>**:
Förbättra följsamhet till kostråd vid RHS

*Mätning av **<u>behandlingsbar hormonell risk</u>** (t.ex. neurotensin)

*VINSTER MED PREVENTION
VS ETIK, JURIDIK, KOSTNADER (hälsoekonomi)
Nya uppdrag?