7th IMAD meeting

Polymorphisms of genes encoding selenoproteins influence the growth of abdominal aortic aneurysm (AAA) – a study in Polish population

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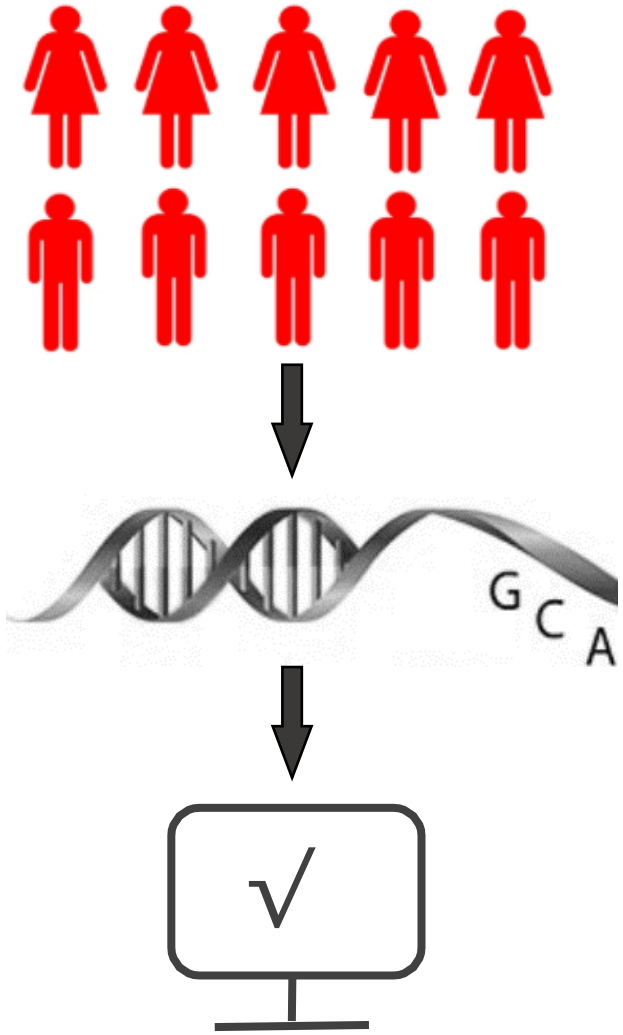
AIM

This study examines the associations of functional SNPs in 11 candidate genes for cardiovascular disease (CVD), including those involved in determining

- blood pressure,
- lipid profile,
- homocysteine levels,
- response to hypoxia and oxidative stress

with the growth rate of AAA.

METHODS



Inclusion criteria:

- AAA ≥30 mm
- ≥2 control examination of aneurysm diameter during 1 year
- both sexes

TaqMan-genotyping of 11 SNPs in genes:

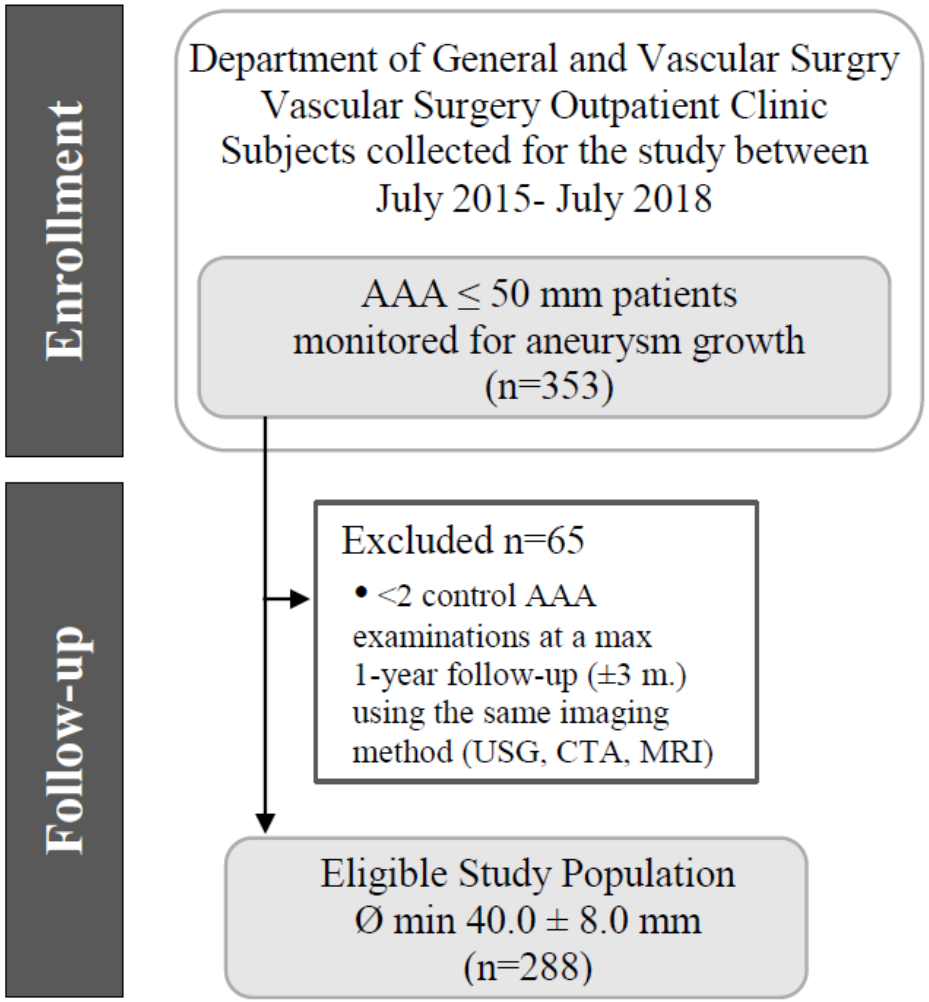
AGTR1, ApoE, GPX4, HIF1A, MTHFR, PON1, SELENOS, SEPP1, SOD2, TXNRD1, TXNRD2,

Statistical analysis:

- the development of AAA progression models using GLM methods
- **growth rates estimated for growth within the specified AAA size ranges, in 10 mm increments (± 2 mm) covering AAA growth from 30 - 70 mm**
- analysis of association

METHODS

Flow chart describing selection of study patients



The characteristics of study group

Parameter	AAA N=288
Age [years]	68.3±7.1
Men	82.3%
Cigarette smoking, current	34.6%
Arterial hypertension	83.6%
Diabetes	28.7%
Hyperlipidemia	85.0%
AAA ≥50 mm	42.8%
AAA growth rate [mm/y]	3.7±4.7
No. of ultrasound scans	6.1 ± 2.9
Follow-up, years	3.9 ±2.2
Elective AAA repair	34.0%

RESULTS

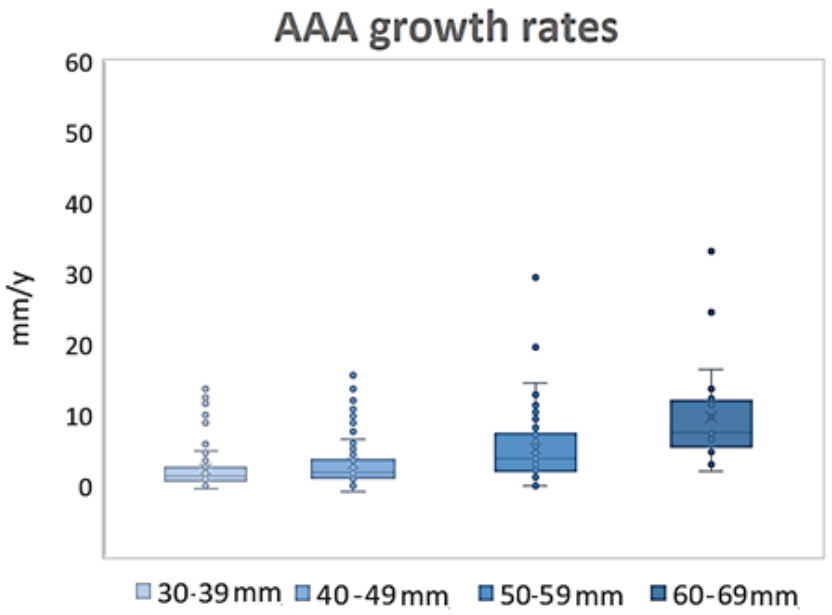


FIGURE AAA growth rates estimated for specified size ranges (**n=442 individual observations**)

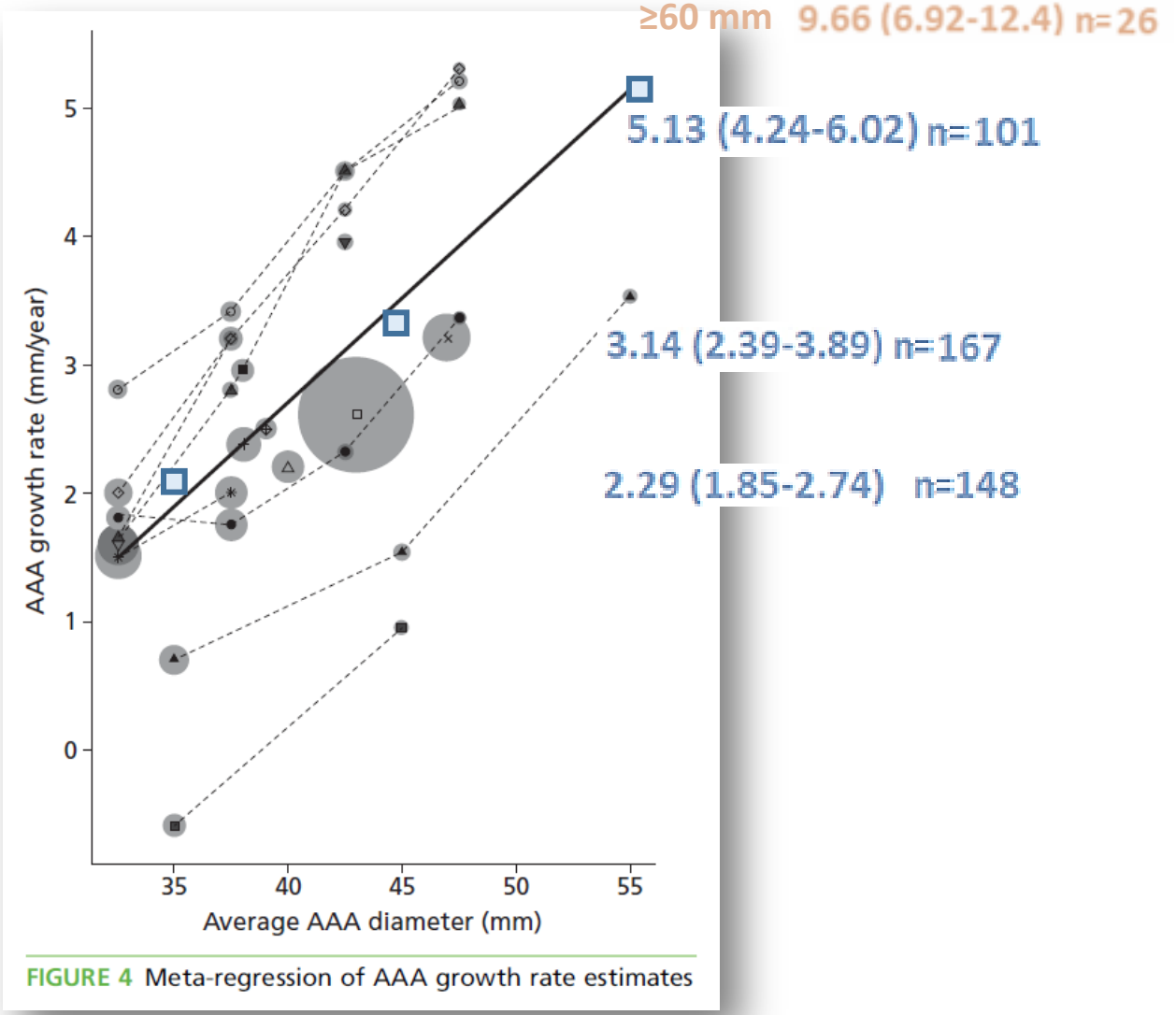
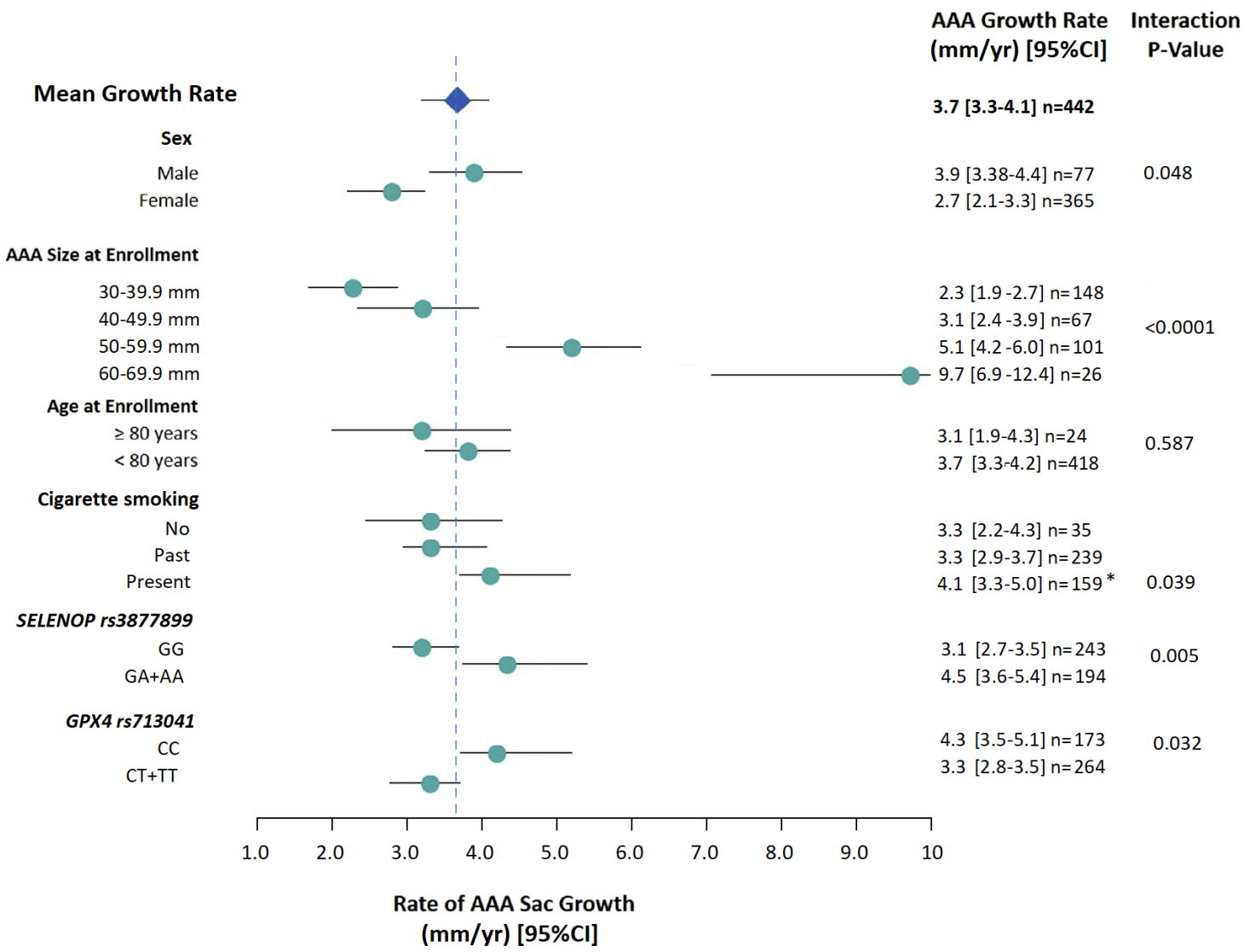


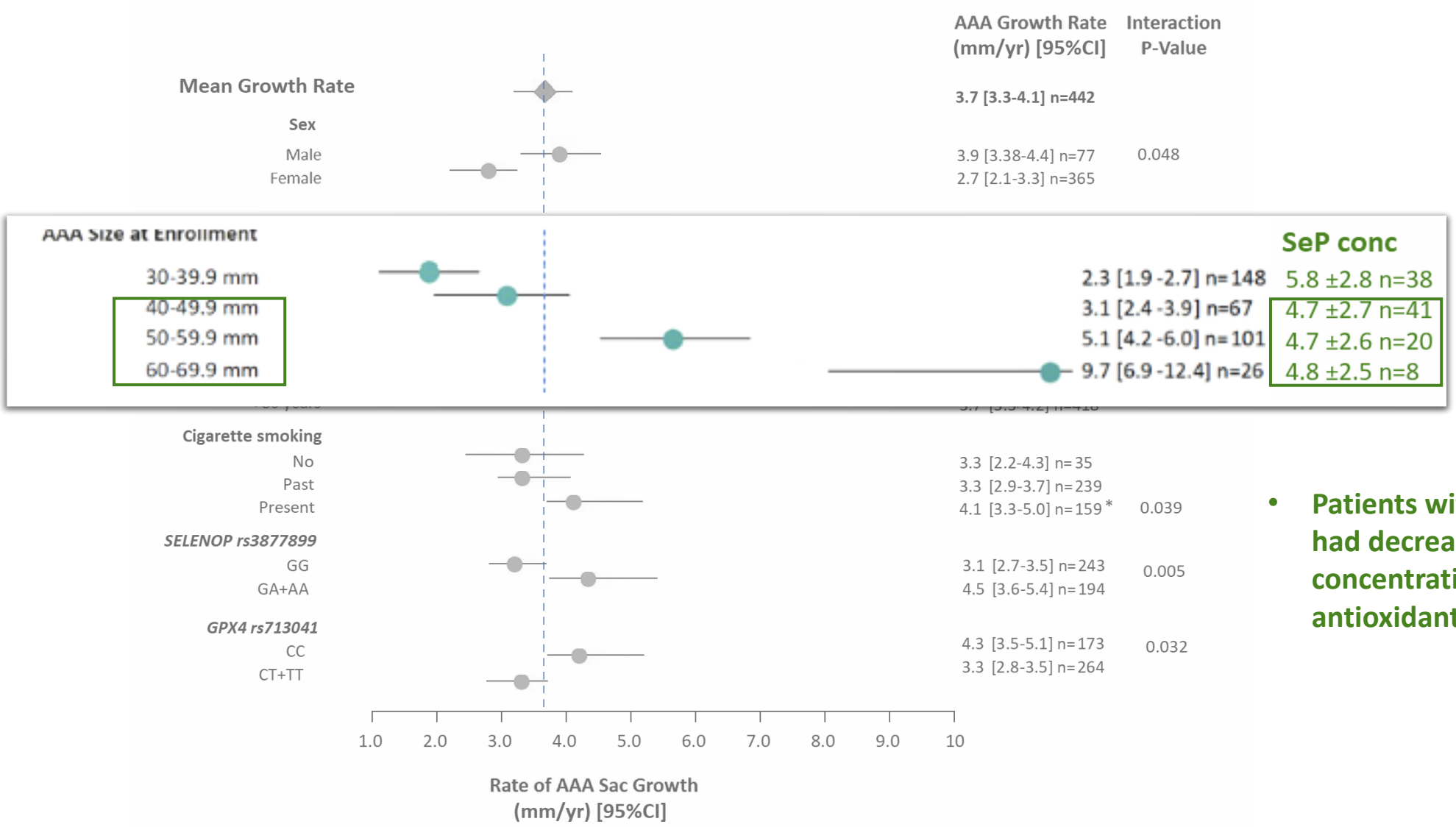
FIGURE 4 Meta-regression of AAA growth rate estimates

Thompson SG, et al. Health Technol Assess. 2013;17:1-118.

FACTORS ASSOCIATED WITH ANNUAL AAA GROWTH RATE

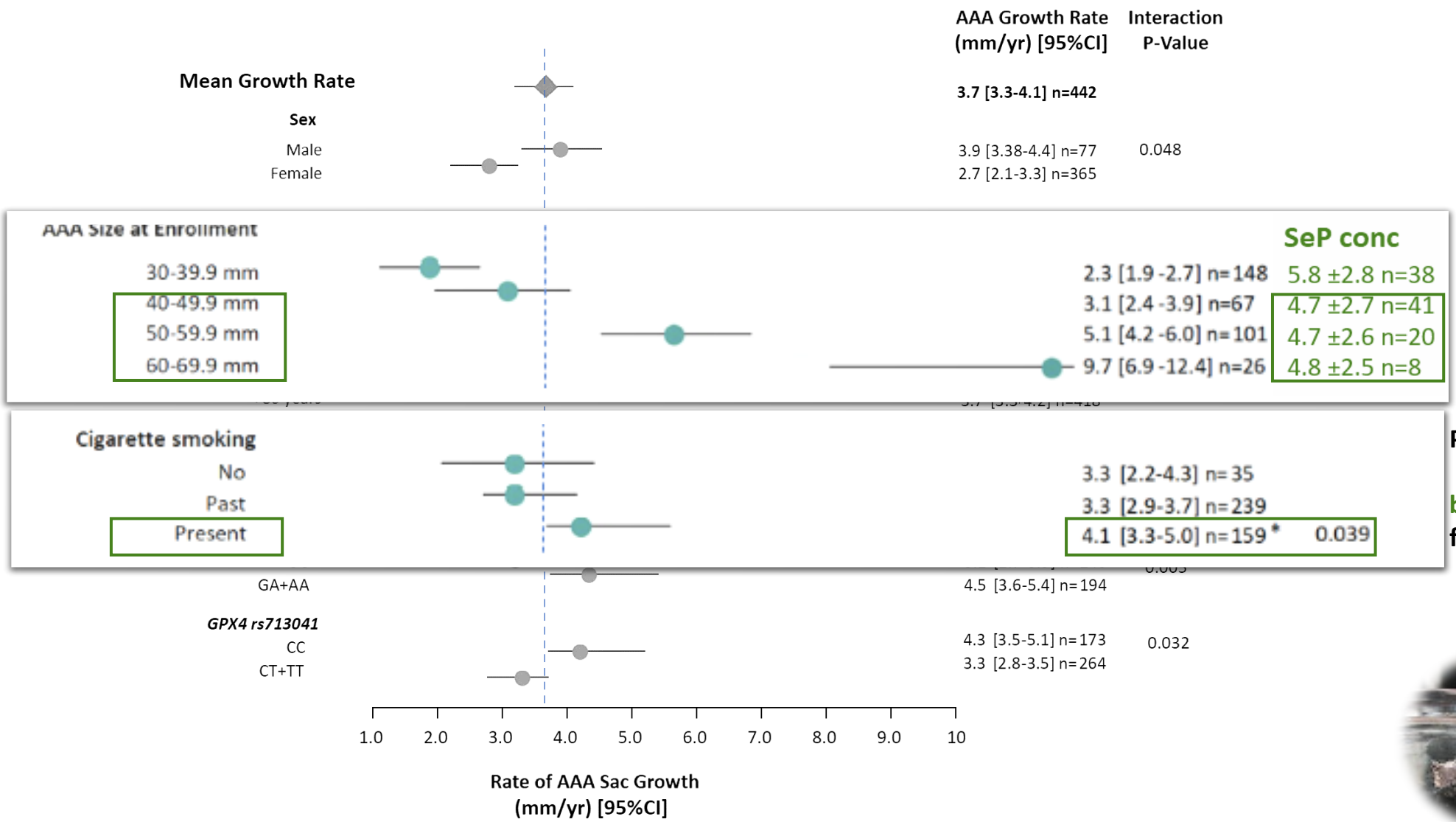


FACTORS ASSOCIATED WITH ANNUAL AAA GROWTH RATE



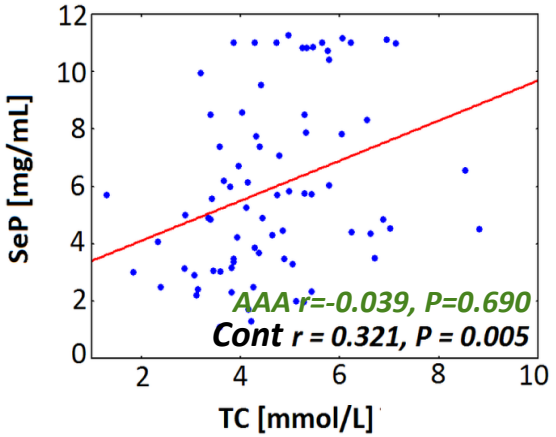
- **Patients with larger AAAs >39 mm had decreased blood SeP [ng/ml] concentration (insufficient antioxidant barier)**

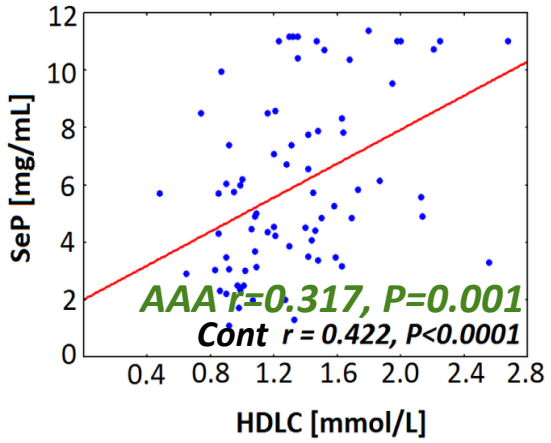
FACTORS ASSOCIATED WITH ANNUAL AAA GROWTH RATE

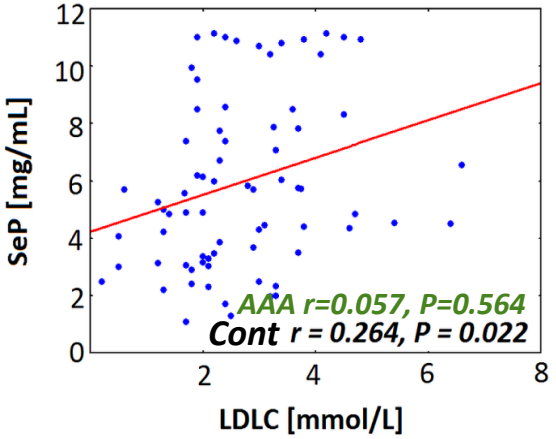


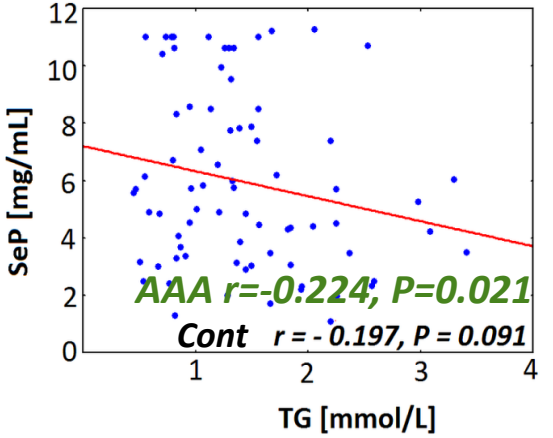
Present SMOKING, the main modifier of Se status in the body , was the only CVD risk factor associated with faster AAA growth.

CORRELATION OF SELENOPROTEIN P (SeP) LEVELS WITH LIPID PROFILES IN THE POPULATION OF 105 PATIENTS WITH AAA AND 75 CONTROL SUBJECTS





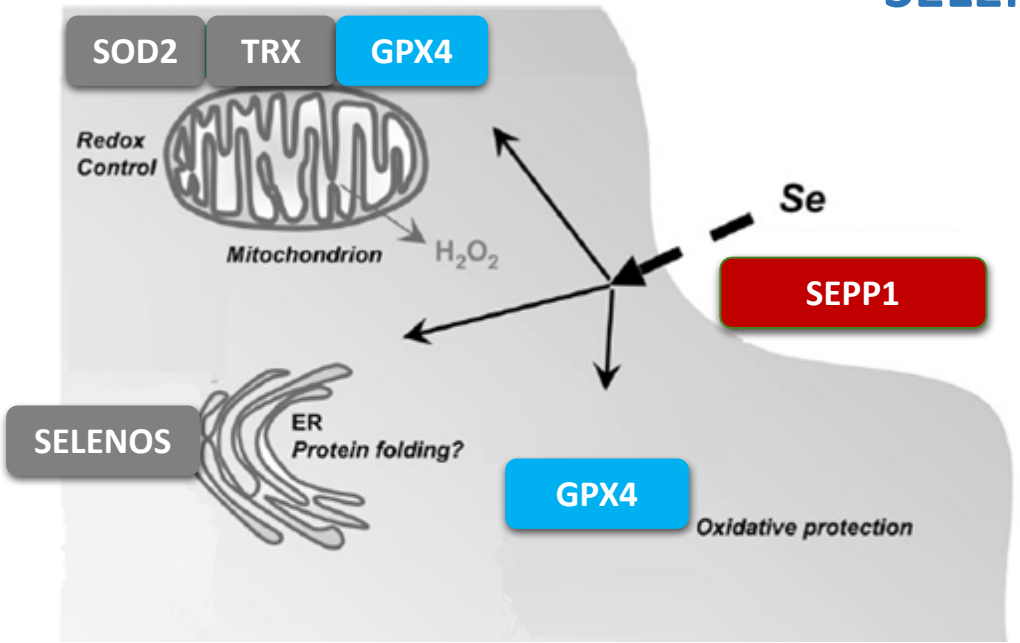




In AAA SeP concentration was

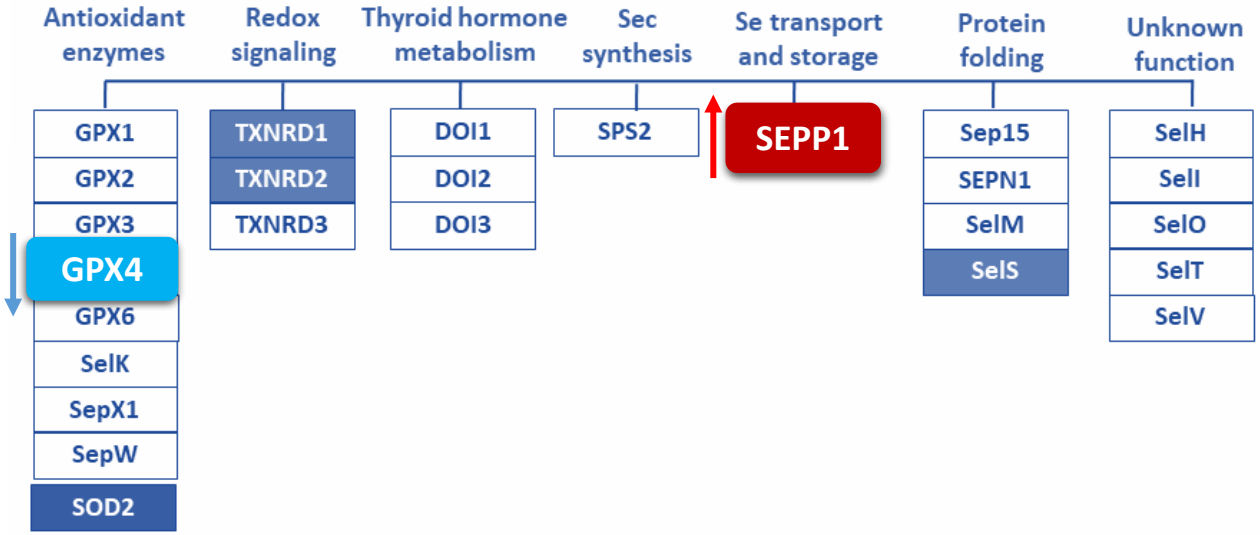
- *positvely corelated with HDLC*
- *negatively corelated with TG*

SELENOPROTEINS



Intracellular oxidative stress

- 25 proteins that include selenium
- act against oxidative stress



SEPP1 : Ex5 –rarer allele favors the production of a low Se isoform **of protein**)
GPX4- 3'-UTR -alters the protein binding to the 3'-UTR and reporter gene activity**,**

SNPs associated with AAA growth influenced the effects of Se supplementation in clinical trials

SeP AND SELENOPROTEIN SNPS vs CVD

Protein/Gene	Parameter/SNP	Effect
SeP	Levels increased	• presence of diabetes • glucose intolerance • thickening of the intima-media complex in the carotid artery
	Levels decreased	• gestational diabetes mellitus
	Expression increased	• in macrophages with anti-atherosclerotic function (implies a protective role of SeP in CVD) • act as an antiangiogenic factor, retarding perfusion recovery in response to ischemia in diabetic peripheral and coronary atherosclerosis
SEPP1	*rs7579A*	• SNPs affect the bioavailability of Se • abdominal aortic aneurysm
	rs3877899	• SNPs affect the bioavailability of Se • abdominal aortic aneurysm

Protein/Gene	Parameter/SNP	Effect
GPX4	*rs713041*	• concentrations of inflammatory biomarkers • cerebral stroke • endothelial dysfunction
	rs4807542	• concentrations of inflammatory biomarkers
SELENOS	*rs4965814*	• ischemic stroke
	rs28628459	• self-reported history of prior CVD • carotid atherosclerosis • self-reported history of prior CVD
	rs7178239	• carotid atherosclerosis • ischemic stroke
	rs8025174	• carotid atherosclerosis • coronary artery disease
	rs9806366	• self-reported history of prior CVD
	rs28665122	• carotid atherosclerosis
	rs12917258	• coronary atherosclerosis

- Primarily studied in malignant diseases,
- Growing evidence on their role in CVD

(*Strauss et all: Scient Rep 2014; PloS One 2018*).

SELENIUM & AAAs

1. Decreased blood Se levels in AAA

Vasa 2011; 40: 381–389
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Original communication

Diet and the content of selenium and lead in patients with abdominal aortic aneurysm

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No	Selenium	n	Control group mean ± SD (min. – max.)	n	Patients with AAA mean ± SD (min. – max.)	p value
1	Serum (µg/L)	22	75.87 ± 22.4 (46.57 – 149.42)	49	60.37 ± 21.2 (17.65 – 113.34)	0.0075*
2	Aortic wall (ng/g)	17	55.44 ± 34.4 (14.07 – 124.70)	40	52.31 ± 47.1 (10.05 – 219.13)	0.839
3	Parietal thrombus (ng/g)	–	–	37	139.82 ± 44.6 (51.91 – 257.21)	–

2. Decrease of plasma levels of Se as AAA size increased

Redox Report
Communications
in Free Radical Research

Table 2 Mean plasma levels of oxidative stress biomarkers in control subjects and AAA patients

Variable	Control group (*n* = 18)	AAA ≤50 mm (*n* = 15)	AAA >50 mm (*n* = 12)	*P*-value**
Vitamin C (µg/ml)	10.9 ± 3.85	9.15 ± 2.73	7.35 ± 3.16	0.011
α-Tocopherol (µg/ml)	14.5 ± 3.34	12.4 ± 3.14	11.6 ± 2.91	0.016
γ-Tocopherol (µg/ml)	0.81 ± 0.38	0.92 ± 0.49	0.66 ± 0.29	0.50
Cholesterol (g/l)	2.04 ± 0.35	1.79 ± 0.54	1.62 ± 0.46	0.020
α-Tocopherol /chol (mg/g)	7.16 ± 1.44	7.10 ± 1.31	7.38 ± 1.64	0.71
β-Carotene (mg/l)	0.29 ± 0.17	0.20 ± 0.18	0.11 ± 0.054	0.0096
Thiol proteins (µM)	311 ± 38	337 ± 45.7	312 ± 41.0	0.48
Ubiquinone (mg/l)	0.84 ± 0.32	0.70 ± 0.23	0.57 ± 0.21	0.014
Copper (mg/l)	0.88 ± 0.12	0.90 ± 0.26	0.90 ± 0.32	0.79
Zinc (mg/l)	0.79 ± 0.14	0.73 ± 0.10	0.63 ± 0.13	0.0035
Copper/zinc ratio	1.14 ± 0.21	1.24 ± 0.38	1.43 ± 0.42	0.046
Selenium (µg/l)	92.7 ± 16.4	83.8 ± 18.3	70.4 ± 21.0	0.0038
Lipid peroxides (µM)*	520 ± 228	574 ± 360	563 ± 307	0.82
Oxidized LDL (ng/ml)*	756 ± 964	205 ± 244	264 ± 220	0.062
Antibodies against oxidized LDL	263 ± 282	255 ± 308	148 ± 87.5	0.32
Isoprostanes (ng/ml)	1.01 ± 0.66	1.19 ± 0.64	1.68 ± 0.89	0.052
Paraoxonase (ng/ml)*	105 ± 61.1	127 ± 89.0	136 ± 72.2	0.26
Total glutathione (µM)*	852 ± 203	960 ± 148	922 ± 209	0.20
Oxidized glutathione (µM)*	1.01 ± 0.67	4.58 ± 11.0	4.93 ± 13.3	0.33
Glutathione peroxidase (UI/g Hb)	51.5 ± 9.97	51.5 ± 11.5	51.0 ± 10.6	0.91
Myeloperoxidase (ng/ml)*	22.0 ± 24.4	53.4 ± 76.6	48.8 ± 95.9	0.28

3. Correlations between serum TRX with AAA size and expansion rate

Contents lists available at ScienceDirect
Atherosclerosis
journal homepage: www.elsevier.com/locate/atherosclerosis
Atherosclerosis 212 (2010) 333–338

Increased levels of thioredoxin in patients with abdominal aortic aneurysms (AAAs). A potential link of oxidative stress with AAA evolution

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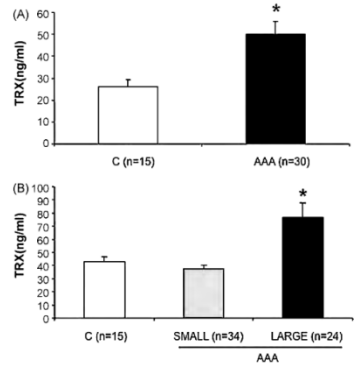
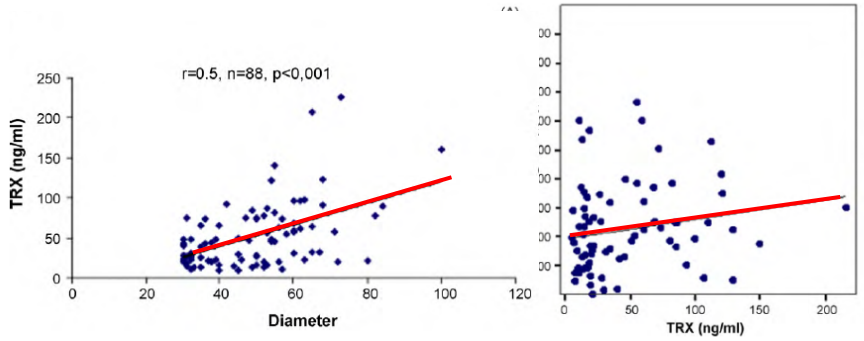


Fig. 2. TRX levels in AAA. (A) TRX levels are significantly increased in serum of patients with AAA ($n = 30$) vs. controls ($n = 15$) (*$p < 0.05$). (B) TRX levels are significantly increased in serum of patients with large AAA ($n = 24$) in relation to small AAA ($n = 34$) and controls ($n = 15$) (*$p < 0.05$).



Conclusions: TRX release is increased in the luminal part of AAA and TRX serum levels are increased in AAA patients compared with healthy subjects. TRX levels correlates with AAA size and expansion, suggesting its potential role as a biomarker of AAA evolution.

Conclusions

- **The observed associations confirm the role of selenoproteins and oxidative stress in the progression of AAA.**

- The role of SNPs *SELENOP* rs3877899 and *GPX4* rs713041 in AAA progression is a novel observation