

#### Epidemiology dictates the genetics of AAA

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### Disclosures

• None

#### Causal factors for abdominal aortic aneurysm



Acquired environmental risk Smoking Specific toxins?

# Recent changes in epidemiology of abdominal aortic aneurysm (AAA)

- Population screening in UK & Sweden shows a decreasing prevalence of AAA in 65y men (from 5% in 1998 to 1% now)
- Decreasing both prevalence AAA & incidence of ruptured AAA are associated with reduction in population smoking
- Increasing age at clinical presentation
- Stronger evidence for association with increased serum cholesterol concentration & diastolic blood pressure
- Questionable evidence for inverse association with diabetes



#### Genetic markers for the big 3 risk factors for AAA

# AgeTelomere shorteningSmokingSNPs associated with smoking onsetMaleY chromosome, steroid hormones

#### Do long telomeres increase the risk of cancer?

Telomere Mendelian Randomisation Collaboration. JAMA Oncol. 2017;3:636-51

~	Disease	Tumor/Disease	Cases	SNPs	OR (95% CI)	Lower Risk	Higher Risk	P Value <sup>a</sup>	P Value <sup>b</sup>	
Cancer	Cancer									
	Glioma	NA	1130	12	5.27 (3.15-8.81)			<.001	.01	
	Ovarian cancer	Serous LMP	972	13	4.35 (2.39-7.94)			<.001	.08	
	Lung cancer	Adenocarcinoma	3442	13	3.19 (2.40-4.22)			<.001	<.001	
	Neuroblastoma	NA	2101	12	2.98 (1.92-4.62)			<.001	.38	
	Bladder cancer	NA	1601	10	2.19 (1.32-3.66)			.003	.25	
	Skin cancer	Melanoma	12 814	13	1.87 (1.55-2.26)		-	<.001	.09	
	Testicular germ-cell cancer	NA	986	11	1.76 (1.02-3.04)			.04	.30	
	Kidney cancer	NA	2461	12	1.55 (1.08-2.23)			.02	.25	
	Endometrial cancer	NA	6608	12	1.31 (1.07-1.61)		-	.01	.14	
	Skin cancer	Basal cell carcinoma	3361	13	1.22 (0.90-1.65)		-	.20	.04	
	Ovarian cancer	Endometrioid	2154	13	1.21 (0.87-1.68)			.25	.33	
	Breast cancer	ER-	7465	13	1.14 (0.91-1.43)		÷	.25	<.001	long telomeres reduce
	Ovarian cancer	Serous invasive	9608	13	1.12 (0.94-1.34)		+	.21	.04	Long teromeres reduce
	Prostate cancer	NA	22 297	11	1.12 (0.96-1.30)		=	.15	<.001	rick of AAA
	Colorectal cancer	NA	14 537	9	1.09 (0.91-1.31)		+	.34	.02	IISK ULAAA
	Lung cancer	Squamous cell carcinoma	3275	13	1.07 (0.82-1.39)		÷	.62	.90	
	Breast cancer	ER+	27 074	13	1.06 (0.95-1.17)		-	.29	.02	
	Ovarian cancer	Clear cell	1016	13	1.04 (0.66-1.63)	-	÷	.87	.32	
	Ovarian cancer	Mucinous	1643	13	1.04 (0.73-1.47)		÷	.84	.31	OR 0.63 [95%CI 0.49-0.81]
	Esophageal cancer	Squamous cell carcinoma	1942	8	1.03 (0.62-1.72)	-	÷	.91	.45	ι,
	Pancreatic cancer	Adenocarcinoma	5105	12	0.86 (0.56-1.32)	-	-	.50	.002	
	Head and neck cancer	NA	2082	12	0.86 (0.57-1.30)	-		.48	.08	
	Cardiovascular diseases									
LVD	Heart failure <sup>c</sup>	NA	2526	13	1.02 (0.77-1.35)		÷	.89	.53	
	Ischemic stroke	Small vessel disease	1894	13	0.94 (0.66-1.33)	-		.71	.24	
	Sudden cardiac arrest	NA	3954	13	0.92 (0.68-1.26)	-	-	.62	.54	
	Hemorrhagic stroke	NA	2963	12	0.92 (0.61-1.37)	-	-	.67	<.001	
	Ischemic stroke	Cardioembolic	2365	13	0.88 (0.64-1.22)	-	-	.45	.04	
	Coronary heart disease	NA	22 233	13	0.78 (0.67-0.90)		1	<.001	.24	
	Ischemic stroke	Large vessel disease	2167	13	0.74 (0.52-1.04)	-	H	.08	.16	
	Abdominal aortic aneurysm	NA	4972	13	0.63 (0.49-0.81)			<.001	.06	- ΔΔΔ
Nourohu	Neurological/psychiatric diseases									
ινευιό/ ψ	Anorexia nervosa	NA	2907	9	1.14 (0.82-1.58)		-	.44	.18	
	Bipolar disorder	NA	7481	9	1.13 (0.89-1.44)		÷	.32	.14	
	Amyotrophic lateral sclerosis	NA	6100	12	1.12 (0.86-1.47)		+	.40	.63	
	Tourette syndrome	NA	1177	13	1.10 (0.68-1.78)	-	-	.69	.50	
	Major depressive disorder	NA	9240	8	1.07 (0.84-1.37)			.56	.25	
	Autism	NA	4949	7	1.01 (0.73-1.39)		•	.95	.82	
	Schizophrenia	NA	35 476	12	1.01 (0.90-1.12)		•	.92	.005	
	Alzhoimor disease	NΔ	17 008	12	0.84 (0.71-0.98)			03	15	

#### Smoking & risk of AAA

Larsson et al Eur Heart J doi: 10.1093/eurheartj/ehaa19326-33

## Smoking initiation scores, using multiple influential SNPs, UK Biobank

Outcome	Cases		OR (95% CI)	P-value	₽ (%)
Peripheral arterial disease	3415	<b>_</b>	1.81 (1.55-2.11)ª	5.9×10 <sup>-14</sup>	10
Abdominal aortic ar AAA C	DR 1.74 [95%CI 1.33-2.26]	<b>—</b>	1.74 (1.33-2.26)ª	4.1×10⁻⁵	4
Heart failure	6712	<b>_</b>	1.53 (1.37-1.71)ª	1.1×10 <sup>-13</sup>	12
Subarachnoid hemorrhage	1084	<b></b>	1.42 (1.09-1.85)	9.3×10⁻³	3
Coronary artery disease	29 278	_ <b></b>	1.36 (1.27-1.45)ª	6.9×10 <sup>-19</sup>	40
Pulmonary embolism	6148	│ — <b>∎</b> —	1.32 (1.17-1.49)ª	6.6×10⁻⁵	17
Transient ischemic attack	3962	<b>-</b>	1.31 (1.13-1.51)ª	2.8×10⁴	10
Ischemic stroke	4602	<b>-</b>	1.30 (1.15-1.48)ª	4.4×10⁻⁵	0
Deep vein thrombosis	9454	<b></b>	1.29 (1.17-1.42)ª	1.9×10 <sup>-7</sup>	15
Aortic valve stenosis	2244	<b></b>	1.22 (1.01-1.46)	0.04	4
Arterial hypertension	125 846		1.21 (1.14-1.28)ª	1.3×10 <sup>-11</sup>	70
Intracerebral hemorrhage	1064	<b></b>	1.19 (0.91-1.55)	0.20	3
Atrial fibrillation	16 945	<b>e</b>	1.18 (1.09-1.28)ª	7.1×10⁵	30
Thoracic aortic aneurysm	347		1.06 (0.67-1.68)	0.80	0
	0.6 0.8	1 1.2 1.5 2	2.5		
	OR (9	5% CI)			

#### Smoking & risk of AAA

Mendelian randomisation analysis from Million Veterans study Circulation 2020



#### Lipids & risk of AAA

Harrison SC et al JAMA Cardiol 2018;3:26-33

Lipid risk scores, using			Drotoction	from AAA	
multiple influential SNPs					
in arterial disease GWAS	OR of AAA per SD Higher Lipid Level		Favors Higher Concentration	Favors Lower Concentration	1
MR Method	(95% CI)		of Lipid	of Lipid	P Value
LDL-C					
Inverse-variance weighted	1.66 (1.41-1.96)				$1.1 \times 10^{-9}$
MR-Egger	1.94 (1.49-2.52)				$8.4 \times 10^{-7}$
Weighted median	1.68 (1.33-2.12)				$1.3 \times 10^{-5}$
Multivariable	1.56 (1.34-1.82)				$1.8 \times 10^{-8}$
HDL-C					
Inverse-variance weighted	0.67 (0.55-0.82)				$8.3 \times 10^{-5}$
MR-Egger	0.56 (0.41-0.78)				$6.0 \times 10^{-4}$
Weighted median	0.74 (0.58-0.95)				.02
Multivariable	0.73 (0.60-0.89)				$2.0 \times 10^{-3}$
TG					
Inverse-variance weighted	1.69 (1.38-2.07)				$5.2 \times 10^{-7}$
MR-Egger	1.71 (1.21-2.40)				$2.0 \times 10^{-3}$
Weighted median	1.68 (1.29-2.19)				$9.8 \times 10^{-5}$
Multivariable	1.21 (0.96-1.51)		-		.10
		0.2			
		0.2	00.05%	.0	3.0
			UR (95% (	_1)	

#### GWAS of abdominal aortic aneurysm summarised

- Currently ~30 SNPs over half the chromosomes
- Some common to coronary heart disease
- Subject to residual confounding
- No strong supporting evidence that any SNP is causal

Many genes of small effect, consistent with known pathobiology. GWAS SNPs may reflect the response to AAA rather than its cause



#### Causal factors for abdominal aortic aneurysm



#### Mendelian randomisation studies use leukocyte DNA Are they representative of tissue DNA?



Demenalis et al Science 2020;360: 11 Sept

Telomere length decreases with age in all tissues except testis & cerebellum

Variation across tissues, but all well correlated with leukocyte telomere length

No evidence for strength of smoking associated SNPs in brain