



Use of genetic profiling of a large biobank combined with prescription patterns to discover genetic loci associated with adverse drug reactions

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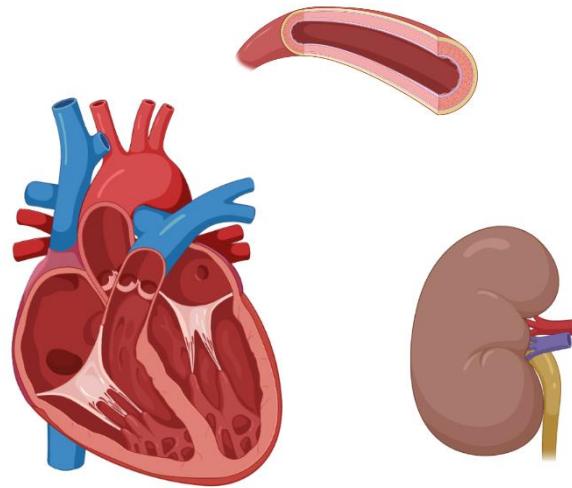
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Nordic Biobank Conference 2022

Conflict of interest

Nothing to disclose.

Background | Why study ACEi?



Background | Adverse drug reactions

“All things are poison and nothing is without poison, only the dose permits something not to be poisonous”

- Paracelsus, 1493-1541

Background | Adverse drug reactions

“All things are poison and nothing is without poison, only the dose **and genetics (?)** permits something not to be poisonous”

- Paracelsus, 1493-1541

Background | Adverse drug reactions

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

You may feel dizzy, visual problems or light-headed for a short time after you take your first dose, or when you first take an increased dose. It may help to lie down until you feel better. If you are worried, or if these effects continue, talk to your doctor or pharmacist.

Stop taking the tablets and tell your doctor immediately or go to the casualty department at your nearest hospital if you experience any of the following side-effects:

- an allergic reaction causing itchy, raised rash, swelling of the lips, face, tongue or neck leading to severe difficulty in breathing or severe skin rash or hives.
- blisters which may burst easily becoming raw and painful or may bleed, red itchy spots, peeling skin leaving red raw patches over the body, blisters/bleeding of the lips, eyes, nose, mouth and genitals.
- a swollen painful abdomen, constipation, being sick, indigestion, loss of appetite, dry mouth; this could be a sign of an obstruction or blockage of the bowel.
- severe pain in the abdomen and back; this could be a sign of pancreatitis.
- blood disorders including anaemia (low blood count causing unusual tiredness or weakness) or bone marrow problems. Symptoms may include fever, chills, sore throat, ulcers in your mouth or throat or unexplained bruising or bleeding.
- lung problems including inflammation of the lung (pneumonia). You may feel unwell or less hungry, have a high temperature (fever) difficulty breathing, shortness of breath, cough.
- high temperature, tiredness, loss of appetite, stomach pain, feeling sick, jaundice (yellowing of the skin or whites of the eyes), liver failure. These may be symptoms of hepatitis (inflammation of the liver).
- a complex side-effect, which may include some or all of the following symptoms: fever, inflammation of the blood vessels often with skin rash, muscle pain and inflammation, joint pain and inflammation, abnormal blood test results, blood disorders, rash, sensitivity to light, other skin conditions and serositis (inflammation of membranes lining the lungs, heart, stomach and some organs).

These are very serious but rare side effects. You may need urgent medical attention or hospitalisation.

The following side effects have been reported at the approximate frequencies shown:

Very common (may affect more than 1 in 10 people):

- blurred vision
- dizziness
- cough

- nausea (feeling sick)
- lethargy.

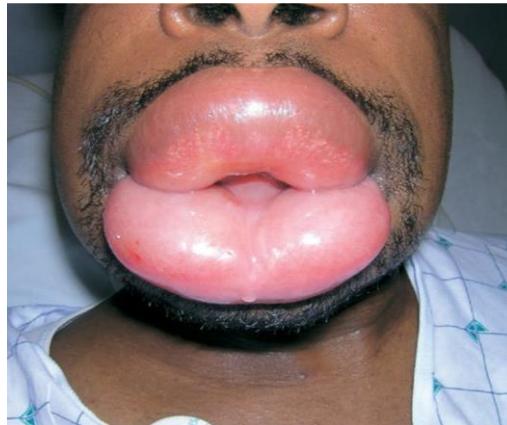
Common (may affect up to 1 in 10 people):

- headache, depression
- low blood pressure (you may feel light-headed or faint), fainting
- chest pain, changes in heart/pulse rate including a fast heart rate
- shortness of breath
- diarrhoea, abdominal pain, changes in sense of taste
- rash
- tiredness.
- allergic reactions with swelling of the face, extremities, lips, tongue, throat with difficulty swallowing or breathing
- change in some blood tests (increased potassium and creatinine level in blood).

Uncommon (may affect up to 1 in 100 people):

- sudden fall in blood pressure (especially when standing up)
- low blood sugar levels or sodium levels, high level of blood urea confusion, sleepiness, difficulty sleeping, nervousness, pins and needles and numbness, vertigo (a sensation that your surroundings are spinning, either up and down or from side to side)
- anemia (low blood count causing unusual tiredness or weakness)
- heart attack, stroke (these are more common in high risk patients)
- palpitations (awareness of your heartbeat)
- runny nose, sore throat and hoarseness, wheezing
- inflammation of your pancreas (swollen painful abdomen), constipation, back pain and vomiting, indigestion, loss of appetite, dry mouth, stomach ulcer
- sweating, itching, nettle rash, hair loss
- kidney problems including kidney failure
- protein in the urine giving the urine a frothy appearance
- impotence (inability to get or maintain an erection)
- muscle cramps, flushing, ringing in the ears, general feeling of being unwell, fever.

Background | Adverse drug reactions



Study I | ACEi-associated angioedema



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Original Investigation

Association of Variants Near the Bradykinin Receptor B₂ Gene With Angioedema in Patients Taking ACE Inhibitors

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Methods | ACEi-associated angioedema

Discovery Cohort (Copenhagen Hospital Biobank)

ACEi-Associated
Angioedema Cases

N = 462

ACEi-Treated
Controls

N = 53,391

Replication Cohort (Swedegene)

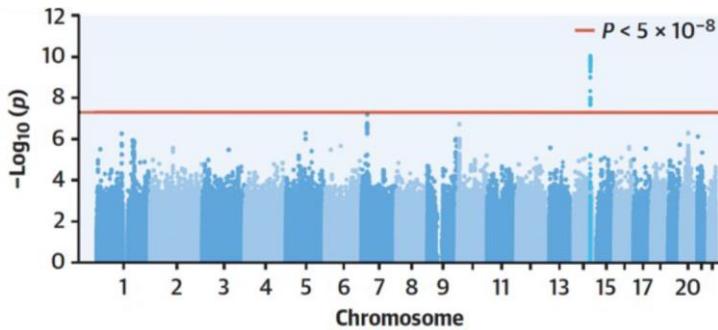
ACEi-Associated
Angioedema Cases

N = 142

ACEi-Treated
Controls

N = 1,345

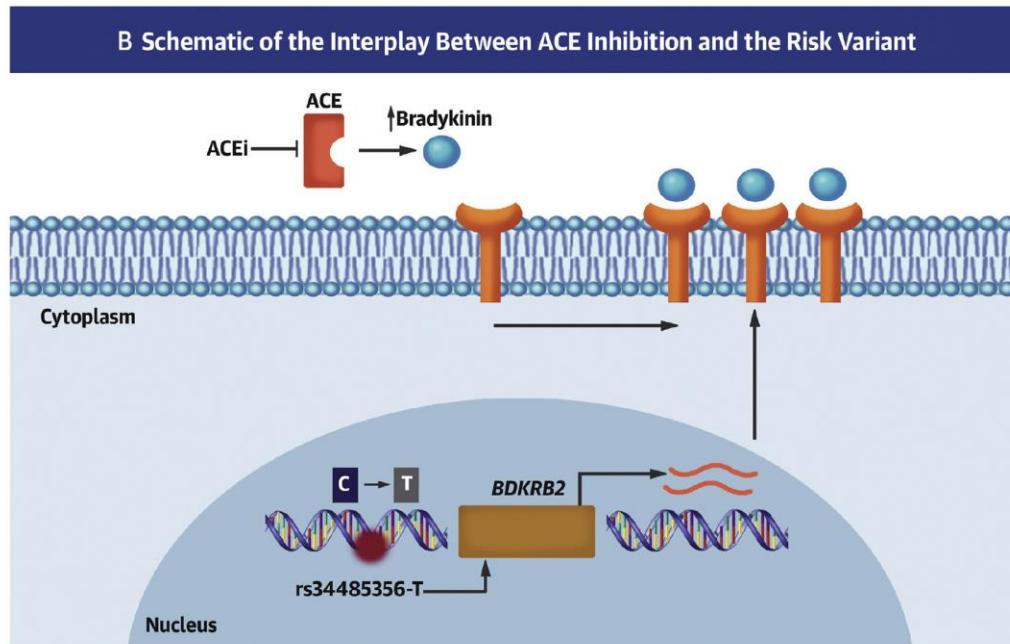
Results | ACEi-associated angioedema



Single-Nucleotide Polymorphism	Position ^a	Number		OR (95% CI)	P Value	P_{HET}
		Cohort	Cases			
rs34485356	14:96611271	Copenhagen Hospital Biobank	462	1.62 (1.38-1.90)	4.3×10^{-9}	0.95
		Swedegene	142	1.60 (1.13-2.25)	7.2×10^{-3}	
		Combined	604	1.62 (1.40-1.87)	1.1×10^{-10}	

Ghouse J et al., J Am Coll Cardiol , 2021

Discussion | ACEi-associated angioedema



Ghouse, J. et al. J Am Coll Cardiol. 2021;78(7):696-709.

Study II | ACEi-associated cough



ESC
European Society
of Cardiology

European Heart Journal (2022) 00, 1–13
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CLINICAL RESEARCH

Genetics

Polygenic risk score for ACE-inhibitor-associated cough based on the discovery of new genetic loci

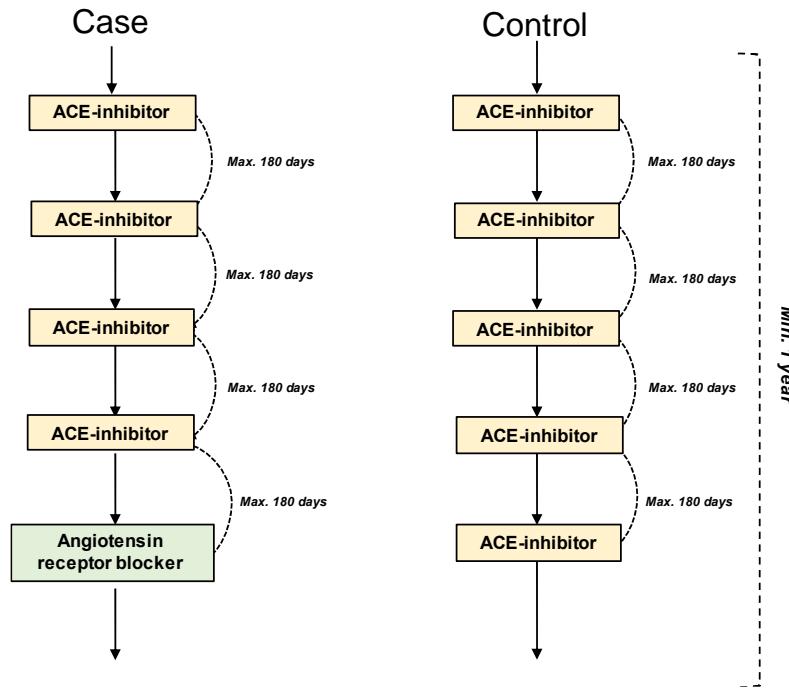
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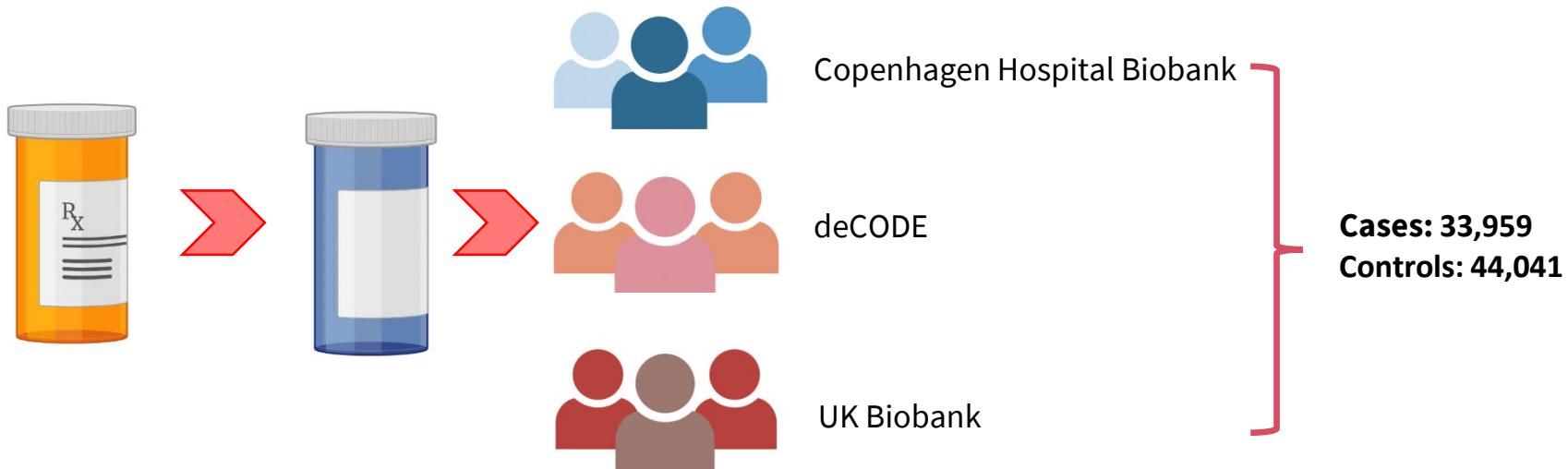
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Methods | ACEi-associated cough

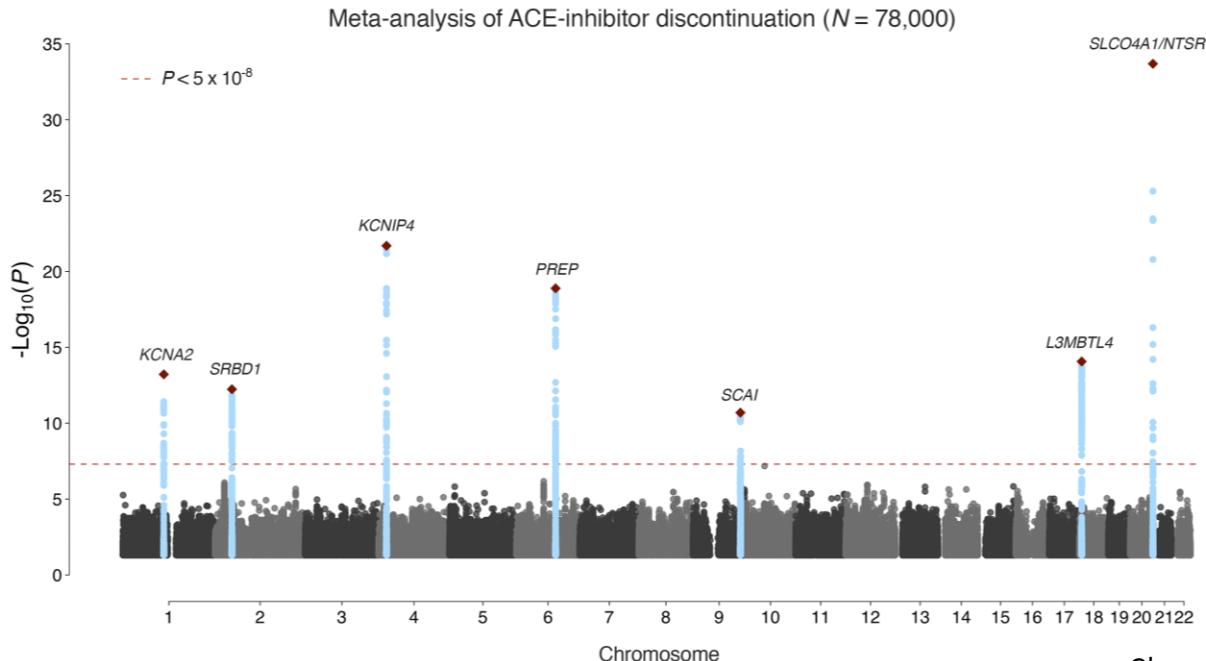


Mahmoudpour et al., Int J Clin Pharm, 2015

Methods | ACEi-associated cough



Results | ACEi-associated cough



Ghouse J et al., Eur Heart J, 2022

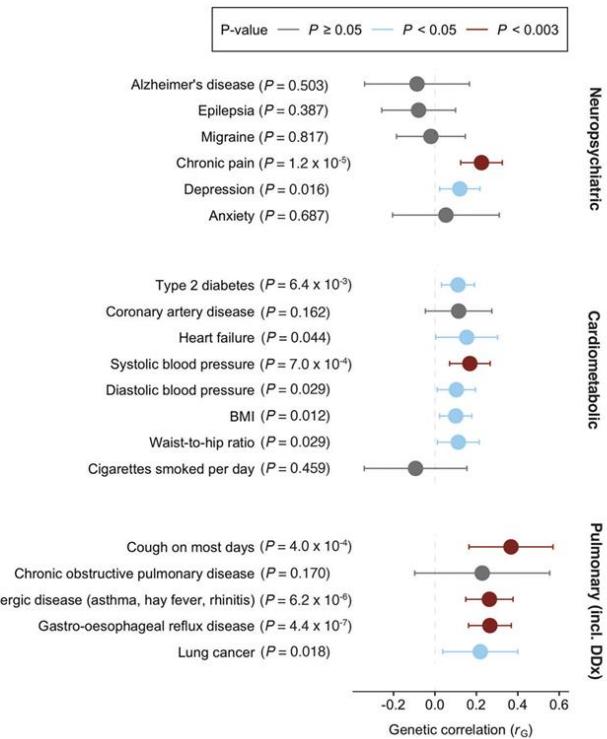
Results | ACEi-associated cough

Table 1 Variants associated with ACE-inhibitor discontinuation at genome-wide significance

Lead SNP	Chr location	Alleles		EAF	Gene context	OR (95% CI)	P-value
		EA	Non-EA				
rs7526729	1:111087058	A	G	0.69	[KCNA2]	1.13 (1.09–1.15)	6.1×10^{-14}
rs1544730	2:45588067	A	G	0.22	SRBD1	1.10 (1.07–1.13)	5.8×10^{-13}
rs16870989	4:21386764	A	T	0.33	[KCNIP4]	1.12 (1.09–1.14)	2.0×10^{-22}
rs12210271	6:105776312	T	C	0.21	[PREP]	1.13 (1.10–1.16)	1.3×10^{-19}
rs360206	9:127795842	C	T	0.19	[SCAI]	1.10 (1.07–1.13)	2.0×10^{-11}
rs8097200	18:6309334	A	G	0.83	[L3MBTL4]	1.12 (1.09–1.15)	8.6×10^{-15}
rs6062847	20:61322018	T	C	0.14	SLCO4A1/NTSR1	1.21 (1.17–1.24)	2.1×10^{-34}

Ghouse J et al., Eur Heart J, 2022

Results | ACEi-associated cough



Ghouse J et al., Eur Heart J, 2022

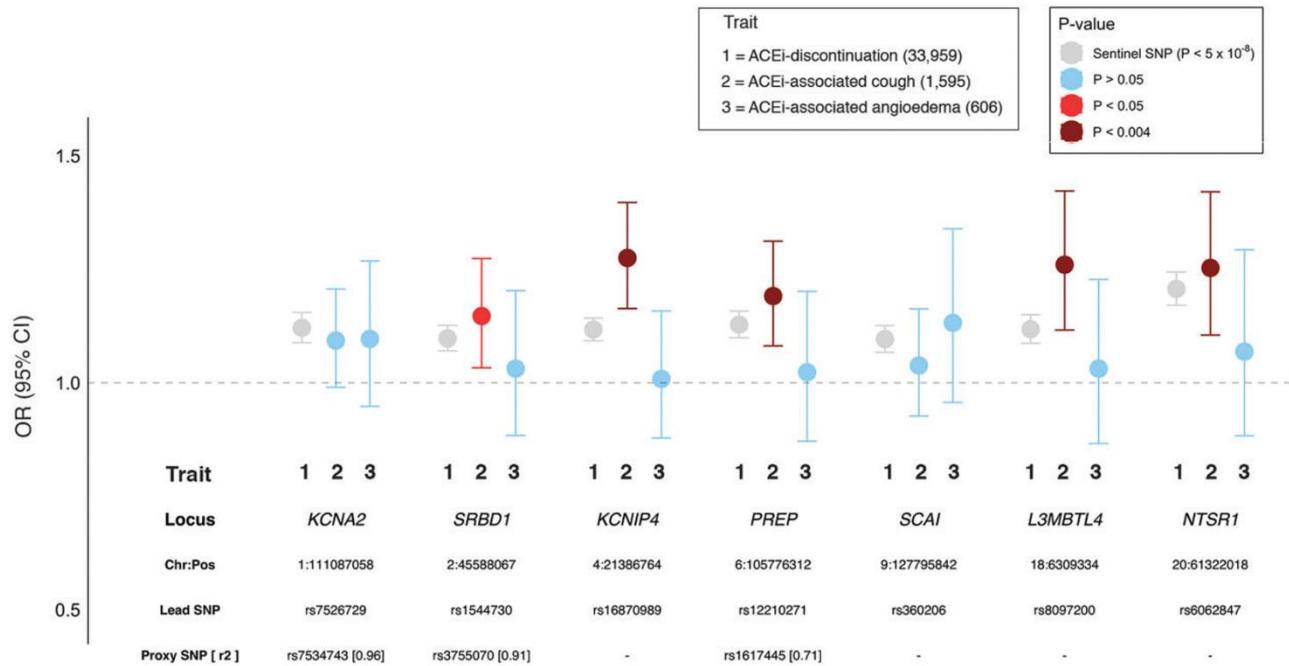
Results | ACEi-associated cough

Table 2 Associations between ACEi discontinuation variants, blood pressure, and eight chronic cough phenotypes in the UK Biobank

Phenotype	N	rs7526729 at KCNA2		rs1544730 at SRBD1		rs16870989 at KCNIP4		rs12210271 at PREP		rs360206 at SCAI		rs8097200 at L3MBTL4		rs6062847 at NTSR1	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
ACEi discontinuation	23 643	1.13 (1.09–1.18)	2.6E-10	1.09 (1.06–1.13)	2.4E-08	1.11 (1.08–1.14)	1.4E-12	1.08 (1.05–1.12)	1.0E-06	1.10 (1.07–1.14)	1.8E-08	1.08 (1.04–1.12)	1.3E-05	1.16 (1.12–1.21)	8.1E-16
Cough on most days	15 069	1.00 (0.97–1.03)	0.918	1.04 (1.01–1.08)	0.005	1.02 (1.00–1.15)	0.062	1.04 (1.01–1.07)	0.011	1.03 (1.00–1.06)	0.064	1.01 (0.98–1.05)	0.453	1.11 (1.08–1.15)	1.0E-09
Asthma	61 664	1.01 (1.00–1.02)	0.195	0.98 (0.97–1.00)	0.017	1.01 (0.99–1.02)	0.386	1.02 (1.00–1.03)	0.029	1.02 (1.01–1.04)	0.005	0.99 (0.98–1.01)	0.448	1.02 (1.00–1.04)	0.380
Chronic obstructive pulmonary disease	18 809	0.99 (0.97–1.01)	0.393	1.00 (0.97–1.03)	0.999	1.00 (0.98–1.02)	0.956	0.98 (0.95–1.00)	0.071	1.04 (1.02–1.07)	0.002	0.98 (0.96–1.01)	0.182	1.03 (1.00–1.06)	0.081
Allergic disease	74 892	1.01 (1.00–1.03)	0.019	1.01 (1.00–1.02)	0.170	0.99 (0.98–1.00)	0.050	1.01 (0.99–1.02)	0.395	1.00 (0.99–1.02)	0.845	1.00 (0.99–1.02)	0.578	0.99 (0.97–1.01)	0.229
Gastro-esophageal reflux disease	63 268	1.00 (0.99–1.01)	0.859	0.99 (0.98–1.01)	0.430	1.00 (0.98–1.01)	0.700	0.99 (0.97–1.00)	0.080	1.01 (1.00–1.03)	0.143	0.98 (0.97–1.00)	0.060	1.01 (0.99–1.03)	0.280
Smoking (current/ever vs. never)	199 350	0.99 (0.98–1.00)	0.138	1.00 (0.99–1.01)	0.683	1.00 (0.99–1.01)	0.876	1.00 (0.99–1.01)	0.635	1.00 (0.99–1.01)	0.667	0.99 (0.98–1.00)	0.019	1.01 (0.99–1.02)	0.416
Heart failure	13 411	1.00 (0.98–1.03)	0.773	1.00 (0.97–1.03)	0.919	1.01 (0.98–1.04)	0.478	0.98 (0.95–1.01)	0.159	1.03 (1.00–1.06)	0.069	1.01 (0.98–1.04)	0.549	1.02 (0.98–1.06)	0.297
Bronchiectasis	5034	1.00 (0.96–1.04)	0.994	1.00 (0.95–1.05)	0.928	1.01 (0.97–1.05)	0.713	1.01 (0.96–1.06)	0.703	1.03 (0.98–1.08)	0.268	0.98 (0.93–1.03)	0.376	1.04 (0.98–1.10)	0.174

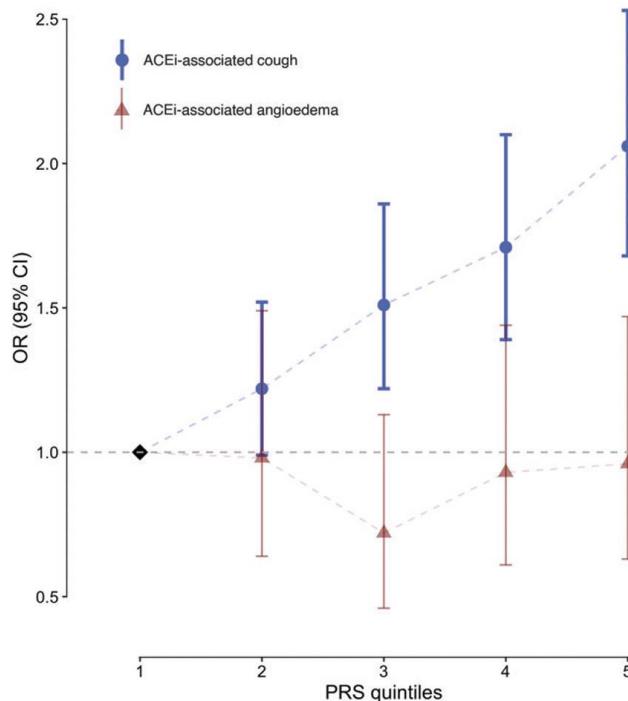
Ghouse J et al., Eur Heart J, 2022

Results | ACEi-associated cough



Ghouse J et al., Eur Heart J, 2022

Results | ACEi-associated cough



ACEi-associated cough

1,346 cases and 4,662 controls from eMERGE consortium

ACEi-associated angioedema

201 cases and 24,394 controls from Copenhagen Hospital Biobank (no sample overlap)

Ghouse J et al., Eur Heart J, 2022

Conclusions

- **What have we learned?**
- Genetic variants associate with ACEi-ADRs
- Future studies will have to evaluate whether genetic information together with non-genetic predictors can aid in meaningful drug selection

Thank you!

Key collaborators:

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Biobanks:

Copenhagen Hospital Biobank
Danish Blood Donor Study
UK Biobank
deCODE
eMERGE
SWEDEGENE

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