# Carriers of *CYP21A2* mutations have a decreased mortality in infectious diseases: A national population registry study

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## Conclusions

- *CYP21A2* carriers have a lower mortality in infectious diseases
- Pneumonia as the cause of death was uncommon
- A higher and more prompt cortisol response could be the explanation for an evolutionary advantage of being a carrier of a *CYP21A2*

## Background

Congenital adrenal hyperplasia (CAH) is a relatively common monogenic recessive disorder with an incidence of 1/15 000 in most populations. It has been suggested that *CYP21A2* deficiency is relatively common because it may confer a survival advantage being a carrier.
Carriers of *CYP21A2* mutations typically do not have clinical symptoms but have a defined phenotype.
The cortisol response to ACTH stimulation in *CYP21A2* carriers has been shown to be both more prompt and increased compared to healthy, non-carrier, controls.
The carrier frequency the Swedish population is about 1:50 individuals for a mutation in the *CYP21A2* gene and 1:70 for a classic *CYP21A2* mutation.
The over all mortality is lower for women than men.

We investigated the mortality, and cause of mortality in carriers compared to population controls, for men and women.

## Methods

A total of 1143 (561 men, 582 women) obligate carriers of a *CYP21A2* mutation, were identified as parents of patients with known CAH. We used the Swedish National CAH Registry encompassing more than 700 CAH patients and the Multigeneration Registry. Controls were identified from the general population, 100 controls per *CYP21A2* carrier.
The mortality and cause of death was identified through the Swedish Cause of Death Registry.
The Hazard Ratio (HR) confidence intervals and p values were calculated.

| Study population | | | | | |
|---|---|---|---|---|---|
| Carriers | | Men | Women | Ctrl Men | Ctrl Women |
| SW | 276 | 136 | 140 | 13583 | 13991 |
| SV | 455 | 223 | 232 | 22293 | 23198 |
| other | 412 | 202 | 210 | 20180 | 20989 |
| total | 1143 | 561 | 582 | 56056 | 58178 |
| | | | | | |
| SW+SV | 731 | 359 | 372 | 35876 | 37189 |
| | | | | | |

| Mortality | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Men | | | Women | | | All | |
| | n | Dead | % | n | Dead | % | n | Dead |
| All, carrier | 561 | 106 | 18.89 | 582 | 65 | 11.17 | 1143 | 171 |
| ctrl | 56056 | 11137 | 19.87 | 58178 | 7362 | 12.65 | 114234 | 18499 |

| Infections | Total carriers | Carriers dead | % | Total controls | Controls dead | % | Hazard Ratio | P |
|---|---|---|---|---|---|---|---|---|
| Infections | 1143 | 45 | 3.94 | 114234 | 5640 | 4.94 | **0.65 (0.49-0.87)** | **0.004** |
| sepsis | | 4 | 0.35 | | 362 | 0.32 | 1.03 (0.38-2.77) | 0.952 |
| erysipelas | | 0 | | | 13 | 0.01 | | 0.993 |
| virus hepatitis | | 0 | | | 51 | 0.04 | | 0.989 |
| influenza | | 0 | | | 23 | 0.02 | | 0.993 |
| pneumonia | | 2 | 0.17 | | 725 | 0.63 | **0.22 (0.06-0.88)** | **0.032** |

## Results

The overall mortality was significantly lower in carriers of one of the classic *CYP21A2* mutations compared to the general population, for women (p=0.05), but not for the whole cohort (p=0.13).

Infection as the cause of death was significantly lower in the whole cohort with Hazard Ratio 0.65
(CI 95%, 0.49-0.87; p=0.004).

In particular, a lower mortality in pneumonia was seen HR 0.22
(CI 95%, 0.06-0.88; p=0.03).
There was no difference in mortality due to cancer.

The lower overall mortality among women compared to men was confirmed, both among the carriers and the controls (p=0.0001).

## Discussion

Obligate *CYP21A2* carriers (parents of CAH patients) had a reduced mortality, and specifically a reduced mortality due to pneumonia.
Our results suggest a better ability to cope with the somatic stress of severe infections among heterozygous carriers of severe *CYP21A2* mutations.

The timing, the prompt and exaggerated increase in cortisol in acute situations, could enable inhibition of the cytokines and other inflammatory factors that induce glucocorticoid resistance, resulting in an evolutionary advantage.

This may contribute to the apparent survival advantage since infectious diseases represent a large cause of death, through evolution.

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