

# Your lifestyle can determine how well your medicine will work

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By examining liver samples from 116 deceased persons with severe mental disorders, researchers have demonstrated that smoking, obesity and alcohol use can be decisive in determining how medicine will work

for an individual patient.

It is already well-known in research circles that an unhealthy lifestyle affects [enzyme](#) levels in the body and thus the possibility of drug metabolism.

However, a study from the Department of Forensic Medicine at Aarhus University has now shed new light on the effects of lifestyle. Liver samples from 116 deceased, mentally ill people have been examined—and the important factor is that a large proportion of the deceased were smokers, alcoholics, and/or obese.

By examining the amounts of enzyme expressed in the livers of the deceased, the researchers can see indications of how well or poorly the deceased metabolized important drugs.

"People suffering from [severe mental illness](#) have a life expectancy of about 20 years lower than the rest of the population. There are several reasons for this; for example, the mentally ill commit suicide more often. They also have an increased incidence of lifestyle-related factors such as diabetes, obesity, smoking, and alcohol or [drug use](#)," explains Kata Wolff Pedersen, MSc and Ph.D. in health science, who is behind the study.

"It's exciting to see how lifestyle affects the amount of drug-metabolizing enzymes in the body because a change in the amount of enzyme can reduce the efficacy of the drugs used by this group of patients," she says.

## **Alcohol and smoking increase drug metabolism**

The study from the Department of Forensic Medicine shows that smokers have twice as much of a particular drug-metabolizing enzyme

(CYP1A2) than non-smokers. This means that smokers metabolize certain drugs (e.g. antipsychotic drugs) faster and thus, in theory, are at greater risk of incorrect treatment.

"We're the first to demonstrate at the protein level that the enzyme level in smokers increases simply because more enzyme is expressed in the body," says Kata Wolff Pedersen.

The [liver tissue](#) was collected during forensic autopsies. Subsequently, a full toxicological analysis was carried out, crossed with information about the deceased's alcohol and smoking history, for example, based on statements in the autopsy report from the police, next of kin, or the general practitioner.

Based on this, Kata Wolff Pedersen concluded that levels of the enzyme CYP2E1 in people with [alcohol use](#) were approximately 30 percent higher compared with people without known alcohol consumption.

"Forty percent of the deceased included in our study were registered alcoholics. It's an interesting group because they have a special lifestyle. With so many individuals, we can prove that alcohol use increases the amount of enzymes in the body," she explains.

"This means that standard doses of a drug may have a lower effect on a significant part of the group of people we've studied," says Kata Wolff Pedersen, and this is certainly noteworthy.

## **Obesity and overweight results in low levels of another enzyme**

Researchers only rarely have access to liver samples from such large groups of people. Studies of enzyme levels are usually made on liver

microsomes in test tubes or in animal experiments. Since the samples in this study come from identifiable people, it is possible to verify that lifestyle factors—including overweight—play a role.

However, obesity and overweight make a difference to an important enzyme with the opposite effect. The study shows that people with a very high BMI produce significantly smaller amounts of the CYP3A4 enzyme—in fact, they only have half as much enzyme in their body as people of normal weight.

This can cause them to metabolize their medicine too slowly, thus increasing the risk for side effects. CYP3A4 is involved in the metabolism of a large number of important drugs, and therefore this may be significant for overweight individuals not receiving the right doses, and potentially receiving incorrect treatment.

"Forty percent of the individuals in the study died from poisoning with a mixture of legal and illegal drugs. But we cannot show that the poisoning was caused by too little enzyme, because several different enzymes metabolize most substances. You have to be very unlucky to die of altered enzyme levels," explains Kata Wolff Pedersen.

## **Chilled pig livers**

The study also includes liver samples from dead pigs, and Kata Wolff Pedersen has used these to determine that the level of the enzyme after two days at room temperature is the same as in a completely fresh pig liver. If the liver is refrigerated, the levels remain the same for a whole week.

This is good news for researchers with an interest in enzyme levels.

"We're the first to show that tissue from deceased people can be used to

examine the level of drug-metabolizing enzymes. This makes it significantly easier to obtain material in a field in which it is otherwise virtually impossible to obtain a high number of liver biopsies," she says.

The paper is [published](#) in the journal *Drug Metabolism and Disposition*.

**More information:** Kata W. Pedersen et al, Sex- and Lifestyle-Related Factors are Associated with Altered Hepatic CYP Protein Levels in People Diagnosed with Mental Disorders, *Drug Metabolism and Disposition* (2023). [DOI: 10.1124/dmd.122.001125](https://doi.org/10.1124/dmd.122.001125)

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