

## Does the treatment of dyslipidemia affect the risk of depression or suicidal behaviour?

Yang CC, Jick SS, Jick H. Lipid-lowering drugs and the risk of depression and suicidal behaviour. *Arch Intern Med* 2003;163:1926-32.

**Background:** Whether a low or lowered serum cholesterol level is associated with harm has been the subject of debate for 2 decades, ever since the unexpected finding of an increased risk of noncardiovascular mortality in early trials of lipid-lowering therapy.<sup>1</sup> Subsequent research has generated conflicting evidence regarding the relation between cholesterol and violent behaviour, mental illness and injury, with positive studies imputing alterations in central serotonergic activity as a potential underlying mechanism.<sup>2</sup>

**Design:** This nested case-control study examined the computerized health records of about 3 million people from 1991 to 1999. Researchers identified 3 groups: patients who received at least 1 prescription for a lipid-lowering drug ( $n = 30\,703$ ), those with a diagnosis of dyslipidemia but no drug therapy ( $n = 13\,738$ ) and those selected randomly from a group of patients without evidence of dyslipidemia ( $n = 50\,000$ ). Health records were examined to identify 2 primary outcomes: newly diagnosed depression and suicidal behaviour (including suicidal ideation, parasuicide, and suicide).

Also identified were potential confounding influences, such as recent life stressors, psychiatric illness and smoking status.

**Results:** In the cohort of 94 441 individuals, 458 had newly diagnosed depression and 105 had a recorded diagnosis of suicide risk. Compared with matched control subjects, depressed patients were more likely to have another treated psychiatric disorder, a recent life stressor or a history of multiple visits to general practitioners. However, even after adjustment for potential confounders, neither hyperlipidemia nor its treatment was associated with an increased risk of depression (Table 1). Similarly, no association was found between treatment and suicide risk.

**Commentary:** In a primary prevention trial comparing pravastatin with placebo in 6595 men, only 3 participants committed suicide.<sup>3</sup> Considering the rarity of this outcome, it is perhaps not surprising that doubt shrouds the putative link between cholesterol, mental illness and suicide, or that researchers have used alternative strategies to explore the issue.<sup>2,4</sup>

Some obvious strengths of the study by Yang and colleagues include its large sample, relatively frequent outcomes and the ability to identify and adjust for important potential confounders such as bereavement and comorbidity. The main threats to the study's validity include reliance on diagnostic codes that have not been validated, the vagaries of identifying depression and suicide with certainty from medical records and the difficulties of establishing causation using case-control methodology. The relative influence of these strengths and limitations is not easily quantified, but the overall approach to the issue is both logical and rigorous.

**Practice implications:** Despite its limitations, this study provides additional evidence that neither dyslipidemia nor its treatment is associated with a major increase in the risk of depression or suicidal behaviour. Conversely, the evidence for a clinical benefit of lipid lowering is compelling. The speculative relation between cholesterol and mental illness is becoming an issue of historical interest that should have no bearing on present-day therapeutics.

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### References

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**Table 1: Distribution of various exposures and association with the risk of depression and suicidal behaviour**

Exposure	Depression			Suicidal behaviour		
	No. (and %) of cases <i>n</i> = 458	No. (and %) of controls <i>n</i> = 1830	Adjusted OR* (95% CI)	No. (and %) of cases <i>n</i> = 105	No. (and %) of controls <i>n</i> = 420	Adjusted OR† (95% CI)
Statins						
Current	15 (3.3)	80 (4.4)	0.4 (0.2-0.9)	10 (9.5)	33 (7.9)	0.5 (0.1-1.5)
Recent or past	13 (2.8)	37 (2.0)	1.2 (0.5-2.7)	2 (1.9)	9 (2.1)	0.6 (0.1-5.1)
Other lipid-lowering drugs						
Current	19 (4.1)	70 (3.8)	1.0 (0.5-2.1)	3 (2.9)	19 (4.5)	0.4 (0.1-1.8)
Recent or past	12 (2.6)	49 (2.7)	1.0 (0.4-2.3)	4 (3.8)	11 (2.6)	1.4 (0.3-6.0)

Note: OR = odds ratio, CI = confidence interval.

\*Adjusted for smoking, body mass index, record of stressful life events, number of general practitioner visits, peripheral vascular disease and history of psychiatric disorders.

†Adjusted for record of stressful life events, number of general practitioner visits, peripheral vascular disease, history of treated psychiatric disorders and current use of benzodiazepines.