

Miller N E, Førde O H, Thelle D S & Mjøs O D. The Tromsø Heart-Study. High-density lipoprotein and coronary heart-disease: a prospective case-control study. *Lancet* 1:965-8, 1977.

[Insts. Clinical Med., Community Med., and Medical Biol., Univ. Tromsø, Norway]

In a prospective study of 6,595 men, those individuals who suffered a coronary event during two years of follow-up had significantly lower plasma concentrations of high-density lipoprotein (HDL) cholesterol than controls. On discriminant analysis, the negative association of coronary risk with HDL was independent of, and stronger than, its positive association with plasma total cholesterol. [The *SCI*® indicates that this paper has been cited in over 580 publications since 1977.]

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The opportunity to do this study was provided by Ole Mjøs, whom I had met and worked with while at Edinburgh Royal Infirmary in 1973-1974. Ole subsequently returned to his native Norway, to take up a chair in Tromsø, while I travelled to La Jolla to learn tissue culture techniques in Dan Steinberg's laboratory. During my stay in California, Ole wrote to me saying how interested he was in the "high-density lipoprotein (HDL) hypothesis" that my brother and I had published earlier that year.<sup>1</sup> He invited me to Tromsø to look at the relationship between coronary disease and plasma HDL cholesterol concentration, using deep-frozen samples that had been collected by Dag Thelle, Olav Førde, and their colleagues two years earlier as part of the Tromsø Heart Study.<sup>2</sup>

Although I had planned to travel directly to Melbourne after the termination of my fellowship, I postponed this arrangement and flew to Norway in early September 1976. Designing the study, matching the cases with controls by computer, doing the laboratory measurements, and analysing the data took us about 10 weeks.

The result made all the travelling well worthwhile because it provided the first evidence for an independent association between coronary risk and HDL cholesterol. What was particularly exciting was the fact that this association appeared to be stronger than that between coronary disease and plasma low-density lipoprotein cholesterol, and I believe that this is why the result has been so frequently cited. After I went to Melbourne, we wrote the paper by correspondence, and *The Lancet* accepted it immediately. Although the manuscript had been completed in less than four weeks, it was almost four months before I received the proofs—sent by surface mail from London to Melbourne! Only a few days after our article appeared, essentially identical results were reported from the Framingham Study in the *American Journal of Medicine*.<sup>3</sup> Since then, the inverse relationship between HDL and atherogenesis has become well accepted; so also has the role of HDL in reverse cholesterol transport.<sup>4</sup> It is not yet established that these are causally related, however, and other possible explanations for the epidemiological association are being investigated.<sup>5</sup>

There was one experience in Tromsø that was just as exciting as the result of our study: The view of Tromsø at night from my temporary home on the other side of Tromsøfjord, against the backdrop of the aurora borealis, was unforgettable. It would have been worth the visit if only for that.

1. Miller G J & Miller N E. Plasma-high-density-lipoprotein concentration and development of ischaemic heart-disease. *Lancet* 1:16-19, 1975. [See also: Miller G J. Citation Classic. *Current Contents/Life Sciences* 24(15):21, 13 April 1981.]
2. Thelle D S, Førde O H, Try K & Lehmann E H. The Tromsø Heart Study: methods and main results of the cross-sectional study. *Acta Med. Scand.* 200:107-18, 1976.
3. Gordon T, Castelli W P, Hjortland M C, Kannel W B & Dawber T R. High-density lipoprotein as a protective factor against coronary heart disease: the Framingham Study. *Amer. J. Med.* 62:707-14, 1977. (Cited 1,170 times.)
4. Miller N E, LaVigne A & Crook D. Direct evidence that reverse cholesterol transport is mediated by high-density lipoprotein in rabbit. *Nature* 314:109-11, 1985.
5. Miller N E & Miller G J, eds. *Clinical and metabolic aspects of high-density lipoproteins*. Amsterdam: Elsevier, 1984. 459 p.