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# This Week's Citation Classic

**Rhoads G G, Gulbrandsen C L & Kagan A.** Serum lipoproteins and coronary heart disease in a population study of Hawaii Japanese men.
*N. Engl. J. Med.* 294:293-8, 1976.
[Honolulu Heart Study, Natl. Heart and Lung Inst., Bethesda, MD]

**This paper compared levels of major lipoproteins between 264 men with and 1,755 men without coronary heart disease (CHD) in a defined population of American Japanese men in Hawaii. The inverse relation between high density lipoprotein (HDL) and disease was as strong as the direct relation for low density lipoprotein (LDL). The protective effect of HDL could not be explained by other risk factors. [The *SCI*® indicates that this paper has been cited in over 470 publications since 1976.]**

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"Following the development of Fredrickson and Levy's[1] lipoprotein phenotyping system, the National Heart, Lung, and Blood Institute undertook a major project to apply the technique to several of the population-based studies of cardiovascular disease. We benefited from the fact that the Honolulu Heart Program had the largest of the cohorts involved in this Cooperative Lipoprotein Phenotyping Study. The main purpose of the project was to look at the frequency of the various phenotypes and to see how they related to coronary heart disease (CHD) in several different clearly defined populations. High density lipoprotein (HDL) was not considered in the phenotyping criteria, but its measurement was included in the protocol as a necessary step in the quantitation of low density lipoprotein (LDL).

"Our interest in the project was largely tied to the opportunity which it provided a) to compare the distribution of lipoproteins in Japanese men in Honolulu with that in Caucasians; and b) to examine the associations of lipoproteins with CHD. The difference in HDL between cases and controls was prominent in the initial analyses, and the relative risk of CHD associated with this difference was as strong as the well-known relation of LDL to this disease. There followed some time in the library which (to our disappointment) confirmed our rediscovery. A number of case-control studies in the 1950s had reported similar findings;[2-7] and Medalie *et al.* had reported the association in their prospective study of Israeli civil servants.[8] Our contribution was mainly to show that the association was independent of other coronary risk factors. Of course the earlier reports strengthened our conviction that the association was important.

"We initially submitted the paper to the *Annals of Internal Medicine*, but in recent years the internists have not published much epidemiology. Since they recommended radical surgery for our modest manuscript, we sent it to the *New England Journal of Medicine* where a cosmetic touch-up was deemed sufficient.

"It is not clear why this report got so much attention while its predecessors got so little. Four factors which may have contributed are a) the advances in statistical methods since the 1950s which allowed us to show that the HDL association was not explained by other lipoprotein levels; b) the work of Glomset[9] and the Millers[10] which provided a possible physiological basis for the findings; c) the fact that many labs were measuring HDL as a step in the assessment of other lipoproteins; and d) the wide circulation of the *New England Journal of Medicine*."

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[Citation Classic. *Current Contents* (3):11, 16 January 1978.]
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