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# Hyperhomocysteinemia and Low Pyridoxal Phosphate : Common and Independent Reversible Risk Factors for Coronary Artery Disease

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## Abstract

*Background* High plasma homocysteine is associated with premature coronary artery disease in men, but the threshold concentration defining this risk and its importance in women and the elderly are unknown. Furthermore, although low B vitamin status increases homocysteine, the link between these vitamins and coronary disease is unclear.

*Methods and Results* We compared 304 patients with coronary disease with 231 control subjects. Risk factors and concentrations of plasma homocysteine, folate, vitamin B12, and pyridoxal 5′-phosphate were documented. A homocysteine concentration of 14 μmol/L conferred an odds ratio of coronary disease of 4.8 ($P$<.001), and 5-μmol/L increments across the range of homocysteine conferred an odds ratio of 2.4 ($P$<.001). Odds ratios of 3.5 in women and of 2.9 in those 65 years or older were seen ($P$<.05). Homocysteine correlated negatively with all vitamins. Low pyridoxal 5′-phosphate (<20 nmol/L) was seen in 10% of patients but in only 2% of control subjects ($P$<.01), yielding an odds ratio of coronary disease adjusted for all risk factors, including high homocysteine, of 4.3 ($P$<.05).

*Conclusions* Within the range currently considered to be normal, the risk for coronary disease rises with increasing plasma homocysteine regardless of age and sex, with no threshold effect. In addition to a link with homocysteine, low pyridoxal-5′-phosphate confers an independent risk for coronary artery disease.

Coronary heart disease is a major public health problem in the Western world. Identifiable risk factors include hypercholesterolemia, hypertension, cigarette smoking, and diabetes mellitus. An increase in plasma homocysteine concentration has also been associated with premature arterial disease,[1][2][3][4][5][6][7][8][9][10][11][12][13] possibly related to a deficiency in the enzyme cystathionine β-synthase.[3][5] This enzyme is deficient in homocystinuria, a rare disorder characterized by high homocysteine concentrations and early, aggressive occlusive arterial disease.[14] Abnormalities of the enzyme methylenetetrahydrofolate reductase, also required for homocysteine metabolism, may also play a role.[15] Other essential biochemical modulators of homocysteine include folic acid,[16] vitamin $B_{12}$,[17] and vitamin $B_6$[18] deficiencies, which are associated with increased plasma homocysteine concentrations.

Although elevated plasma homocysteine is associated with coronary artery disease, the precise level associated with increased risk is unknown. The potential for an increased risk of coronary disease in women and in older hyperhomocysteinemic subjects has not been previously explored. Finally, the relation between homocysteine concentrations and B group vitamins in patients with coronary artery disease has been incompletely defined. The present study was undertaken to explore the level of homocysteine associated with an increased coronary risk and to detect a similar effect, if any, in women and the elderly. The interrelations among plasma homocysteine, essential B group vitamin concentrations, and coronary disease were also studied.

# Methods

## Patients

Three hundred four patients (201 men and 103 women; mean age, 62±11 years) with established coronary artery disease were studied. The baseline demographic, laboratory, and angiographic features of both cases and controls are summarized in Table 1.

## Control Subjects

Consecutive subjects attending an executive health screening program at The Cleveland Clinic Foundation served as control subjects. There was no clinical or ECG evidence of coronary artery disease in any of these individuals.

## Diagnosis of Coronary Artery Disease

All patients had angiographic documentation of stenosis of ≥70% of at least one major epicardial coronary vessel diagnosed at the time of coronary angiography carried out in standard manner.

## Risk Factors

Hypercholesterolemia (elevated total serum cholesterol) was defined as a total serum cholesterol concentration of ≥200 mg/dL or a history of medication for hypercholesterolemia. Cigarette smokers were categorized as either nonsmokers (those who had never smoked) or ever smokers (current smokers or those who had stopped). Hypertension was diagnosed if the blood pressure was more than 150/90 mm Hg or, in the presence of a history of hypertension, if the patient was taking antihypertensive medications. Diabetes mellitus was diagnosed if the fasting glucose concentration was more than 140 mg% or if the patient was taking insulin or oral hypoglycemic therapy.

## Measurements of Total Plasma Homocysteine

Total fasting plasma homocysteine was measured according to the method of Jacobsen et al.[19] In this assay, all forms of plasma homocysteine are determined, including reduced and oxidized forms (homocystine, homocysteine-cysteine mixed disulfide, and protein-bound mixed disulfide).

## Vitamin Concentrations and Other Assays

Concentrations of folic acid and of vitamin $B_{12}$ were measured using a commercial radioligand binding technique (Simultrac; Becton Dickinson). Pyridoxal 5′-phosphate concentrations were measured according to the technique of Camp et al.[20] Vitamin $B_{12}$ deficiency was defined as a plasma concentration of less 125 pmol/L. Folate deficiency was defined as a concentration of less than 6.4 nmol/L. Pyridoxal 5′-phosphate deficiency was defined as a level of less than 20 nmol/L.

## Statistical Analysis

Percentages are computed as a function of nonmissing data. Mean age is reported ±1 SD. Homocysteine and continuous variables other than age are reported as mean and median values. Percentages were compared using Pearson's $\chi^2$ test or Fisher's exact test depending on the factor prevalences. Ages were compared using Student's *t* test, and other continuous variables were compared using a Wilcoxon rank-sum test. Correlations presented here are Spearman correlations. For the full sample, odds ratios and 95% confidence intervals (CI) were computed based on the parametric estimates and standard errors from a multiple logistic regression. Diabetes, hypertension, smoking history, and hypercholesterolemia were all considered as potential covariates. Hypercholesterolemia showed no association with coronary artery

disease in this sample, perhaps because of behavior modification, so it was not used as a covariate. Age and sex were used as covariates in all logistic regression models. The coronary disease covariates were not, however, included in subset models. No positive association between any of the risk factors and homocysteine concentration or high homocysteine was detected. To have adequate power to assess the odds ratio for coronary artery disease conferred by hyperhomocysteinemia, only age and sex were used as covariates in the subset models. Creatinine was not used as a covariate, but patients with a history of renal failure were excluded from the study to protect against the possibility that high creatinine values are a confounder in the relation between hyperhomocysteinemia and coronary artery disease. The 80th percentile values of plasma homocysteine concentration were arbitrarily selected to allow the calculation of prevalences of higher homocysteine concentrations and odds ratios in different patient groups. This value permitted the comparison of levels of essential B group vitamins in individuals with higher and lower plasma homocysteine concentrations and yielded larger sample sizes than if higher percentile values had been chosen.

# Results

## Distribution of Plasma Homocysteine Concentrations

Homocysteine concentrations were higher (14.4± 15.4 versus 10.9±3.4 μmol/L, *P*<.001) in patients than in control subjects (Tables 2 and 3), and values for patients were shifted and skewed to the right. A correlation was observed between homocysteine and creatinine that persisted when adjusted for age and sex (*r*=.29, *P*<.001).

## Definitions of Hyperhomocysteinemia and Relation of Odds Ratios to Plasma Homocysteine Concentration

### All Patients

Alternate models of high homocysteine concentration were applied. First, with an absolute plasma homocysteine concentration of 8 μmol/L as a cutoff point, an odds ratio of 4.6 (CI, 1.8 to 11.6; *P*=.001) was seen. Odds ratios of 2.9 (CI, 1.6 to 5.1; *P*<.001) and 2.8 (CI, 1.6 to 4.6; *P*<.001) were observed with cutoff points of 10 and 12 μmol/L, respectively. A concentration of 14 μmol/L conferred an odds ratio of 4.8 (CI, 2.6 to 8.9; *P*<.001). Second, with increments of 5 μmol/L in absolute plasma homocysteine concentrations, odds ratios of 2.4 (CI, 1.7 to 3.5; *P*<.001) were seen. These models are shown in the Figure. An odds ratio of 2.3 was seen for the second tertile of plasma homocysteine compared with the first (*P*<.05). A further increase of 2.1 was seen for the third tertile compared with the second (*P*<.05).

### Effects of Sex

Homocysteine levels were higher in male than female control subjects (11.2±2.9 versus 10.1±4.7 μmol/L, *P*=.004) and were higher in male patients than in male control subjects (13.9±4.5 versus 11.2±2.9 μmol/L, *P*<.001) (Tables 2 and 4). A sex-adjusted 80th percentile cutoff point of plasma homocysteine concentration (13.5 μmol/L) resulted in a prevalence of hyperhomocysteinemia of 45% in male patients (Table 4, *P*<.01). A plasma homocysteine at this concentration conferred an odds ratio of 2.9 (CI, 1.7 to 4.7) in men, adjusted for all other risk factors (*P*<.001).

Mean homocysteine concentrations were higher in female patients than in their control subjects (15.3±25.7 versus 10.1±4.7 μmol/L), although the standard deviation was high due to one folate-deficient patient (plasma folate 3.1 nmol/L) with a homocysteine concentration of more than 250 μmol/L. Nevertheless, the median homocysteine value for female patients was higher than that for the female control group (12.1 versus 9.5 μmol/L, *P*<.01). A sex-adjusted 80th percentile cutoff point of plasma homocysteine concentration (11.8 μmol/L) resulted in a prevalence of hyperhomocysteinemia of 56% in female patients (Table 4, *P*<.001), significantly higher than the prevalence of 45% for male patients (*P*<.05). A plasma homocysteine at this concentration conferred an odds ratio of 3.4 (CI, 1.4 to 8.5) in women (*P*<.05).

### Effects of Age

Overall, homocysteine concentrations correlated with age (*r*=.27, *P*=.001) (Tables 3 and 4). In patients less than 65 years old, mean homocysteine concentrations were higher than in control subjects (14.2±20.4 versus 10.8±3.4 μmol/L, *P*<.001). A sex-adjusted 80th percentile cutoff point of plasma homocysteine

concentration for control subjects resulted in a 42% prevalence of hyperhomocysteinemia among patients less than 65 years old (Table 4, *P*<.001). A plasma homocysteine at this concentration conferred an odds ratio 2.9 (CI, 1.8 to 4.6; *P*<.001) for those less than 65 years old.

In patients 65 years or older, mean homocysteine concentrations were higher than in both control subjects (14.5±5.1 versus 11.9±3.5 μmol/L, *P*=.016) and patients less than 65 years old (median, 13.4 versus 12.1 μmol/L; *P*=.002; Table 3). A sex-adjusted 80th percentile cutoff point of plasma homocysteine concentration resulted in a 58% prevalence of hyperhomocysteinemia among patients 65 years of age or older (*P*<.05, Table 4). A plasma homocysteine at this concentration conferred an odds ratio of 3.2 (CI, 1.2 to 8.4; *P*<.05) for those 65 years of age or older.

### Relation Between Concentrations of Vitamin Cofactors and Plasma Homocysteine

Significant negative correlations were seen between homocysteine and folate in both patients and control subjects (*r*=−.29 and −.41, respectively; *P*<.001). In both patients and control subjects, similar correlations between homocysteine and vitamin $B_{12}$ (*r*=−.39 and −.38, *P*<.001) and pyridoxal 5′-phosphate (*r*=−.19 and −.28, *P*<.01) were observed.

Overall, folate values were higher in patients (mean, 22.6±12.4 nmol/L; median, 19.2 nmol/L) than in control subjects (mean, 17.9±9.4 nmol/L; median, 15.4 nmol/L; *P*<.001). Folate levels were lower in those with homocysteine levels of more than 14 μmol/L (mean, 19.4±11.3 nmol/L; median, 14.0 nmol/L) compared with those with homocysteine concentrations of less than this value (mean, 23.5±12.1 nmol/L; median, 18.1 nmol/L; *P*=.006). Similar findings were seen in relation to vitamin $B_{12}$ (230±113 versus 310±150 pmol/L, *P*<.001) and pyridoxal 5′-phosphate levels (55±52 versus 83±74 nmol/L, *P*<.001, Table 5).

### Prevalence of Vitamin Deficiencies

Deficiency of folate (defined as less than 6.4 nmol/L) was seen in 2 patients (1%) and 2 control subjects (1%). Deficiency of vitamin $B_{12}$ (defined as less than 125 pmol/L) was seen in 22 patients (7.8%) and 12 control subjects (5.3%; *P*=NS). Deficiency of pyridoxal 5′-phosphate (defined as less than 20 nmol/L) was seen in 22 patients but only 5 control subjects (10% versus 2%, *P*<.01).

### Relation of Vitamin Deficiencies to Coronary Artery Disease

The odds ratios for coronary disease in those with folate or vitamin $B_{12}$ deficiency were 0.7 (CI, 0.1 to 11.4) and 1.6 (CI, 0.5 to 5.0) respectively (*P*=NS for both).

In contrast, the odds ratio for coronary disease in those with low pyridoxal 5′-phosphate adjusted for all traditional risk factors was 3.8 (CI, 1.1 to 13.7; *P*=.04). When hyperhomocysteinemia was included in a multivariate analysis, an odds ratio of 4.3 (CI, 1.1 to 16.9) persisted for coronary disease in those with low pyridoxal (*P*=.04). Furthermore, when patients with coronary disease and coexisting vitamin deficiency were excluded, homocysteine concentrations remained higher than in control subjects (13.3±4.0 versus 10.8±3.3 μmol/L, *P*<.001). The odds ratio for coronary heart disease in those in whom all vitamin deficiencies had been excluded also remained high (3.8; CI, 2.1 to 7.0; *P*<.001).

## Discussion

The rare syndrome of homocystinuria[21] is characterized by excessively high homocysteine concentrations and vascular disease with a 50% risk of such an episode before age 30.[14] Many studies have confirmed that milder elevations of homocysteine also confer an independent risk of stroke, coronary disease, and peripheral vascular disease.[1,2,3,4,5,6,7,8,9,10,11,12,13] The results of the present study broaden the definition of hyperhomocysteinemia to include many individuals currently categorized as falling within a “normal” range and demonstrates the absence of a threshold phenomenon. Furthermore, the increased risk associated with high homocysteine has been extended to include women and the elderly. Highly significant negative correlations have been shown between all essential B group nutrients studied and homocysteine. In the evaluation of the relation between pyridoxal phosphate and homocysteine concentrations, an independent association between low concentrations of this cofactor and coronary disease has been revealed. Even when all patients with vitamin deficiency are excluded, however, high homocysteine concentrations are still associated with an increased risk of coronary artery disease.

The precise level, if any, of plasma homocysteine at which an increased risk of vascular disease may begin has not been clearly defined. Many studies have used arbitrary definitions of abnormality based on homocysteine concentrations of more than 2 SD above the mean for controls[3 4 7 8 9] or more than the 95th percentile for normal control subjects.[10 12] Others have used simple comparisons of mean values for patients and control subjects[2] or other techniques.[1 5 6 13] Plasma homocysteine concentrations are not normally distributed, and these arbitrary definitions of hyperhomocysteinemia may not be appropriate. Furthermore, because gender influences plasma homocysteine significantly, definitions of hyperhomocysteinemia using mixed-sex control group may also be unsuitable for definitions of normality. To circumvent the various biological variations, we explored a number of different models of "high" plasma homocysteine concentrations and used sex-specific definitions as well as log-transformed data. The results show that homocysteine concentrations now widely accepted as normal are associated with an increased likelihood of coronary artery disease and that this risk increases with rising homocysteine concentrations.

In both men and women, higher homocysteine concentrations were associated with increased odds ratios of coronary disease. The prevalence of hyperhomocysteinemia in women was greater than in men, although the numbers were too small to establish any statistically significant sex differences in odds ratios for coronary heart disease. Little attention has been given to the risk of coronary disease conferred by high homocysteine concentrations in women, although higher levels have been reported in women with vascular disease.[2 7 9] It is now clear, however, that hyperhomocysteinemia also increases the risk for coronary disease in women.

Most studies of patients with coronary disease have focused on subjects 65 years of age or younger,[1 3 5 6 11 12 13] although some studies of stroke and peripheral vascular disease have included older patients.[7 8 9] Older patients, who form a large proportion of the coronary population, have received little attention. Our study extends the coronary risk associated with hyperhomocysteinemia to these patients. The mechanisms for the increased homocysteine concentrations in this age group may relate to prerenal factors,[9] inadequate nutrient intake,[22] or even age-related decreases in the activity of enzymes responsible for the metabolism of homocysteine.[23] Regardless of mechanism, increased plasma homocysteine is a common risk factor for coronary disease in older people: more than 50% of our older patients were hyperhomocysteinemic (based on an 80th percentile definition). Homocysteine concentrations correlate negatively with folate[4 9 12 13 19 22] as well as vitamins $B_{12}$[4 12 13 19 22] and $B_6$.[9 12 22] Our study confirms this in both patients and control subjects.

Frank folate or vitamin $B_{12}$ deficiency was, however, rare and was not associated with an increased risk of coronary disease. There was no evidence that the increased homocysteine concentrations in patients in the present study were due to poorer nutrition compared with control subjects. In this study, folate levels were actually higher in patients.

Vitamin $B_6$ deficiency (pyridoxal-5′-phosphate levels of less than 20 nmol/L) was more frequent in our patients than control subjects. An independent increased risk of coronary disease was seen in these patients even when an allowance was made for hyperhomocysteinemia. Vascular lesions have been seen in animals deficient in pyridoxine,[24] and Selhub et al[25] reported an association between inadequate pyridoxal status and carotid arteriosclerosis, although this diminished after adjustment for homocysteine. An increase in antithrombin III activity has been shown after administration of vitamin $B_6$,[26] and the activated form, pyridoxal 5′-phosphate, inhibits platelet aggregation.[27] Furthermore, plasma homocysteine levels may also be reduced by essential vitamins, including folic acid[4 28 29 31] and vitamin $B_6$.[3 4 30] In two studies of patients with coronary disease, homocysteine concentrations were reduced with combinations of vitamins $B_6$ and folic acid[31] or vitamin $B_{12}$,[32] which is also consistent with correction of an underlying deficiency.

Conversely, the elevated homocysteine in our patients was not entirely explained by low vitamin concentrations as both high homocysteine concentrations and an increased odds ratio of coronary disease persisted when such patients were excluded. Although heterozygosity for cystathionine β-synthase deficiency[3 5] could be responsible for hyperhomocysteinemia in some patients with coronary artery disease, the gene frequency of this condition is too low to account for the large number of hyperhomocysteinemic patients seen in everyday clinical practice.[33] Recently, the cDNA for the gene coding for methylenetetrahydrofolate reductase was isolated,[34] and nine mutations were described in patients with severe methylenetetrahydrofolate reductase deficiency.[34 35] A C→T substitution at nucleotide 677, resulting in the conversion of an alanine to a valine residue, has also been reported[36] in association

with thermolabile methylenetetrahydrofolate reductase. This has important implications for studies of patients with vascular disease as, in the study of Frosst et al,[36] the substitution occurred at a frequency of ≈38% of unselected chromosomes and was associated with homocysteine concentrations well within the range associated with vascular disease. The relation of this to underlying nutrient disturbances in patients with vascular disease requires further study.

In summary, high homocysteine concentrations and low pyridoxal 5′-phosphate are independent risk factors for coronary artery disease. The risk associated with homocysteine rises with increasing concentrations, has no threshold, and is evident in women and the elderly.

## Statistical Footnote

The estimated homocysteine effect from three different logistic regression models is shown in the Figure. The threshold model is the maximum likelihood estimate (MLE) based on the constraint that all persons with a value less than this are equal and that all those with a value greater than this are equal. In this model, the odds of developing coronary disease increase only when the threshold of 14 μmol/L is passed. The basic logistic regression model is the MLE based on the constraint that an increase of *n* μmol/L will have the same impact on the odds of coronary disease regardless of the baseline value. The generalized additive model is constrained only by local smoothing, and the fit of this model appears to validate the absence of a threshold effect. It shows that persons at the upper end of the "normal" range may have odds of coronary disease three to four times higher than persons at the lower end of the range.

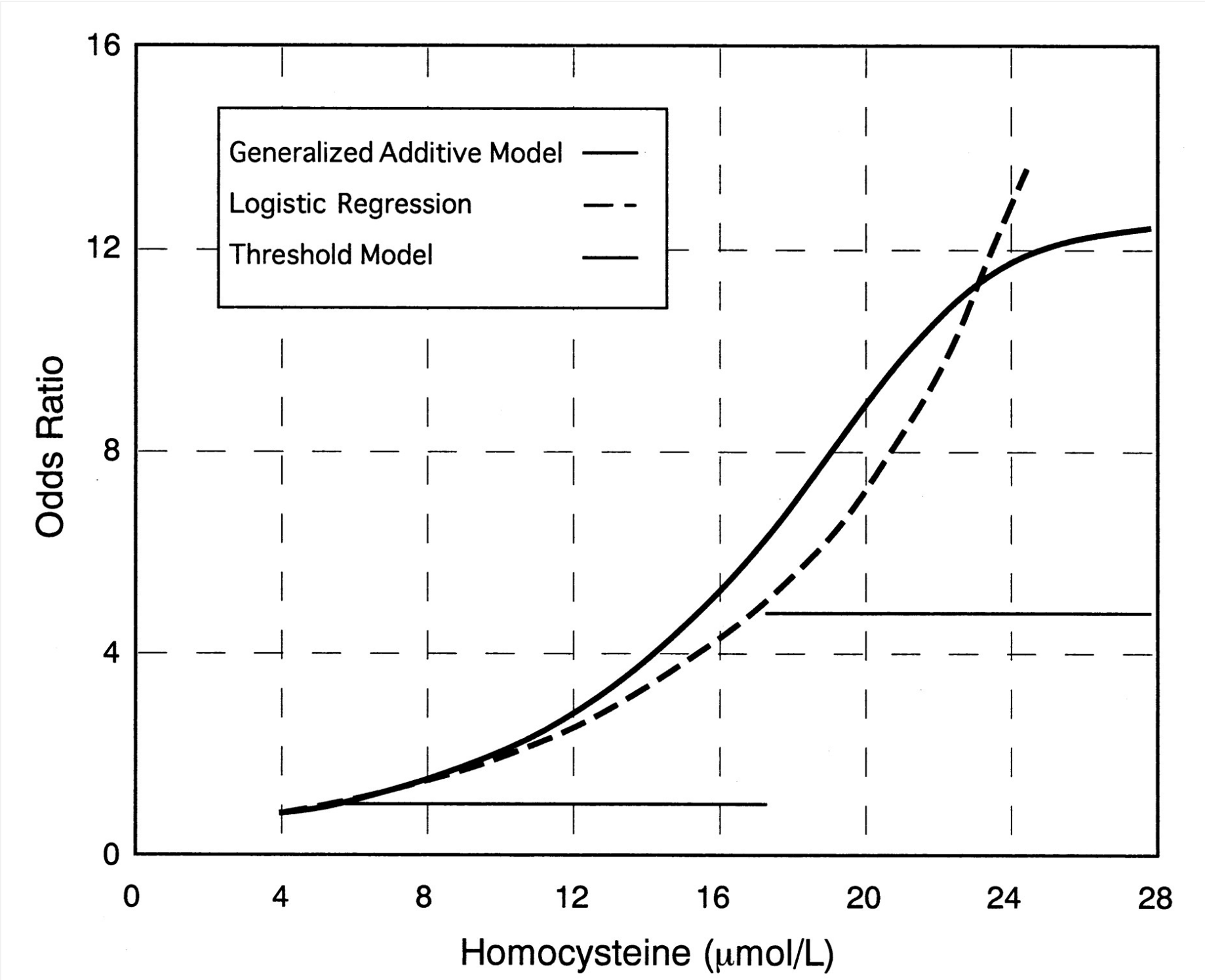


**Figure 1**. Plot of odds ratio for coronary artery disease using three different models. The simple threshold model uses a cutoff-point at 14 μmol/L to yield an odds ratio of 4.8 in those with levels greater than this value. When logistic regression or generalized additive models are used, increased odds ratios for coronary artery disease are seen at plasma homocysteine concentrations below 14 μmol/L and within a "normal" range.

**Table 1**. Baseline Demographic and Angiographic Characteristics of Patients and Control Subjects

| | Patients (n=304) | Control Subjects (n=231) | *P* |
|---|---|---|---|
| Male, % | 66 | 81 | <.001 |
| Age, y | 62±11 | 51±10 | <.001 |
| Hypercholesterolemic, % | 71 | 63 | NS |

EXPAND TABLE

**Table 2**. Mean Total Plasma Homocysteine Concentrations in Patients and Control Subjects

| | Homocysteine Concentration, µmol/L | | |
|---|---|---|---|
| | Mean | SD | Median |
| Male control subjects[1] (n=185) | 11.2 | 2.9 | 10.8 |
| Male patients[2] (n=201) | 13.9 | 4.5 | 13.1 |

EXPAND TABLE

1 *P*<.01 vs female control subjects.

2 *P*<.01 vs control subjects of same sex.

One folate-deficient female patient with a high (250 µmol/L) homocysteine concentration substantially increased the mean and the SD for this subgroup, but the median remains significantly higher than that of the control subjects.

**Table 3**. Mean Total Plasma Homocysteine Concentrations in Patients and Control Subjects Younger and Older Than 65 Years

| | Homocysteine Concentration, µmol/L | | |
|---|---|---|---|
| | Mean | SD | Median |
| Control subjects <65 years (n=206) | 10.8 | 3.4 | 10.4 |
| Patients <65 years[1] (n=165) | 14.2 | 20.4 | 12.1 |

EXPAND TABLE

1 *P*<.01 vs control subjects.

2 *P*<.01 vs patients less than 65 years old.

**Table 4**. Prevalence of Hyperhomocysteinemia and Odds Ratios of Coronary Heart Disease

| | HHE, % | Odds Ratio |
|---|---|---|
| All patients (n=304) | 49[1] | 2.9 (CI, 1.7 to 5.0)[1] |
| Male patients (n=201) | 45[1] | 2.9 (CI, 1.7 to 4.7)[1] |
| Female patients (n=103) | 56[1] | 3.5 (CI, 1.4 to 8.5)[2] |

EXPAND TABLE

HHE indicates hyperhomocysteinemia, defined as a concentration at the sex-adjusted 80th percentile for control subjects.

1 *P*<.01.

2 *P*<.05.

**Table 5**. Concentrations of B Group Vitamins in Patients With Homocysteine Concentrations Above and Below 14 µmol/L

| | Homocysteine | |
|---|---|---|
| | ≥14 µmol/L | <14 µmol/L |
| Vitamin $B_{12}$, pmol/L | 230±113 | 310±150[2] |
| Vitamin $B_6$, nmol/L | 55±52 | 83±74[1] |
| Folic acid, nmol/L | 17.2±10.8 | 21.7±11.5[2] |

1 *P*<.05 vs those with homocysteine ≥14 µmol/L.

2 *P*<.01 vs those with homocysteine ≥14 µmol/L.

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# References

1. Wilcken DEL, Wilcken B. The pathogenesis of coronary artery disease: a possible role for methionine metabolism. *J Clin Invest.*. 1976;*57*:1079-1082.

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2. Kang S-S, Wong PWK, Cook HY, Norusis M, Messer JV. Protein-bound homocysteine: a possible risk factor for coronary artery disease. *J Clin Invest.*. 1986;*77*:1482-1486.

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3. Boers GHJ, Smals AGH, Trijbels FJM, Fowler B, Bakkeren JAJM, Schoonderwaldt HC, Kleijer WJ, Kloppenborg PWC. Heterozygosity for homocystinuria in premature peripheral and cerebral occlusive arterial disease. *N Engl J Med.*. 1985;*313*:709-715.

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