JOURNAL OF INSURANCE MEDICINE

J Insur Med 2009;41:244–253

Association of Cholesterol, LDL, HDL, Cholesterol/HDL and Triglyceride with All-Cause Mortality in Life Insurance Applicants

Michael Fulks, MD; Robert L. Stout, PhD; Vera F. Dolan, MSPH

Objective.—Determine the relationship between various lipid tests and all-cause mortality in life insurance applicants stratified by age and sex.

Method.—By use of the Social Security Death Master File, mortality was determined in 1,488,572 life insurance applicants from whom blood samples were submitted to Clinical Reference Laboratory. There were 41,020 deaths observed in this healthy adult population during a median follow-up of 12 years (range 10 to 14 years). Results were stratified by 4 age-sex subpopulations: females, ages 20 to 59 or 60+; and males, ages 20 to 59 or 60+. Those with serum albumin <3.6 mg/dL or fructosamine ≥ 2.1 mmol/L were excluded. The middle 50% of lipid values specific to each of these 4 age-sex subpopulations was used as the reference band. The mortality rates in bands representing other percentiles of lipid values were compared with the mortality rate in the reference band within each age-sex subpopulation.

Results.—In contrast to some published findings from general populations, lipid test results are only moderately predictive of all-cause mortality risk in a life insurance applicant population and that risk is dependent on age and sex. At ages below 60, HDL values are associated with a ''J'' shaped mortality curve and at ages 60+, total cholesterol is associated with a ''U'' shaped curve. The total cholesterol/HDL ratio may serve as a useful single measure to predict mortality risk, but only if stratified by age and sex, and only if high HDL values at younger ages and lower total cholesterol values at ages 60+ are recognized as being associated with increased risk as well. Using LDL or non-HDL cholesterol instead of total cholesterol does not improve mortality risk discrimination; neither does using total cholesterol or triglyceride values in addition to the total cholesterol/HDL ratio.

Conclusion.—The total cholesterol/HDL ratio is the best single measure of all-cause mortality risk among the various lipid tests but is useful only if viewed on an age- and sex-specific basis and is only a modest risk predictor.

Address: 601 North State Street, Suite 2000, Ukiah, California, 95482; ph: 707-463-3200; fax: 707-463-3209; e-mail: dolanvp@consultancy.com.

Correspondent: Vera F. Dolan, MSPH.

Key words: Lipids, cholesterol, cholesterol/HDL, HDL, LDL, triglyceride, mortality, life insurance.

Author affiliation: Fulks, Medical Director, Clinical Reference Laboratory, Jackson, CA; Stout, President, Clinical Reference Laboratory, Lenexa, KS; Dolan, Research Associate, Clinical Reference Laboratory, Ukiah, CA.

Received: August 11, 2009

Accepted: December 18, 2009

INTRODUCTION

The Framingham study began looking at lipids as well as other cardiovascular risk factors in 1948. Based on that study, Castelli et al in 1986, showed the relationship between cardiovascular risk, HDL cholesterol (HDL) and total cholesterol (TC) in an often copied 3-D plot.[1] That article and most articles on lipids before and since have used the prevalence of coronary heart disease or deaths from CHD as the end-points and viewed the relationship of lipid levels to events through use of regression testing of their entire study populations.[1–3] These analyses generally found that higher HDL decreases risk and higher TC increases risk. Kinosian et al also found the ratio between total cholesterol and HDL to be more effective than looking at LDL alone.[3] Further work led to the ATP III guidelines of 2001 and later modifications, which focused on low density lipoprotein cholesterol (LDL) and HDL levels.[4] The impact of triglyceride on CHD has also been studied and though some authors have found it independently predictive, other have not.[5]

A few studies have looked at all-cause mortality risk stratified by age and sex instead of the entire study population combined.[6–11] These studies have not always shown risk increasing as HDL decreases and as TC or LDL increases. At older ages, all-cause mortality may actually be flat or increase as TC decreases.[6,7] In addition to the disparity when all-cause mortality is considered, TC levels in the US general population have fallen and other risk factors such as hypertension and smoking are better controlled, leading to a continuing reduction in the prevalence of CHD.[12,13] This and improved treatment have led to an even greater reduction in the relative risk of cardiovascular mortality as a contributor to all-cause mortality.[14] Our investigation utilizing serum from a recent cohort of adult individual life insurance applicants including both sexes and a wide age range is designed to answer questions about the relative all-cause mortality risk associated with various tests of lipids in an age- and sex-stratified healthy population.

METHODS

The population studied for this article is the same as that analyzed for our study of mortality risk and LFTs, which is described in depth in that article.[15] Briefly, by use of the Social Security Death Master File, mortality was examined in 1,488,572 life insurance applicants from whom blood samples were submitted to Clinical Reference Laboratory and lipid results obtained. There were 41,020 deaths observed after a median follow-up of 12 years (range 10 to 14 years). Since the study was designed to describe the relationship between lipids and mortality in an otherwise healthy population, those with a fructosamine of 2.1 mmol/L or higher or a serum albumin <3.6 mg/dL were excluded. The fructosamine restriction excluded approximately 80% of applicants with HbA1c of 7% or higher and over 40% of those with HbA1c 6% to 6.9% (CRL data not shown), both potentially associated with adverse lipids and higher mortality risk. The exclusion of applicants with low albumin should eliminate many applicants with advanced cancer, heart failure and inflammatory disease associated with reduced food intake or catabolic state leading to low TC. The cut-off for excluding cases with low albumin was chosen based on a separate CRL study looking at all-cause mortality and albumin (data not shown, in press).

Results were stratified by 4 age-sex subpopulations: females, ages 20 to 59 (females <60); males, ages 20 to 59 (males <60); females, ages 60+ (females 60+); and males, ages 60+ (males 60+) based on relatively homogeneous distributions and mortality ratios within each of those subpopulations. Mean ages were 38, 40, 66 and 65 years, respectively. TC, HDL, LDL and the TC/HDL ratio were grouped into bands using percentiles of their distribution within these

Table 1. TC, HDL and TC/HDL Values Associated with Each Percentile Band for Females

Percentile of population	Females <60			Females 60+		
	TC mg/dL	HDL mg/dL	TC/HDL ratio	TC mg/dL	HDL mg/dL	TC/HDL ratio
0.5	114.0	26.6	1.8	137.0	26.3	1.9
1	121.0	28.9	1.9	146.0	29.3	2.1
2.5	130.0	32.5	2.1	159.0	33.3	2.2
5	139.0	35.7	2.3	169.0	36.7	2.4
10	149.0	39.5	2.4	182.0	40.9	2.6
25	168.0	46.5	2.8	203.0	48.7	3.1
75	218.0	65.1	4.2	253.0	71.0	4.7
90	246.0	75.7	5.2	279.0	83.3	5.8
95	264.0	82.8	5.9	295.0	90.4	6.5
97.5	281.0	89.0	6.6	312.0	96.0	7.3
99	304.0	95.5	7.6	334.0	102.0	8.3
99.5	320.0	98.7	8.4	350.0	110.0	9.2

4 age-sex subpopulations. The lowest HDL values were assigned to the highest percentile bands, while the highest TC, TC/HDL and LDL values were assigned to the highest percentile bands (see Tables 1 and 2).

The middle 50% band of lipid values in each age-sex subpopulation (25^{th} to 74^{th} percentile) was assigned a mortality ratio of 100%. Mortality results for other percentile bands for various lipid values within each subpopulation were compared to this reference mortality, creating mortality ratios or relative risk estimates. An initial analysis was done for each lipid measure studied without regard to other lipid measures. Further analysis for each lipid test was then performed with stratification of other lipid measures by quartiles and through use of Cox regression and receiver operating characteristics (ROC) testing.

Data points displayed in Figures 1–8 have solid centers if there are 30 or more deaths, and open centers if there are 8 to 29 deaths observed. Data points and their associated trend lines are not displayed where there are fewer than 8 deaths observed. Ninety-five percent confidence intervals (CIs) were calculated for each mortality ratio shown for the TC/HDL ratios in the tobacco and nontobacco combined group in Figures 7 and 8.[16] Since the number of deaths is similar within the same percentile band for each lipid test, the width of the 95% CIs is very similar for the other lipid measures and other figures.

Tests for TC and triglyceride were performed on Hitachi Chemistry analyzers with Roche chemistry reagents; settings were as specified by the manufacturer. HDL cholesterol was determined by precipitation with phosphotungstic acid, Sigma Chemical Reagent for *in vitro* diagnosis. LDL was calculated with the Freidewald equation (TC-(HDL+triglyceride/5)).[17] Non-HDL cholesterol was TC minus HDL.[18,19] Statistical analysis was performed with PASW for Windows, version 17.0.2 (SPSS Inc.).

RESULTS

Attention was first paid to whether TC or LDL was superior in mortality risk prediction. To evaluate this, Cox regression testing stratified by the 4 age-sex subpopulations was performed including age, TC and LDL and was limited to applicants with TC >160 mg/dL and LDL >100 mg/dL. The reason for those limits is apparent from Figures 1–4 where it can be seen that low TC values are also associated with increasing mortality risk. Not surprisingly, the same is true for low LDL values (data not shown). By

Table 2. TC, HDL and TC/HDL Values Associated with Each Percentile Band for Males

Percentile of population	Males <60			Males 60+		
	TC mg/dL	HDL mg/dL	TC/HDL ratio	TC mg/dL	HDL mg/dL	TC/HDL ratio
0.5	116.0	21.0	2.2	123.0	22.0	2.2
1	124.0	22.9	2.3	133.0	23.8	2.4
2.5	136.0	25.6	2.6	145.0	26.4	2.6
5	146.0	28.0	2.8	155.0	28.9	2.9
10	158.0	30.9	3.1	167.0	31.9	3.2
25	179.0	36.3	3.8	187.0	37.4	3.8
75	231.0	51.2	5.8	235.0	53.5	5.7
90	258.0	60.1	7.0	259.0	63.4	6.7
95	275.0	66.3	7.8	274.0	70.5	7.5
97.5	291.0	72.5	8.7	289.0	77.6	8.2
99	312.0	80.7	9.8	308.4	86.4	9.1
99.5	327.0	86.8	10.7	322.0	92.7	9.8

Cox regression, each of the two lipid tests had a similar mortality impact to the other and to both together (ie, they are not additive) at ages <60, and none were predictive for ages 60+.

To evaluate further, ROC testing of TC and LDL was performed for each of the 4 age-sex subpopulations, again limited to cases with TC >160 mg/dL and LDL >100 mg/dL. This testing showed TC to be the superior mortality risk predictor (larger area under the curve or ''C statistic'') for females <60 and males <60; both tests had identical but limited predictive ability for females 60+ and males 60+. Non-HDL cholesterol was also examined by ROC testing against TC and LDL since it has been promoted as a superior mortality predictor to TC.[19] It performed in a nearly identical manner to TC on ROC testing. Therefore, we limited further analysis to TC since, relative to LDL and non-HDL cholesterol, TC was either superior or equal in risk prediction, was simpler and/or more commonly used, and captured all the risk observed in each age-sex subpopulation.

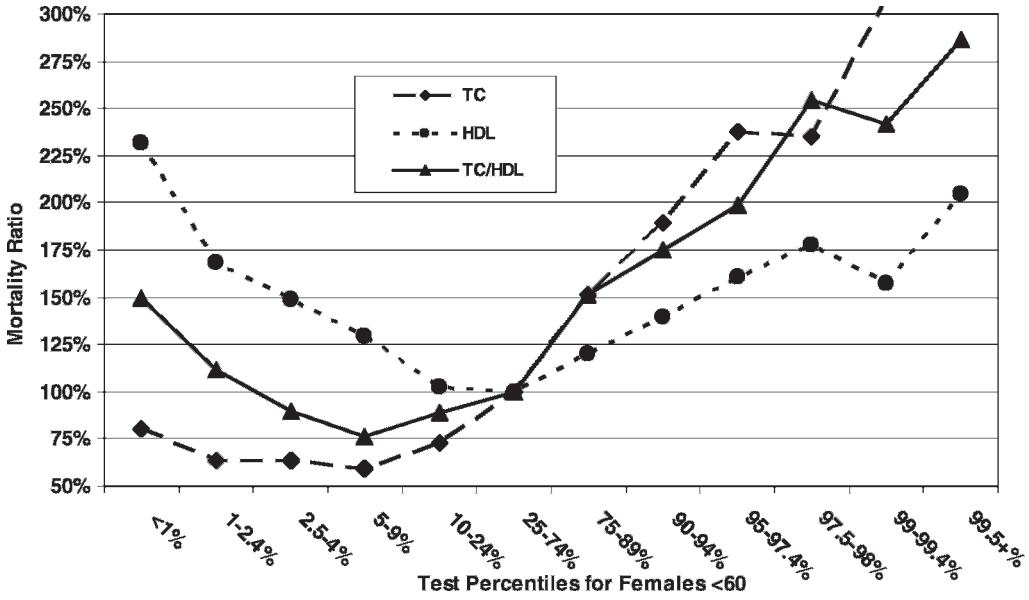

Figure 1. *Mortality in females ages 20 to 59 by lipid test.*

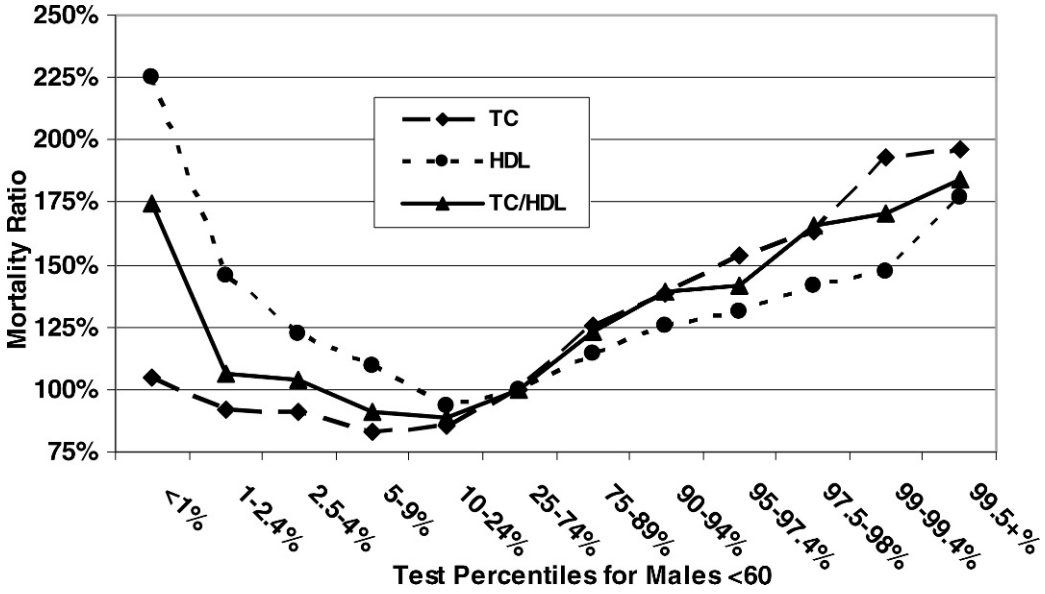

Figure 2. *Mortality in males ages 20 to 59 by lipid test.*

TC, HDL and the TC/HDL ratio were then evaluated independently as predictors of all-cause mortality. The results can be seen in Figures 1–4. Although there are differences by sex even when the figures use sex-specific percentile bands rather than actual lipid test values, the larger differences are by age. For females <60, TC and the TC/HDL ratio are predictive of risk across a wide range of values. HDL has more of a ''U'' shaped relationship with mortality risk increasing at high and low values. For males <60, the relationship of all lipid tests to mortality is less steep (less mortality impact per unit of increase) relative to females but otherwise similar.

For males and females 60+, the prediction of risk based on elevations of TC, TC/HDL ratio and HDL is reduced relative to those ages <60, with the largest loss of impact seen

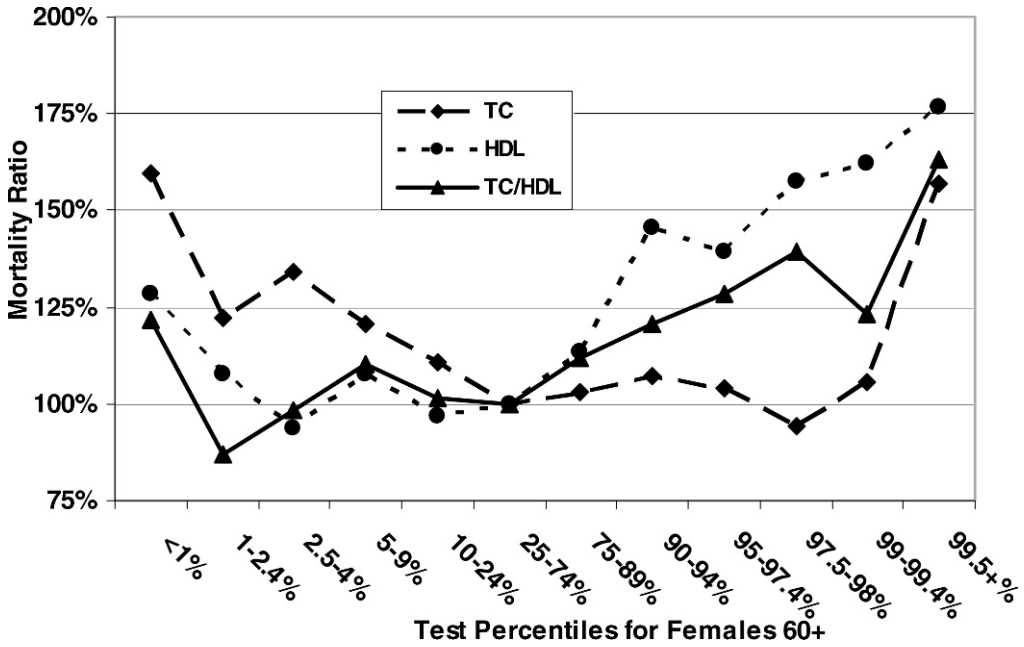

Figure 3. *Mortality in females ages 60+ by lipid test.*

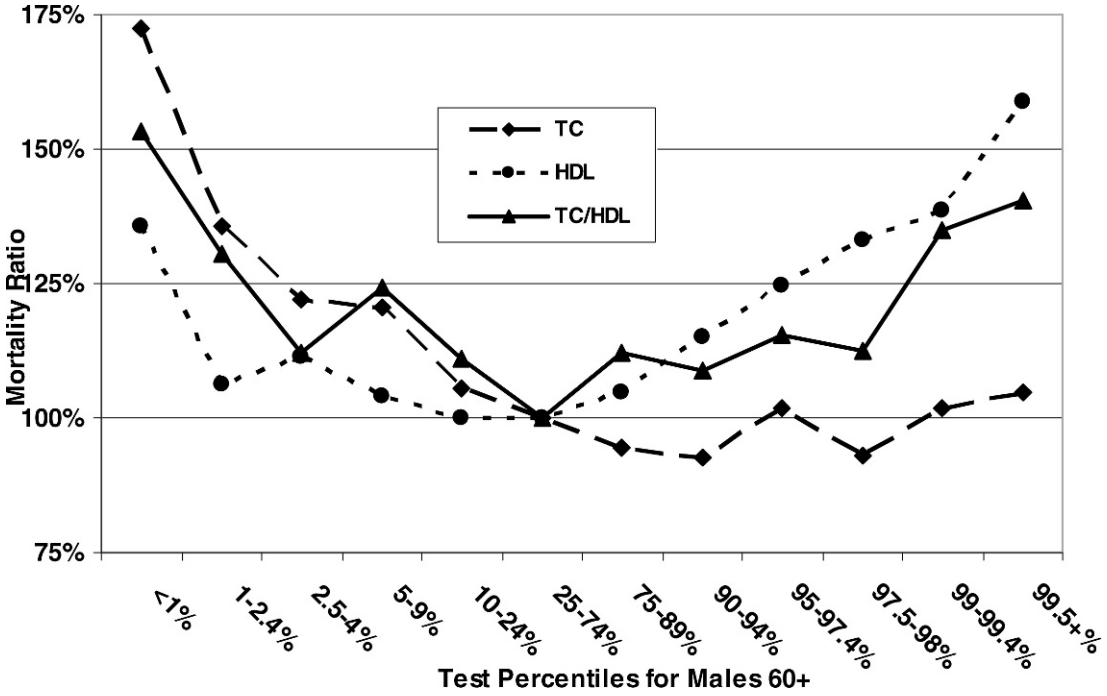

Figure 4. *Mortality in males ages 60+ by lipid test.*

for TC. Decreasing levels of TC below the middle 50% band are actually associated with higher risk than are increasing levels of TC levels above the middle 50% band.

Very high HDL is associated with increased mortality risk for ages <60 in males and females, while low TC is associated with increased risk beginning at age 50 (data shown for 60+ only). Although its relationship with risk varies by age-sex subpopulation, the TC/HDL ratio has a more consistent mortality impact across these groups than TC or HDL.

Since the TC/HDL ratio appeared to be the only lipid test that might potentially serve as a single measure of mortality risk in

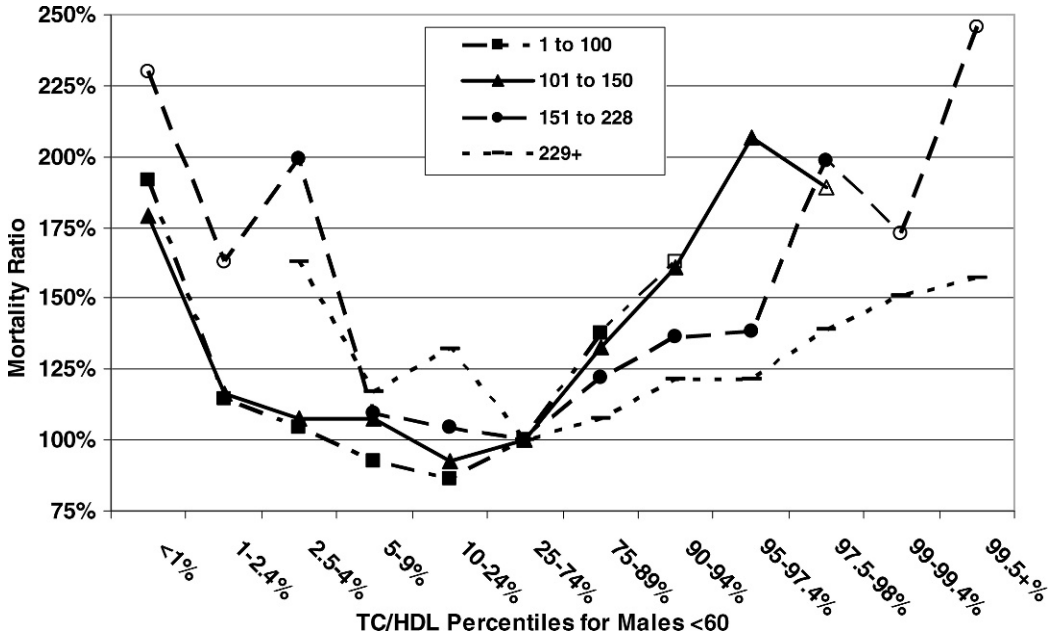

Figure 5. *Mortality in males ages 20 to 59 by TC/HDL and quartile of triglyceride values.*

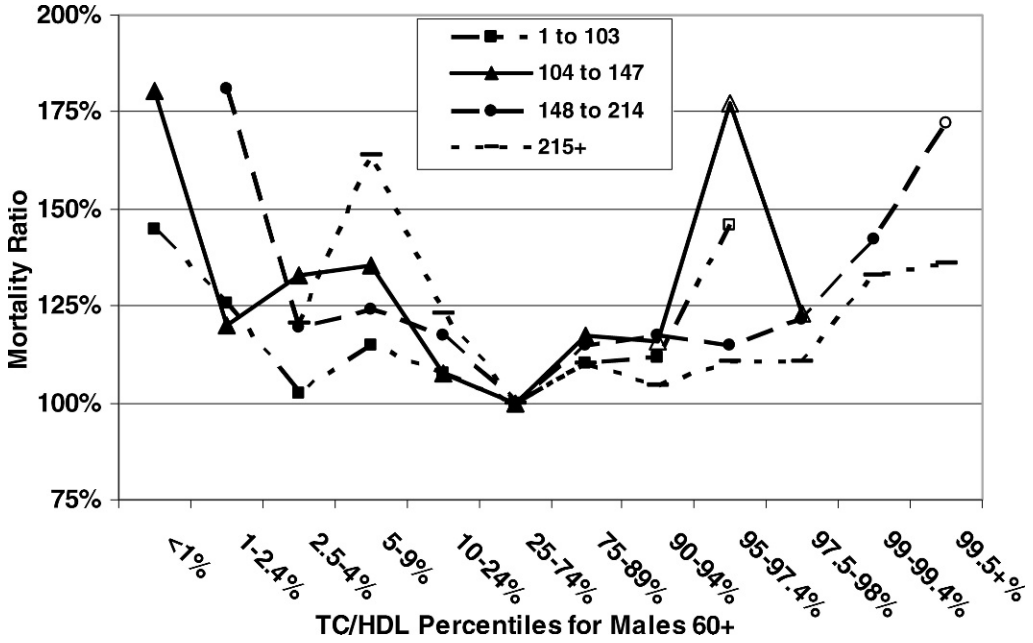

Figure 6. *Mortality in males ages 60+ by TC/HDL and quartile of triglyceride values.*

all 4 age-sex subpopulations, we further examined any additional mortality impact of tobacco use, TC, HDL or triglyceride once the TC/HDL ratio was known. Cox regression testing including all 4 lipid tests and limited to those applicants with LDL >100 mg/dL, TC >160 mg/dL, and HDL <80 mg/dL demonstrated that the addition of TC, HDL or triglyceride to the TC/HDL ratio did not improve mortality risk prediction in any of the 4 age-sex groups.

Using an alternative approach, we also looked at the impact of TC on the TC/HDL ratio mortality by dividing each age-sex

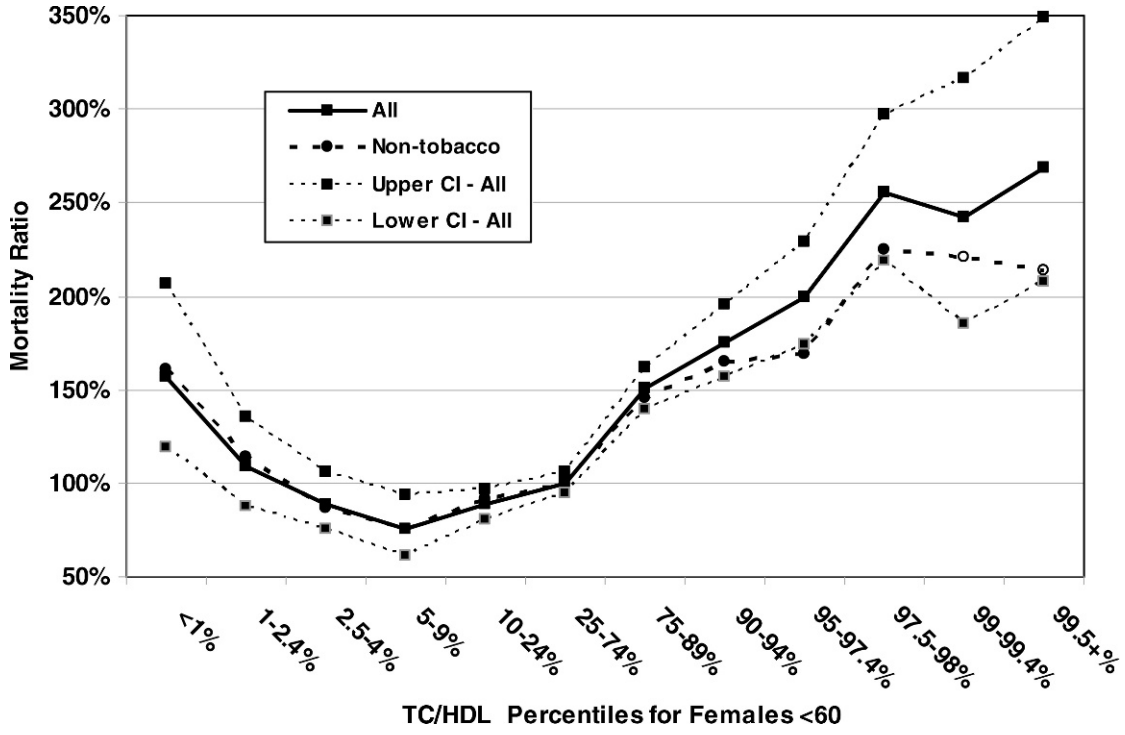

Figure 7. *Mortality in females ages 20 to 59 by tobacco status.*

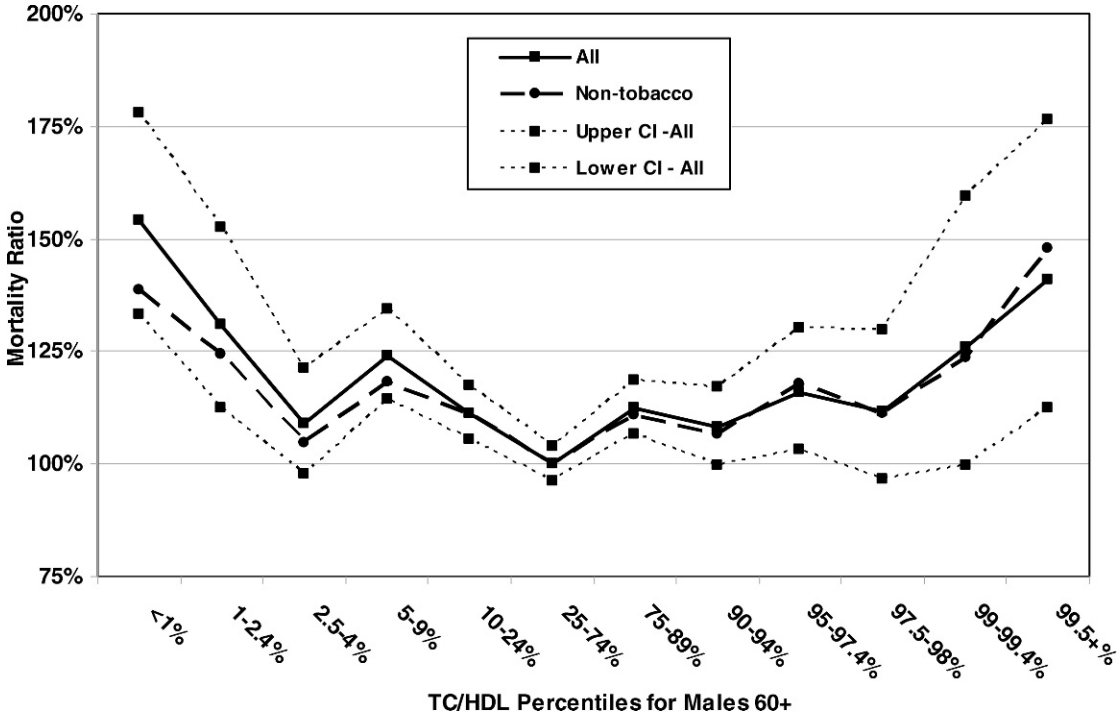

Figure 8. *Mortality in males ages 60+ by tobacco status.*

subpopulation by quartiles of TC. For ages 60+, as the TC/HDL ratio increased, the highest quartile of TC values had the lowest mortality while for ages <60, no clear association with risk was seen (data not shown).

The impact of triglyceride on the TC/HDL ratio risk was explored in an identical manner. Representative results for males <60 and 60+ are shown in Figures 5 and 6. Deaths are limited for some data points and are handled as noted in the ''Methods'' section. Risk did not increase as the triglyceride level increased within any age-sex subpopulation (females <60 and 60+ not shown). Rather, the highest quartile of triglyceride values generally had the lowest mortality risk.

We also compared the mortality ratios for each of the age-sex subpopulations of non-tobacco users (urine cotinine values <0.2 ng/mL) comprising approximately 88% of applicants vs all combined, each compared to its own reference band. Non-tobacco and ''all'' curves for males 60+ shown in Figure 8 are almost identical and were not significantly different from each other. Curves for females <60 in Figure 7 show a slightly lower risk for non-tobacco users only at the highest TC/HDL ratios but had widely overlapping 95% CIs. Results for the other 2 age-sex subpopulations, females 60+ and males <60 (neither shown), are similar to the opposite sex within the same age group. The ranges of TC, HDL and the TC/HDL ratio values associated with each percentile band are provided in Table 1A for females and Table 1B for males.

DISCUSSION

The pattern of mortality risk based on lipid testing is dependent on age and sex for this population of mostly healthy employed or retired US adults with access to health care. This is consistent with other studies of older individuals[6–10] but has been largely ignored by general medicine and those providing treatment recommendations, which have been based on the entire population studied, rather than studying different age and sex subpopulations independently.

Not only are the patterns of mortality based on various lipid tests different by age

and sex, but the importance of low TC values at ages 60+, though reported, has not been widely appreciated. As coronary and vascular deaths fall relative to other causes, this relationship becomes even more important. Breaking down results by decade of age (data not shown) reveals increasing risk as TC falls below the mid 50% band beginning around age 50 and becoming more prominent by age 60. This increased mortality risk is present even though we excluded applicants with albumin levels <3.6 mg/dL in an effort to exclude individuals with poor nutrition or hepatic function.

Higher HDL values are also of concern at younger ages; the risk is presumably associated with heavy alcohol intake as no other cause of high HDL aside from heredity and exercise is apparent. This association of heavy alcohol use and high HDL is known, but the extent of mortality risk associated with high HDL has not been previously described.

Once the TC/HDL ratio is known, additional consideration of elevated levels of TC or decreased levels of HDL does not improve risk discrimination. Neither did consideration of triglyceride or LDL levels. Although a fasting state is encouraged when testing insurance applicants, it is not required and is impossible to assure. Triglyceride levels are dependent on the degree of fasting, and the LDL value is not directly measured but rather calculated using the Freidewald equation. It may be that with true fasting, triglyceride or LDL values might be of more value but this is unclear from our data or from the clinical literature. What is clear is that for laboratory studies obtained for insurance purposes where fasting is uncertain, neither triglyceride nor LDL add value in risk selection. Whether extraordinary high values of triglyceride occasionally seen are important in risk prediction cannot be determined by this study.

None of the lipid tests we studied show the level of mortality risk prediction one might expect from reviewing the clinical literature. A possible reason is the roughly 50% reduction in cardiovascular mortality that has occurred over the past 30 years, with half of that attributable to a reduction in risk factors.[13] This reduced cardiovascular risk makes lower TC possibly associated with malignancy, heart failure or inflammatory disease more important to all-cause mortality relative to higher TC that is associated with coronary or vascular mortality.

A related issue is that the outcomes assessed in most published lipid studies are either cardiovascular events or CV death. We use the more relevant, if less specific, all-cause mortality where competing risks are included, reducing or even reversing the impact of lipids for some age-sex subpopulations.

Finally, we excluded most of those with HbA1c ≥7% and many of those with HbA1c ≥6% by testing almost all applicants with fructosamine and excluding those with fructosamine ≥2.1 mmol/L. This exclusion reduced the mortality impact of lipids by eliminating mortality more appropriately associated with elevated glucose levels that has been included in lipid studies where such screening or exclusion was not performed. When non-tobacco users were examined separately, little difference in mortality risk relative to the combined population was noted at ages 60+, but there is a non-significant trend toward lower risk at high TC/HDL ratios in non-tobacco users ages <60. This is consistent with the premise that when fewer cardiovascular risk factors are present, less favorable lipid values have a smaller impact on all-cause mortality.

A limitation of this study is a lack of medical history so that those with known cardiovascular disease or those on lipid-lowering therapy could not be evaluated separately. However, since those with known disease make up a small percentage of individual life and disability insurance applicants, and since atherosclerotic disease is distributed across lipid values, exclusion would likely have limited impact on our conclusions.

CONCLUSIONS

Compared to other testing, lipid tests are only moderately predictive of all-cause mortality risk in a life insurance applicant population, and the risk is highly dependent on age and sex.[15]

The TC/HDL ratio may serve as a useful single measure to predict risk, but only if stratified by age and sex, and only if high HDL at younger ages and low TC at older ages are also recognized as being associated with increased mortality risk. Considering elevations of TC or triglyceride values in addition to the TC/HDL ratio does not improve risk discrimination in any age-sex subpopulation studied.

REFERENCES

1. Castelli WP, Garrison RJ, Wilson PW, et al. Incidence of coronary heart disease and lipoprotein cholesterol levels. The Framingham Study. *JAMA*. 1986;256:2835–2838.
2. Stamler J, Wentworth D, Neaton J. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? *JAMA*. 1986;256:2823–2828.
3. Kinosian B, Glick H, Garland G. Cholesterol and coronary heart disease: Predicting risks by levels and ratios. *Ann Intern Med*. 1994;121:641–647.
4. Detection, evaluation and treatment of elevated cholesterol in adults (ATP III). www.nhlbi.nih.gov/guidelines/.
5. Criqui MH, Heiss G, Cohn R, et al. Plasma triglyceride level and mortality from coronary heart disease. *N Eng J Med*. 1993;328:1220–1225.
6. Kronmal RA, Cain KC, Zhan Y, et al. Total serum cholesterol levels and the mortality risk as a function of age. *Arch Intern Med*. 1993;153: 1065–1073.
7. Nilsson G, Öhrvik J, Lönnberg I, et al. Ten year survival in 75 year old men and women: predictive ability of total cholesterol, HDL-C and LDL-C. *Curr Gerontol Geriatr Res*. 2009:158425, Epub 2009Apr 27.
8. Ettinger WH, Wahl PW, Kuller LH, et al. Lipoprotein lipids in older people. Results from the Cardiovascular Health Study. *Circulation*. 1992;86:858–869.
9. Shai I, Rimm EB, Hankinson SE, et al. Multivariate assessment of lipid parameters as predictors of coronary heart disease among postmenopausal women. *Circulation*. 2004;110:2824–2830.
10. Clarke R, Emberson JR, Parish S, et al. Cholesterol fractions and apoplipoproteins as risk factors for heart disease mortality in older men. *Arch Intern Med*. 2007;167:1373–1378.
11. Ivanovic B, Pinkham CA. Relationships between serum lipids and subsequent mortality in an insured population. *J Insur Med*. 2003;35:11–16.
12. Johnson CL, Rifkind BM, Sempos CT, et al. Declining serum total cholesterol levels among US adults. *JAMA*. 1993;269:3002–3008.
13. Ford ES, Ajani UA, Croft JB, et al. Explaining the decrease in US deaths for coronary disease, 1980–2000. *N Engl J Med*. 2007;356:2388–2398.
14. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. *CA Cancer J Clin*. 2008;58:71–96.
15. Fulks M, Stout RL, Dolan VF. Using liver enzymes as screening tests to predict mortality risk. *J Insur Med*. 2008;40:191–203.
16. Kleinbaum DG, Sullivan KM, Barker ND. *ActivEPI Companion Textbook*. New York, NY: Springer; 2003:364–369.
17. Freidewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of preparative ultracentrifugation. *Clin Chem*. 1972; 18:499–502.
18. Cui Y, Blumenthal RS, Flaws JA, et al. Non-high-density lipoprotein cholesterol levels as a predictor of cardiovascular disease mortality. *Arch Intern Med*. 2001;161:1413–1419.
19. Bittner B, Hardison R, Kelsey SJ, et al. Non-high density lipoprotein cholesterol levels predict five-year outcome in BARI. *Circulation*. 2002;106: 2537–2542.