

Prognostic Value of Fasting Versus Nonfasting Low-Density Lipoprotein Cholesterol Levels on Long-Term Mortality Insight From the National Health and Nutrition Examination Survey III (NHANES-III)

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Background—National and international guidelines recommend fasting lipid panel measurement for risk stratification of patients for prevention of cardiovascular events. However, the prognostic value of fasting versus nonfasting low-density lipoprotein cholesterol (LDL-C) is uncertain.

Methods and Results—Patients enrolled in the National Health and Nutrition Examination Survey III (NHANES-III), a nationally representative cross-sectional survey performed from 1988 to 1994, were stratified on the basis of fasting status (≥ 8 or < 8 hours) and followed for a mean of 14.0 (± 0.22) years. Propensity score matching was used to assemble fasting and nonfasting cohorts with similar baseline characteristics. The risk of outcomes as a function of LDL-C and fasting status was assessed with the use of receiver operating characteristic curves and bootstrapping methods. The interaction between fasting status and LDL-C was assessed with Cox proportional hazards modeling. Primary outcome was all-cause mortality. Secondary outcome was cardiovascular mortality. One-to-one matching based on propensity score yielded 4299 pairs of fasting and nonfasting individuals. For the primary outcome, fasting LDL-C yielded prognostic value similar to that for nonfasting LDL-C (C statistic=0.59 [95% confidence interval, 0.57–0.61] versus 0.58 [95% confidence interval, 0.56–0.60]; $P=0.73$), and LDL-C by fasting status interaction term in the Cox proportional hazards model was not significant ($P_{\text{interaction}}=0.11$). Similar results were seen for the secondary outcome (fasting versus nonfasting C statistic=0.62 [95% confidence interval, 0.60–0.66] versus 0.62 [95% confidence interval, 0.60–0.66]; $P=0.96$; $P_{\text{interaction}}=0.34$).

Conclusions—Nonfasting LDL-C has prognostic value similar to that of fasting LDL-C. National and international agencies should consider reevaluating the recommendation that patients fast before obtaining a lipid panel. (*Circulation*. 2014;130:546–553.)

Key Words: cholesterol ■ mortality

Current national and international guidelines on cholesterol management recommend that lipid panel measurement should be performed after an 8- to 12-hour fast.^{1–3} The reason often stated for obtaining a fasting lipid panel is for greater precision for certain lipid parameters (especially triglycerides), which can be variable, based on time and content of the last meal. From a practical standpoint, it is cumbersome for patients to fast before obtaining a blood draw and may delay diagnosis and treatment of hyperlipidemia.

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Prior data have shown that levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) vary little with respect to fasting time, whereas triglycerides may vary by up to 20% to 30%.^{4,5} Recently, studies have suggested that nonfasting lipids may be equivalent (and potentially superior) in predicting cardiovascular outcomes because the nonfasting state may more accurately reflect the body's exposure to circulating lipids.^{6–8} Studies have demonstrated no benefit from fasting or even improved risk prediction with the use of nonfasting compared with fasting triglycerides.^{9–12} No prior studies have examined the relationship of fasting versus nonfasting LDL-C and mortality. Our objective was to use the National Health and Nutrition Examination

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Survey III (NHANES-III), a nationally representative database of the US population, to evaluate the prognostic value of fasting versus nonfasting LDL-C for prediction of all-cause mortality and cardiovascular mortality in men and women.

Methods

Study Population

We used the NHANES-III linked to the National Death Index, a nationally representative civilian cohort of noninstitutionalized individuals within the United States. Baseline data were collected between 1988 and 1994 with the use of a multistage stratified probability cluster sampling design in which certain groups were intentionally oversampled and participant weights were added to reflect the demographics of the 1990 US census. Comprehensive data about the validation and collection of data are available elsewhere.¹³ The inclusion criteria for this study were adults aged ≥ 18 years residing in the United States who had participated in the NHANES-III study with data on fasting time. We excluded those in whom LDL-C calculations were not possible because of missing HDL-C, TC, or triglyceride levels and those with triglycerides ≥ 400 mg/dL in whom the Friedewald equation may not be accurate.

Data Collection

Participants were interviewed in their homes and examined in a mobile examination center where blood samples were obtained and physical examinations were performed. If participants were unable to attend an examination at a center, home examination was performed. Institutional review board approval and documented consent were obtained from individuals through the Centers for Disease Control and Prevention.

Laboratory Methods

Blood samples were collected through venipuncture and shipped on dry ice to the laboratory analyzing the sample. Serum HDL-C, triglyceride, and TC levels were measured enzymatically at Johns Hopkins University Lipoprotein Analytic Laboratory with the use of a Hitachi 704 Analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN). Lipid collection and analyses were standardized to Centers for Disease Control and Prevention criteria.¹⁴ LDL-C was derived with the use of the Friedewald formula [$\text{LDL-C} = \text{TC} - \text{HDL-C} - (\text{triglycerides}/5)$],¹⁵ with prior studies showing excellent correlation between fasting direct and indirect methods of LDL-C measurement^{16–18} and a 0.97 correlation coefficient between Friedewald and directly measured LDL-C in nonfasting individuals.¹⁹

Variable Definitions

We classified individuals as fasting if they had fasted for at least 8 hours and stratified individuals on the basis of fasting status at the time of phlebotomy. The Adult Treatment Panel III (ATP-III) guidelines define fasting time as 9 to 12 hours in the United States, with new guidelines from the American College of Cardiology/American Heart Association Task Force recommending obtaining fasting lipids but not specifying the duration of fast.^{1,20} We used 8 hours to define fasting in keeping with recent studies examining lipids^{4,10,21} and to reflect a more conservative fasting definition. Hypertension was defined as systolic blood pressure of ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg according to the 2014 evidence-based hypertension guidelines.²² We defined diabetes mellitus as serum glycosylated hemoglobin $\geq 6.5\%$ according to the World Health Organization's updated definition of diabetes mellitus²³ or self-reported history of diabetes mellitus. We used enlarged waist circumference (defined as >88 cm for women and >102 cm for men) as a proxy for obesity because waist circumference has been shown to be more highly correlated with mortality and reflective of central adiposity than body mass index.^{24,25}

Outcome Measures

The primary outcome analyzed was mortality from all causes, and the secondary outcome was cardiovascular mortality. Data on mortality

were obtained with the use of death records from the National Death Index cross-matched to NHANES-III by probabilistic record matching. *International Classification of Diseases, Ninth Revision* and *International Classification of Diseases, Tenth Revision* codes were recoded as underlying classification of death within the NHANES-III National Death Index. Deaths from cardiovascular-related diseases included deaths from ischemic heart disease (I20 through I25), heart failure (I50), essential hypertensive heart disease (I11 through I13), cerebrovascular disease (I60 through I69), and atherosclerosis (I70 and I71).

Statistical Analysis

All analyses were performed with the use of SAS software version 9.3 (SAS Institute Inc). We adjusted for the complex, stratified study sampling design using survey weights for examination and interview portions of survey according to the Centers for Disease Control and Prevention recommendations.²⁶ Sensitivity analyses were performed without the use of survey weights.

Propensity Score Matching

We used propensity score matching to assemble a cohort of paired participants on the basis of fasting status with similar baseline characteristics. Propensity score was calculated with the use of a nonparsimonious multivariable logistic regression model with fasting status (dichotomized as yes or no) as the dependent variable. Cardiovascular risk factors were entered into the model as covariables to control for possible confounders (including race, smoking history, prior cerebrovascular disease, cholesterol medication use, diabetes mellitus, elevated TC, low HDL-C, hypertension, enlarged waist circumference, and low socioeconomic status). Matching was performed with the use of SAS 9.3 and SAS macro (GMATCH) with greedy matching in a 1 to 1 ratio without replacement, with caliper width of 0.2 times the standard deviation of the logit of the propensity scores. The discriminatory power of the fasting and nonfasting LDL-C model was evaluated with the use of the area under the receiver operating characteristic curve with the use of the Hosmer-Lemeshow C statistic. Fasting and nonfasting receiver operating characteristic curves were compared by bootstrapping methods to evaluate for a statistically significant difference. Absolute standardized differences were calculated between the fasting and nonfasting cohorts before and after propensity score matching.

We generated Kaplan-Meier curves to assess survival functions in both fasting and nonfasting cohorts. Primary analysis was performed on the matched cohort. The prognostic values of fasting versus nonfasting LDL-C measurement for primary and secondary outcomes were assessed with the use of receiver operating characteristic curves. Sensitivity analysis to assess whether the prognostic significance of fasting versus nonfasting LDL-C varies by length of fast was performed on the unmatched cohort with the use of different cut points to define fasting status (<4 versus ≥ 4 hours, <8 versus ≥ 8 hours, <12 versus ≥ 12 hours). We stratified by presence of diabetes mellitus to determine whether diabetic status influenced the prognostic significance of fasting in unmatched models. Further sensitivity analyses were performed including patients with triglycerides ≥ 400 mg/dL. We conducted sensitivity analyses at different follow-up time cut points (5, 10, and 15 years) to ensure that the significance of fasting status did not vary by follow-up length. Analyses were also performed to evaluate the influence of fasting versus nonfasting TC and triglycerides levels on all-cause and cardiovascular mortality.

Cox proportional hazards models were used to evaluate the association of LDL-C levels with outcomes after adjustment for potential confounders. Individuals were stratified by tertiles of LDL-C levels (<100 [referent], ≥ 100 – 130 , and ≥ 130 mg/dL), with the lowest tertile used as the reference group. Secondary analyses were performed with the use of clinical cut points (LDL-C levels <130 , ≥ 130 – 160 , and ≥ 160 mg/dL). Interaction between fasting status and LDL-C was tested in both primary and secondary outcome models with the use of interaction terms for fasting state and LDL-C tertiles. Two tailed P values ≤ 0.05 were considered statistically significant.

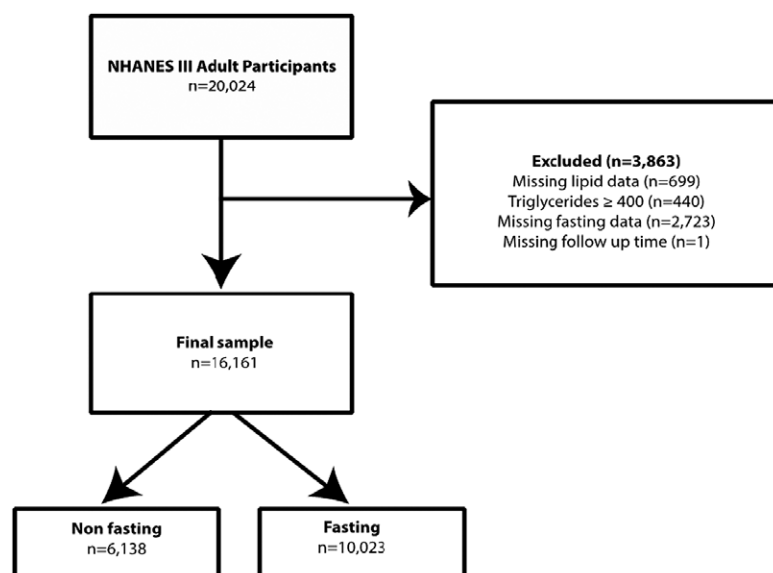


Figure 1. Participant flow chart. NHANES III indicates National Health and Nutrition Examination Survey III.

Results

Our initial data set included 20024 adults. As shown by Figure 1, we excluded those in whom LDL-C calculation was not possible ($n=699$), those with triglycerides ≥ 400 mg/dL ($n=440$; see sensitivity analyses below), and those in whom fasting time was missing ($n=2723$) or final mortality status was missing ($n=1$). Thus, our final data set included 16161 individuals representing 172332619 adults in the US population.

During a mean follow-up of 14.0 (± 0.22) years, there were a total of 3788 deaths (23.4%) and 1454 cardiovascular deaths (9.0%). Among the 16161 individuals, 10023 participants (62.0%) were fasting and 6138 individuals (38.0%) were non-fasting at the time of phlebotomy. Before propensity score matching, there were significant differences in the baseline variables between the 2 groups (Table 1). Propensity score matching matched 4299 individuals (42.9% of fasting; 70.0% of nonfasting) with similar propensity scores. After matching, there were no significant differences between the baseline characteristics of the 2 groups, and the absolute standardized differences were $<10\%$ for all matched variables, indicating an adequate match.²⁷

All-Cause Mortality

In the unmatched cohort, there was an increased risk of all-cause mortality with increasing LDL-C tertile (hazard ratios [HRs] 1 [referent], 1.57 [95% confidence interval {CI}, 1.34–1.83] [second tertile], 2.00 [95% CI, 1.70–2.33] [third tertile], respectively). Test for interaction between fasting status and all-cause mortality was not significant ($P_{\text{interaction}}=0.64$), indicating lack of association between fasting status and LDL-C with all-cause mortality (Table I in the online-only Data Supplement). Furthermore, the C statistics for fasting versus nonfasting groups for predicting all-cause mortality were similar (0.58 [95% CI, 0.57–0.60] versus 0.58 [95% CI, 0.56–0.59]; $P=0.55$; Figure I in the online-only Data Supplement), suggesting a similar prognostic value of fasting and nonfasting LDL-C levels. Analyses including individuals with triglycerides of ≥ 400 mg/dL did not show a significant difference between fasting versus nonfasting C statistics (0.58 [95% CI, 0.57–0.60] versus 0.57 [95% CI, 0.55–0.59]; $P=0.34$; Figure

II in the online-only Data Supplement). Results were largely similar on the basis of diabetic status: Fasting versus nonfasting C statistics in nondiabetics were not significantly different (0.59 [95% CI, 0.57–0.60] versus 0.59 [95% CI, 0.57–0.61]; $P=0.79$), nor were C statistics in diabetics significantly different (0.51 [95% CI, 0.46–0.56] versus 0.51 [95% CI, 0.46–0.56]; $P=0.98$; Figures III and IV in the online-only Data Supplement).

Sensitivity analysis using different cut point definitions for fasting of <4 versus ≥ 4 hours (0.58 [95% CI, 0.57–0.59] versus 0.60 [95% CI, 0.56–0.64]; $P=0.37$) or for <12 versus ≥ 12 hours (C statistics 0.57 [95% CI, 0.56–0.59] versus 0.59 [95% CI, 0.57–0.60]; $P=0.37$; Figures V and VI in the online-only Data Supplement) showed largely concordant results with the use of an 8-hour fasting cut point definition and did not show significant difference between fasting and nonfasting groups. Sensitivity analysis with the use of different follow-up times did not show significant differences between fasting and nonfasting groups (data not shown).

Within the propensity score-matched cohort, there was an increased risk of all-cause mortality by increasing LDL-C tertile (HRs 1 [referent], 1.61 [95% CI, 1.25–2.08] [second tertile], 2.10 [95% CI, 1.70–2.61] [third tertile], respectively). There was no difference between fasting versus nonfasting LDL-C and all-cause mortality within each tertile of LDL-C (Figure 2). Test for interaction between fasting status and all-cause mortality was not significant ($P_{\text{interaction}}=0.11$), indicating lack of association between fasting status and LDL-C with all-cause mortality (Table 2). Similarly, the C statistics for the fasting and nonfasting groups for predicting all-cause mortality were similar (C statistics 0.59 [95% CI, 0.56–0.61] versus 0.58 [95% CI, 0.56–0.60]; $P=0.73$; Figure 3).

In the unmatched cohort, C statistics of triglyceride levels in fasting versus nonfasting groups for predicting all-cause mortality were not significantly different (C statistics 0.60 [95% CI, 0.59–0.62] versus 0.61 [95% CI, 0.59–0.62]; $P=0.96$; Figure VII in the online-only Data Supplement). Similarly, C statistics of TC level in fasting and nonfasting groups for predicting all-cause mortality were not significantly different (C statistics

Table 1. Baseline Characteristics of Fasting and Nonfasting LDL-C Cohorts Before and After Propensity Score Matching

Clinical Variables	Before Match				After Match			
	Fasting (n=10 023)*	Nonfasting (n=6138)*	P Value	ASD, %	Fasting (n=4299)*	Nonfasting (n=4299)*	P Value	ASD, %
Age, mean (SE), y	42.68 (0.43)	45.43 (0.55)	<0.001	6.4	42.7 (0.54)	43.43 (0.57)	0.2	1.8
Women, %	51.35	54.07	0.02	5.5	51.66	53.13	0.36	2.9
White, %	75.38	77.17	0.06	4.2	76	77.04	0.41	2.5
Enlarged waist circumference, %	34.44	37.54	0.01	6.5	33.03	34.59	0.27	3.3
Smoker, %	52.23	53.24	0.29	2	52.69	52.55	0.93	0.3
Diabetes mellitus, %	4.93	8.39	<0.001	13.9	5.76	6.88	0.08	4.6
Hypertension, %	15.98	18.82	<0.001	7.5	17.42	16.47	0.45	2.5
Elevated cholesterol, %	26.62	28.66	0.07	4.6	25.89	26.78	0.52	2
Prior CVD, %	4.93	6.3	<0.001	6	4.55	4.74	0.75	0.9
Cholesterol-lowering medication, %	3.08	3.69	0.16	3.4	3.48	3.51	0.96	0.2
Low socioeconomic status, %	13.41	12.24	0.22	3.5	12.07	12.57	0.68	1.5
LDL-C, mean (SE), mg/dL†	125.04 (0.77)	123.71 (0.84)	0.07	1.9	118.55	118.33	0.84	0.3
Low HDL-C, %	35.74	35.09	0.54	1.4	33.12	33.39	0.85	0.6

ASD indicates absolute standardized difference; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; and LDL-C, low-density lipoprotein cholesterol.

*n reported on the basis of unweighted numbers; P values based on weighted values.

†To convert to mmol/L, multiply values by 0.0259.

0.60 [95% CI, 0.59–0.62] versus 0.59 [95% CI, 0.57–0.61]; $P=0.31$; Figure VIII in the online-only Data Supplement).

Cardiovascular Mortality

Outcomes for cardiovascular mortality before propensity score matching similarly demonstrated increased risk of cardiovascular mortality by increasing LDL-C tertile (HRs 1 [referent], 1.82 [95% CI, 1.38–2.39] [second tertile], 2.94 [95% CI, 2.20–3.93] [third tertile]). The test for interaction between fasting status and all-cause mortality was not significant ($P_{\text{interaction}}=0.11$), indicating lack of association between fasting status and LDL-C with cardiovascular mortality (Table I in the online-only Data Supplement). Fasting versus nonfasting C statistics were also similar (0.62 [95% CI, 0.59–0.64] versus 0.62 [95% CI, 0.60–0.64]; $P=0.80$; Figure IX in the online-only Data Supplement), suggesting similar prognostic value of fasting and nonfasting LDL-C levels on cardiovascular mortality. Fasting versus nonfasting C statistics in nondiabetics

were similar (0.62 [95% CI, 0.60–0.65] versus 0.64 [95% CI, 0.61–0.67]; $P=0.42$) as well as in diabetics (0.55 [95% CI, 0.49–0.61] versus 0.53 [95% CI, 0.47–0.60]; $P=0.67$; Figures X and XI in the online-only Data Supplement). Sensitivity analysis including individuals with triglycerides of ≥ 400 mg/dL showed largely concordant results with similar prognostic values of fasting and nonfasting LDL-C levels (0.62 [95% CI, 0.60–0.64] versus 0.61 [95% CI, 0.58–0.63]; $P=0.51$; Figure XII in the online-only Data Supplement).

Sensitivity analysis with the use of different cut points for fasting of <4 versus ≥ 4 hours (0.62 [95% CI, 0.60–0.64] versus 0.65 [95% CI, 0.59–0.70]; $P=0.34$; Figure XIII in the online-only Data Supplement) or for <12 versus ≥ 12 hours (0.61 [95% CI, 0.59–0.63] versus 0.63 [95% CI, 0.61–0.66]; $P=0.27$; Figure XIV in the online-only Data Supplement) showed largely concordant results with an 8-hour fasting cut point definition, showing similar prognostic value of fasting versus nonfasting LDL-C. Sensitivity analysis with the use of different follow-up time cut points did not show significant differences between fasting and nonfasting groups (data not shown).

In the propensity score-matched cohort, there was an increased risk of cardiovascular mortality by increasing LDL-C tertile (HR 1 [referent], 1.68 [95% CI, 1.13–2.51] [second tertile], 3.04 [95% CI, 2.00–4.62] [third tertile]). Test for interaction between fasting status and cardiovascular mortality remained nonsignificant ($P_{\text{interaction}}=0.34$; Table 2), indicating lack of association between fasting status and LDL-C with cardiovascular mortality. Similarly, the C statistics for the fasting and nonfasting groups for predicting cardiovascular mortality were similar (0.62 [95% CI, 0.60–0.66] versus 0.62 [95% CI, 0.60–0.66]; $P=0.96$; Figure 4), suggesting similar prognostic value of fasting and nonfasting LDL-C.

In the unmatched cohort, C statistics of triglyceride levels in fasting versus nonfasting groups predicting cardiovascular mortality were not significantly different (C statistics

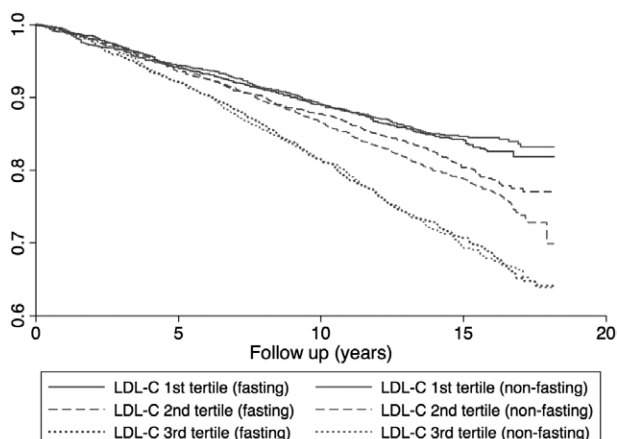


Figure 2. Kaplan-Meier curve for fasting vs nonfasting low-density lipoprotein cholesterol (LDL-C) levels and all-cause mortality.

Table 2. Cox Proportional Hazards Model of All-Cause and Cardiovascular Mortality by LDL-C Level in Fasting and Nonfasting Cohorts in Matched Participants

Outcome	Fasting			Nonfasting		
	LDL-C Range, mg/dL*	Hazard Ratio (95% CI)	P Value	LDL-C Range, mg/dL*	Hazard Ratio (95% CI)	P Value
All-cause mortality						
LDL-C tertile 1	≤99.60	1 (referent)		≤100.73	1 (referent)	
LDL-C tertile 2	99.60–129.68	1.61 (1.25–2.08)	<0.001	100.73–129.22	1.21 (0.92–1.60)	0.17
LDL-C tertile 3	129.68–361.40	2.10 (1.70–2.61)	<0.001	129.22–438.00	2.23 (1.76–2.83)	<0.001
LDL-C × fasting status			0.11			
Cardiovascular mortality						
LDL-C tertile 1	≤99.60	1 (referent)		≤100.73	1 (referent)	
LDL-C tertile 2	99.60–129.68	1.68 (1.13–2.51)	0.012	100.73–129.22	1.59 (0.97–2.61)	0.063
LDL-C tertile 3	129.68–361.40	3.04 (2.00–4.62)	<0.001	129.22–438.00	4.00 (2.58–6.19)	<0.001
LDL-C × fasting status			0.34			

CI indicates confidence interval; and LDL-C, low-density lipoprotein cholesterol.

*To convert to mmol/L, multiply values by 0.0259.

0.62 [95% CI, 0.60–0.64] versus 0.61 [95% CI, 0.59–0.64], respectively; $P=0.81$; Figure XV in the online-only Data Supplement). The C statistics of TC levels for cardiovascular mortality in fasting and nonfasting groups were similarly not significantly different (C statistics 0.64 [95% CI, 0.62–0.66] versus 0.63 [95% CI, 0.60–0.65]; $P=0.49$; Figure XVI in the online-only Data Supplement).

Sensitivity analyses without the use of survey weights yielded largely similar results for both primary and secondary outcomes (data not shown).

Discussion

Every year, millions of blood samples are drawn across the world for the measurement of lipid panels, in particular LDL-C, with most national and international guidelines recommending a fasting panel for such measurement. The results of this nationally representative cohort study with 16 161 individuals followed for 14.0 years representing >172 million adults in the US population show similar prognostic value of nonfasting LDL-C levels compared with fasting LDL-C levels for prediction of both all-cause mortality and cardiovascular mortality, thereby questioning this traditional practice.

Fasting Lipid Panel

The origin of the need for a fasting lipid panel is not entirely clear. It is known that certain lipid parameters, especially triglycerides, may be sensitive to fasting status and to the content of the last meal (and in particular high-fat loads). As such, fasting panels have been recommended to provide accurate lipid measurements. However, there are a number of drawbacks with this approach, including the need to reschedule a visit for a separate blood draw if a patient is not fasting, thereby decreasing compliance and delaying treatment. Moreover, because individuals are in a nonfasting state for the majority of time during the day, obtaining a fasting lipid panel may not accurately reflect postprandial abnormalities in lipid metabolism, and thus obtaining a nonfasting lipid panel may reflect a more relevant physiological state.^{7,8} Obtaining a nonfasting blood sample may also offer the opportunity to assess nonfasting blood glucose, which may add accuracy in identifying glucose intolerance.^{28,29}

Recently, several studies have questioned the need for a fasting lipid profile, primarily involving the use of nonfasting triglycerides in cardiovascular risk assessment. Although the role of triglycerides as an independent cardiovascular risk factor is less clear than the role of LDL-C, studies have shown that postprandial triglycerides are similar or possibly even superior to fasting triglycerides in cardiovascular risk prediction.^{9,10,30–32} Recent recommendations suggest a potential move toward the use of nonfasting triglycerides for risk assessment, but further research is needed before definitive recommendations can be made.^{33,34}

Fewer studies have addressed the use of nonfasting LDL-C in risk prediction. Numerous animal, population-based, and clinical studies have shown that LDL-C is associated with increased cardiovascular mortality,^{35–37} with genetic studies also showing a causative mortality linkage.^{38–40} These studies

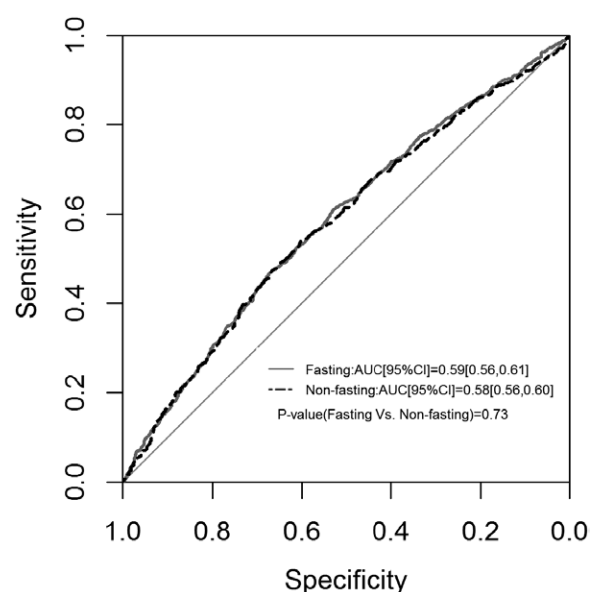


Figure 3. Prognostic value of fasting vs nonfasting low-density lipoprotein cholesterol levels on all-cause mortality in the matched cohort. AUC indicates area under the curve; and CI, confidence interval.

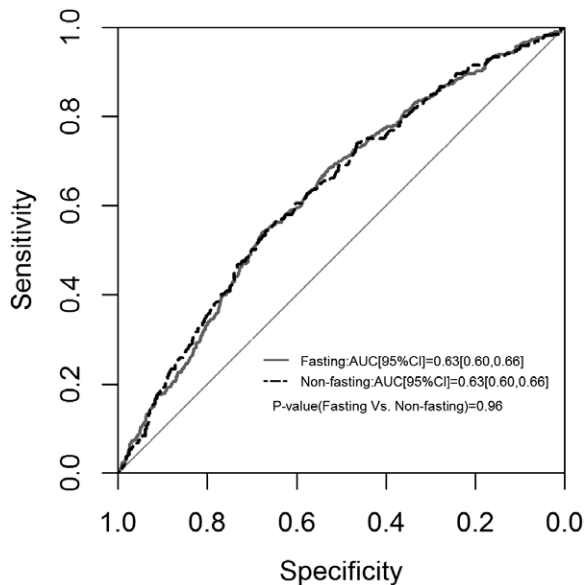


Figure 4. Prognostic value of fasting vs nonfasting low-density lipoprotein cholesterol levels on cardiovascular mortality in the matched cohort. AUC indicates area under the curve; and CI, confidence interval.

have traditionally used fasting LDL-C as convention, and thus recommendations made by various agencies such as the ATP-III have generally been for obtaining fasting lipids. However, multiple trials, including the Heart Protection Study and Anglo-Scandinavian Cardiac Outcomes Trial, included individuals who were not fasting during the time of phlebotomy when the effects of lipid-lowering agents were analyzed, suggesting that some of the data supporting lipid-lowering therapy actually springs from studies involving nonfasting individuals.^{41,42}

Prior studies examining cardiovascular events have demonstrated increased cardiovascular risk by LDL-C level for individuals in a nonfasting state,^{21,43–45} but none have examined long-term mortality outcomes in a representative sample. A recent population-based study by Sidhu and Naugler⁴ in 2012 showed that in a population-based sample, lipid levels by subclass varied little with respect to fasting time and by >10% for LDL-C. Other studies also have shown little variation with postprandial LDL-C levels compared with fasting levels.^{44,46} These studies suggest that the variation between fasting and nonfasting LDL-C levels, if any, is small. Our study is the first to show that in a population-based sample, the association between LDL-C and cardiovascular and all-cause mortality does not differ by fasting status. Our analyses also suggest that fasting TC and triglyceride levels do not have improved prognostic significance over nonfasting levels.

These data provide further evidence that it may be unnecessary to use fasting lipid levels to risk stratify patients. In our primary analyses, we excluded patients with a triglyceride level ≥ 400 mg/dL or $\approx 2\%$ of the total population. However, the results were largely concordant in a sensitivity analysis after the aforementioned patients were included. Thus, our results are broadly applicable to all patients undergoing a blood draw to assess the lipid panel and are applicable to LDL-C measurement as well as triglyceride and TC measurement.

2013 American College of Cardiology/American Heart Association Guidelines and LDL-C Measurement

The recently published 2013 American College of Cardiology/American Heart Association guidelines recommend obtaining fasting lipids, but the guidelines do not specify the length of time for fasting or cite data to support the need for fasting LDL-C. The guidelines move away from recommending lowering LDL-C to specific targets but recommend moderate- to high-intensity statin for patients with atherosclerotic cardiovascular disease, an intensity of statins that would reduce baseline LDL-C by 40% to 50%, which can be assessed easily with a nonfasting sample.

This has important implications in clinical practice. Requiring patients to fast causes patients increased stress, potential hypoglycemia in patients with diabetes mellitus, increased transportation costs, and potentially missed days of work. In addition, the inconvenience of fasting may also delay treatment or diagnosis of hyperlipidemia if patients are unable to fast before clinic visits. Enabling patients to obtain nonfasting lipid profiles would improve patient satisfaction and potentially avoid delays in detection and treatment of hyperlipidemia while at the same time providing prognostic value similar to that of a nonfasting LDL-C value.

Limitations

The design of this study with the use of data from an existing database limits our ability to prove that fasting and nonfasting lipids have the same prognostic value. In addition, fasting and nonfasting LDL-C were not collected on the same individuals. Moreover, in nonfasting patients, data were not available on the composition of patient meals.

Conclusions

In conclusion, the results of this study of 16 161 individuals followed for 14.0 years and representative of the US population fail to show a superior prognostic value of fasting LDL-C levels compared with nonfasting LDL-C levels for the prediction of both all-cause and cardiovascular mortality. Our study suggests that a nonfasting LDL-C measurement offers a more convenient method of phlebotomy while preserving the prognostic value of the test. National and international guideline societies should reconsider the need for fasting LDL-C. Similar results were seen for triglycerides and TC, thus questioning the value of obtaining fasting lipid profile.

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Disclosures

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CLINICAL PERSPECTIVE

National and international guidelines recommend fasting lipid panel measurement for risk stratification. However, the prognostic value of fasting versus nonfasting low-density lipoprotein cholesterol is uncertain. Using data from the National Health and Nutrition Examination Survey (NHANES), we found that fasting low-density lipoprotein cholesterol yielded prognostic value similar to that of nonfasting low-density lipoprotein cholesterol for all-cause mortality (C statistics 0.59 [95% confidence interval, 0.57–0.61] versus 0.58 [95% confidence interval, 0.56–0.60; $P=0.73$] as well as cardiovascular mortality (fasting versus nonfasting C statistics 0.62 [95% confidence interval, 0.60–0.66] versus 0.62 [95% confidence interval, 0.60–0.66]; $P=0.96$; $P_{\text{interaction}}=0.34$). This study shows similar prognostic value of fasting versus nonfasting low-density lipoprotein cholesterol on long-term mortality in a nationally representative US cohort. National and international agencies should consider reevaluating the recommendation that patients fast before a lipid panel is obtained.

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Prognostic Value of Fasting Versus Nonfasting Low-Density Lipoprotein Cholesterol Levels on Long-Term Mortality: Insight From the National Health and Nutrition Examination Survey III (NHANES-III)

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SUPPLEMENTAL MATERIAL

Supplemental Table 1 – All Cause and Cardiovascular Mortality by LDL-C Level in Fasting and Non-Fasting Cohorts Prior to Propensity Score Matching

Outcome	Fasting			Non-Fasting		
	LDL-C (mg/dL)*	Hazard Ratio (95% CI)	P Value	LDL-C (mg/dL)*	Hazard Ratio (95% CI)	P Value
All-Cause Mortality						
LDL-C 1 st tertile (reference)	≤106.41	1 (referent)		≤104.76	1 (referent).	
LDL-C 2 nd tertile	106.41-138.28	1.57 (1.34-1.83)	<0.001	104.76-137.11	1.28 (1.05-1.55)	0.015
LDL-C 3 rd tertile	138.28-380.00	2.00 (1.70-2.33)	<0.001	137.11-438.00	2.07 (1.67-2.57)	<0.001
LDL-C x Fasting Status			0.11			
CV Mortality						
LDL-C 1 st tertile (reference)	≤106.41	1 (referent)		≤104.76	1 (referent)	
LDL-C 2 nd tertile	106.41-138.28	1.82 (1.38-2.39)	<0.001	104.76-137.11	1.62 (1.15-2.28)	<0.001
LDL-C 3 rd tertile	138.28-380.00	2.94 (2.20-3.93)	<0.001	137.11-438.00	6.18 (2.21-4.76)	<0.001
LDL-C x Fasting Status			0.64			

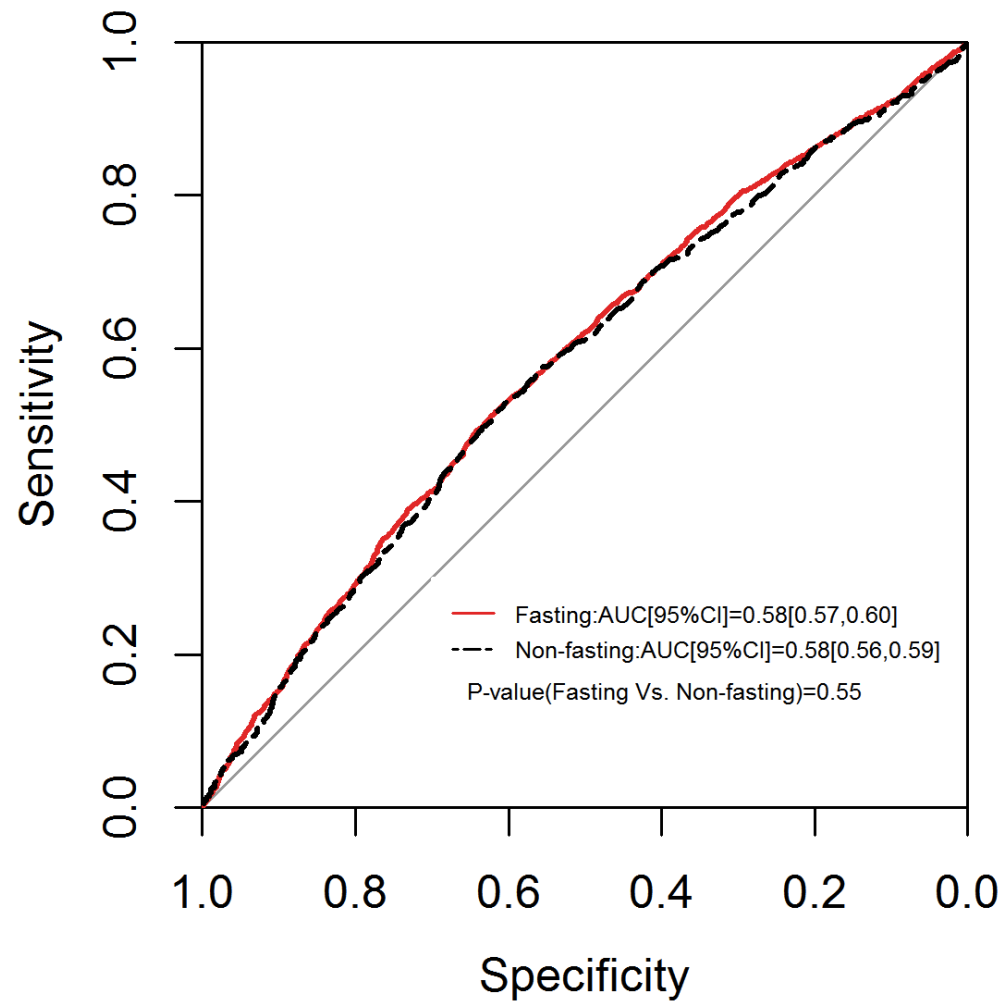
Abbreviations: CV = cardiovascular; LDL-C = low density lipoprotein cholesterol

*To convert to mmol/L, multiply values by 0.0259

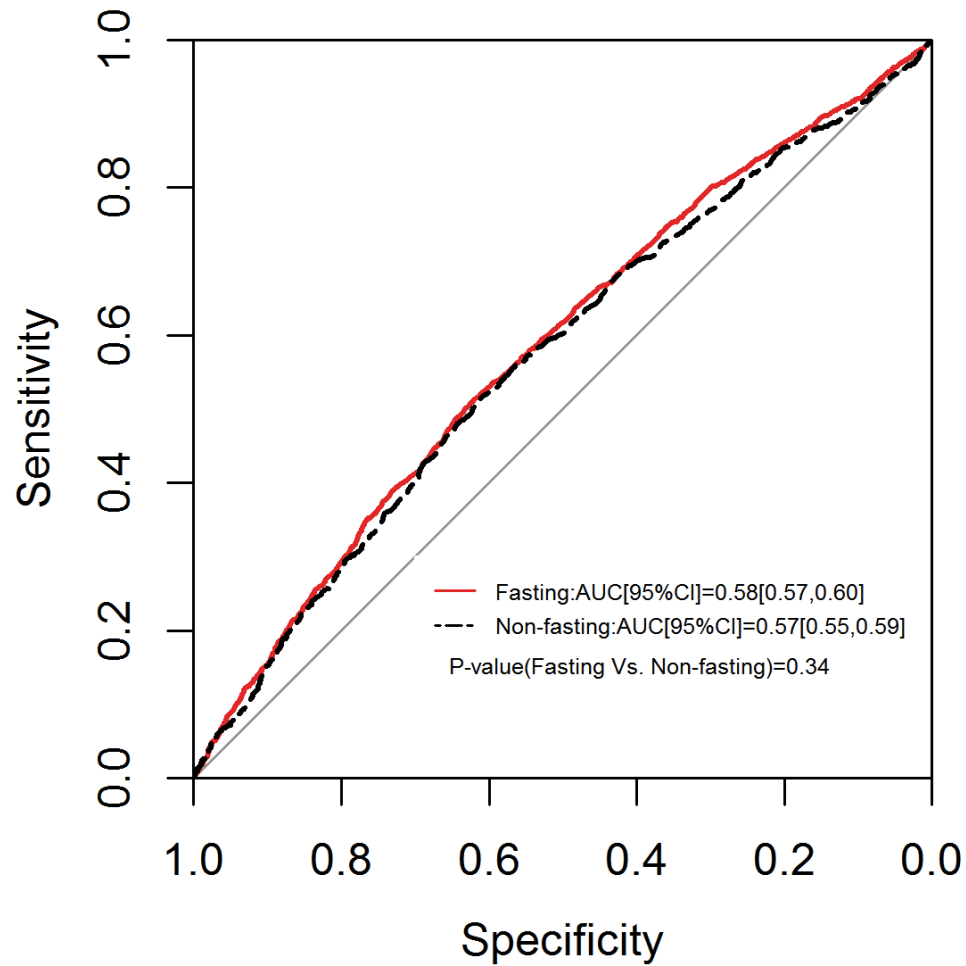
FIGURE LEGENDS

- Figure 1** - Prognostic value of fasting vs. non-fasting LDL-C level on all-cause mortality in the unmatched cohort
- Figure 2** - Sensitivity analysis: Prognostic value of fasting vs. non-fasting LDL-C level including patients with triglycerides ≥ 400 mg/dL on all-cause mortality in the unmatched cohort
- Figure 3** - Prognostic value of fasting vs. non-fasting LDL-C level on all-cause mortality in patients without diabetes in the unmatched cohort
- Figure 4** - Prognostic value of fasting vs. non-fasting LDL-C level on all-cause mortality in diabetic patients in the unmatched cohort
- Figure 5** - Sensitivity Analysis: Prognostic value of fasting (<4 hours) vs. non-fasting (≥ 4 hours) LDL-C level on all-cause mortality in the unmatched cohort
- Figure 6** - Sensitivity Analysis: Prognostic value of fasting (<12 hours) vs. non-fasting (≥ 12 hours) LDL-C level on all-cause mortality in the unmatched cohort
- Figure 7** - Prognostic value of fasting vs. non-fasting triglyceride level on all-cause mortality in the unmatched cohort
- Figure 8** - Prognostic value of fasting vs. non-fasting total cholesterol level on all-cause mortality in the unmatched cohort
- Figure 9** - Prognostic value of fasting vs. non-fasting LDL-C level on cardiovascular mortality in the unmatched cohort
- Figure 10** - Prognostic value of fasting vs. non-fasting LDL-C level on cardiovascular mortality in patients without diabetes in the unmatched cohort
- Figure 11** - Prognostic value of fasting vs. non-fasting LDL-C level on cardiovascular mortality in diabetic patients in the unmatched cohort
- Figure 12** - Sensitivity analysis: Prognostic value of fasting vs. non-fasting LDL-C level including those with triglycerides ≥ 400 mg/dL on cardiac mortality in the unmatched cohort
- Figure 13** - Sensitivity Analysis: Prognostic value of fasting (<4 hours) vs. non-fasting (≥ 4 hours) LDL-C level on cardiovascular mortality in the unmatched cohort
- Figure 14** - Sensitivity Analysis: Prognostic value of fasting (<12 hours) vs. non-fasting (≥ 12 hours) LDL-C level on cardiovascular mortality in the unmatched cohort
- Figure 15** - Prognostic value of fasting vs. non-fasting triglyceride level on cardiovascular mortality in the unmatched cohort
- Figure 16** - Prognostic value of fasting vs. non-fasting cholesterol level on cardiovascular mortality in the unmatched cohort

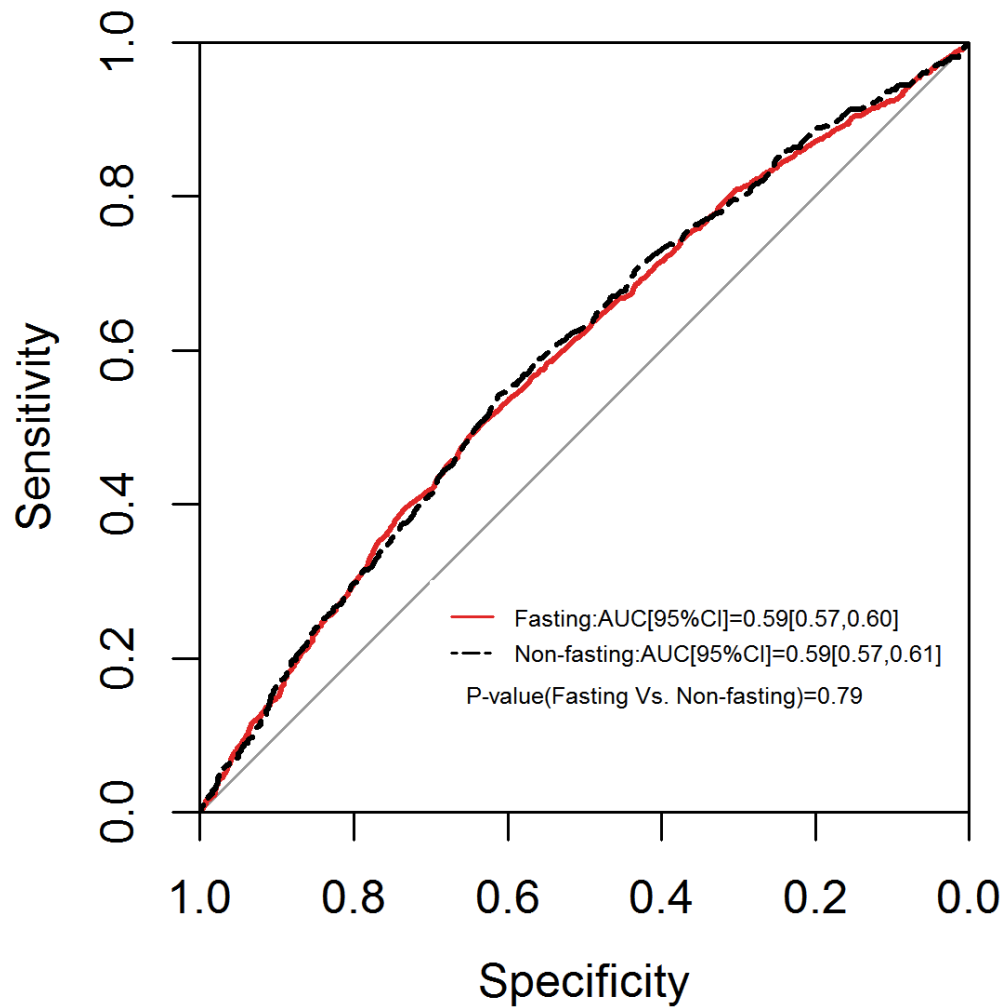
Supplemental Figure 1 – Prognostic value of fasting vs. non-fasting LDL-C level
on all-cause mortality in the unmatched cohort



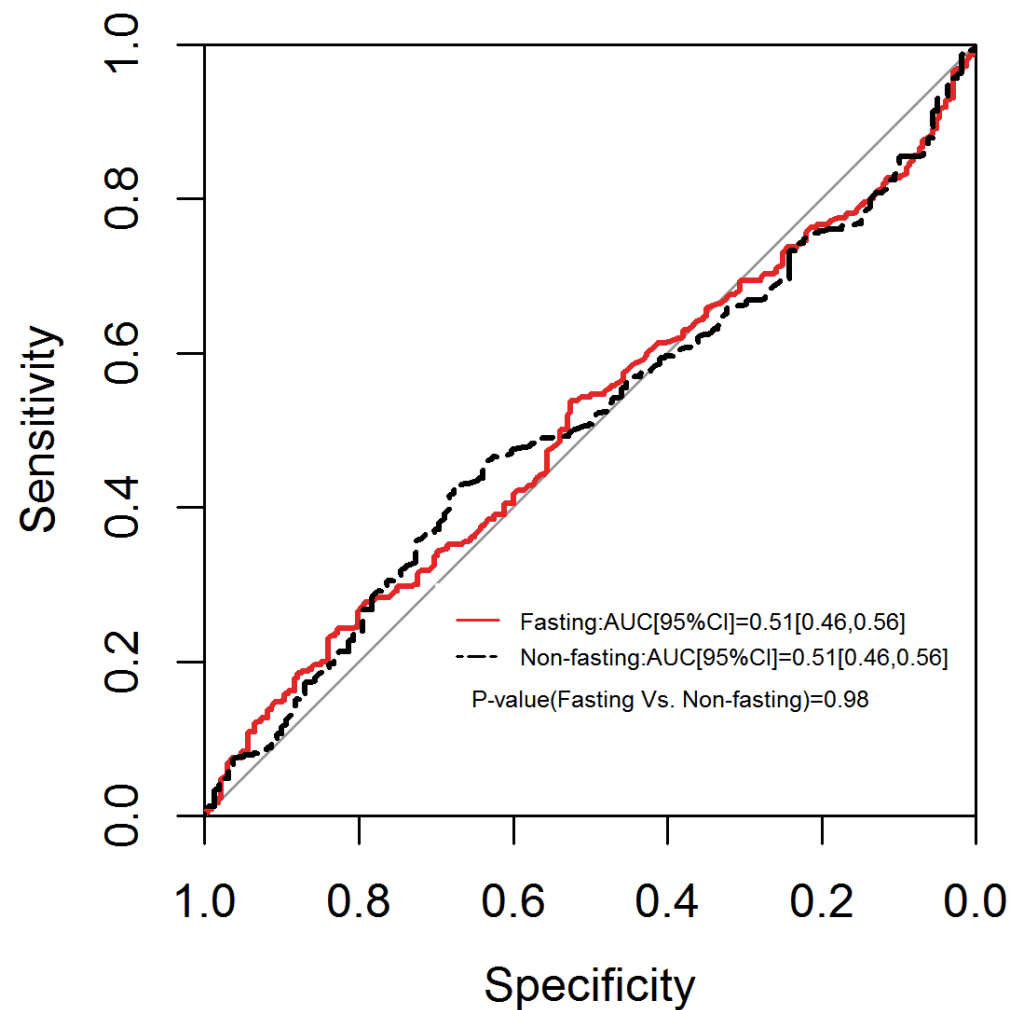
Supplemental Figure 2 – Sensitivity analysis: Prognostic value of fasting vs. non-fasting LDL-C level including those with triglycerides ≥ 400 mg/dL on all-cause mortality in the unmatched cohort



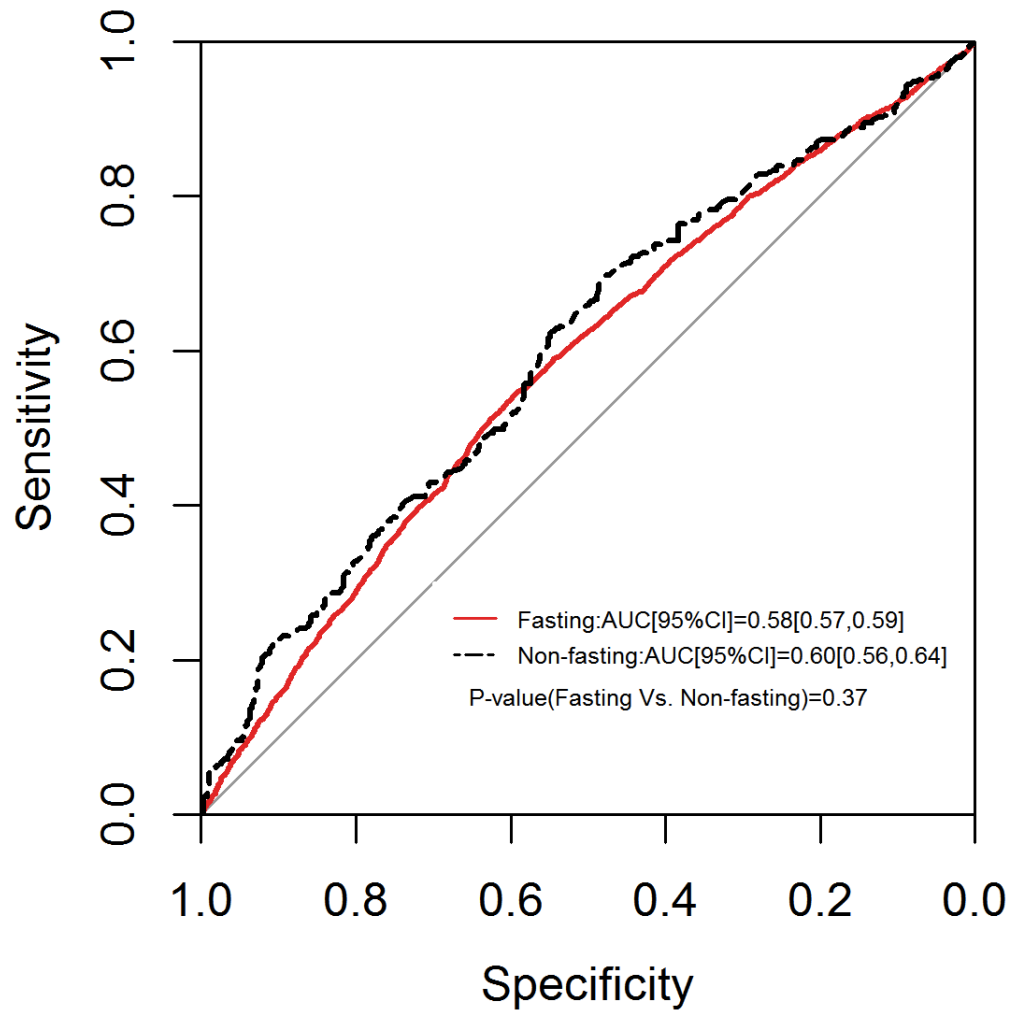
Supplemental Figure 3 – Prognostic value of fasting vs. non-fasting LDL-C level
on all-cause mortality in patients without diabetes in the unmatched cohort



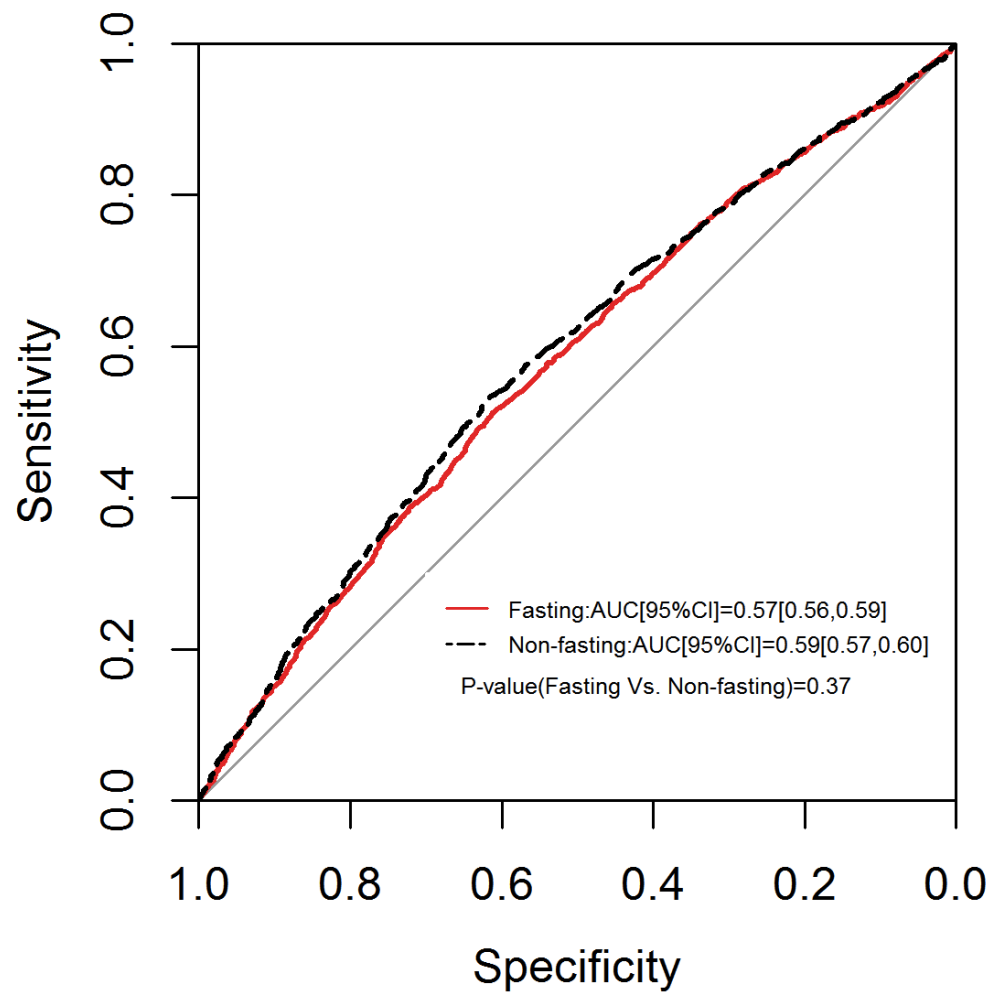
Supplemental Figure 4 – Prognostic value of fasting vs. non-fasting LDL-C level
on all-cause mortality in diabetic patients in the unmatched cohort



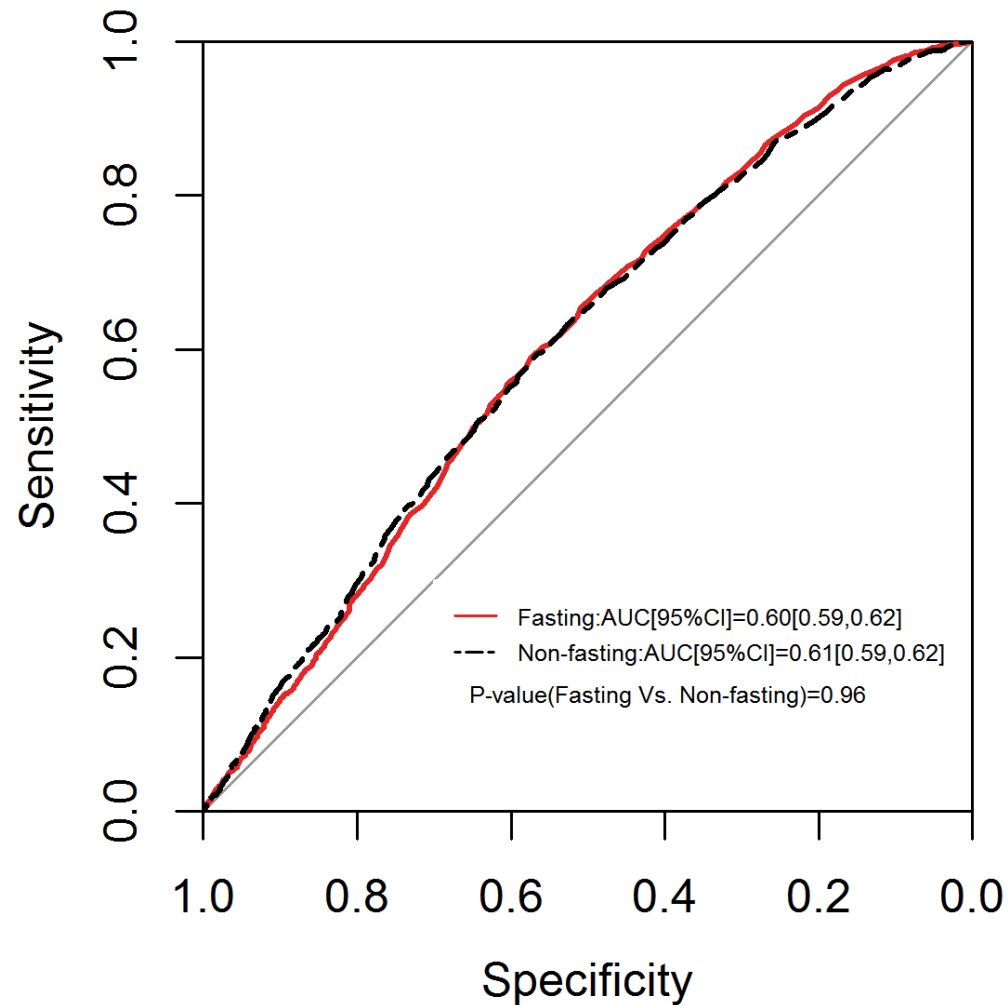
Supplemental Figure 5 – Sensitivity Analysis: Prognostic value of fasting (<4 hours) vs. non-fasting (≥ 4 hours) LDL-C level on all-cause mortality in the unmatched cohort



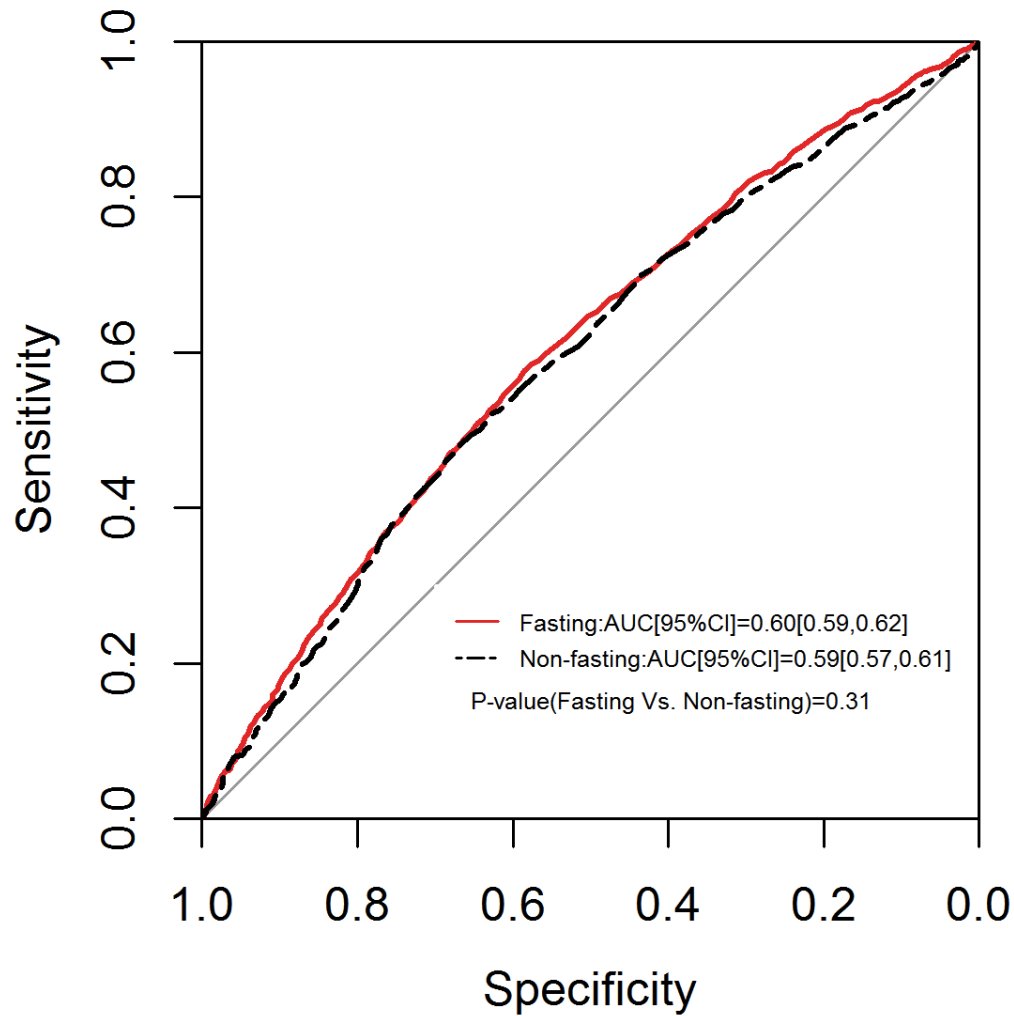
Supplemental Figure 6 - Sensitivity Analysis: Prognostic value of fasting (<12 hours) vs. non-fasting (≥ 12 hours) LDL-C level on all-cause mortality in the unmatched cohort



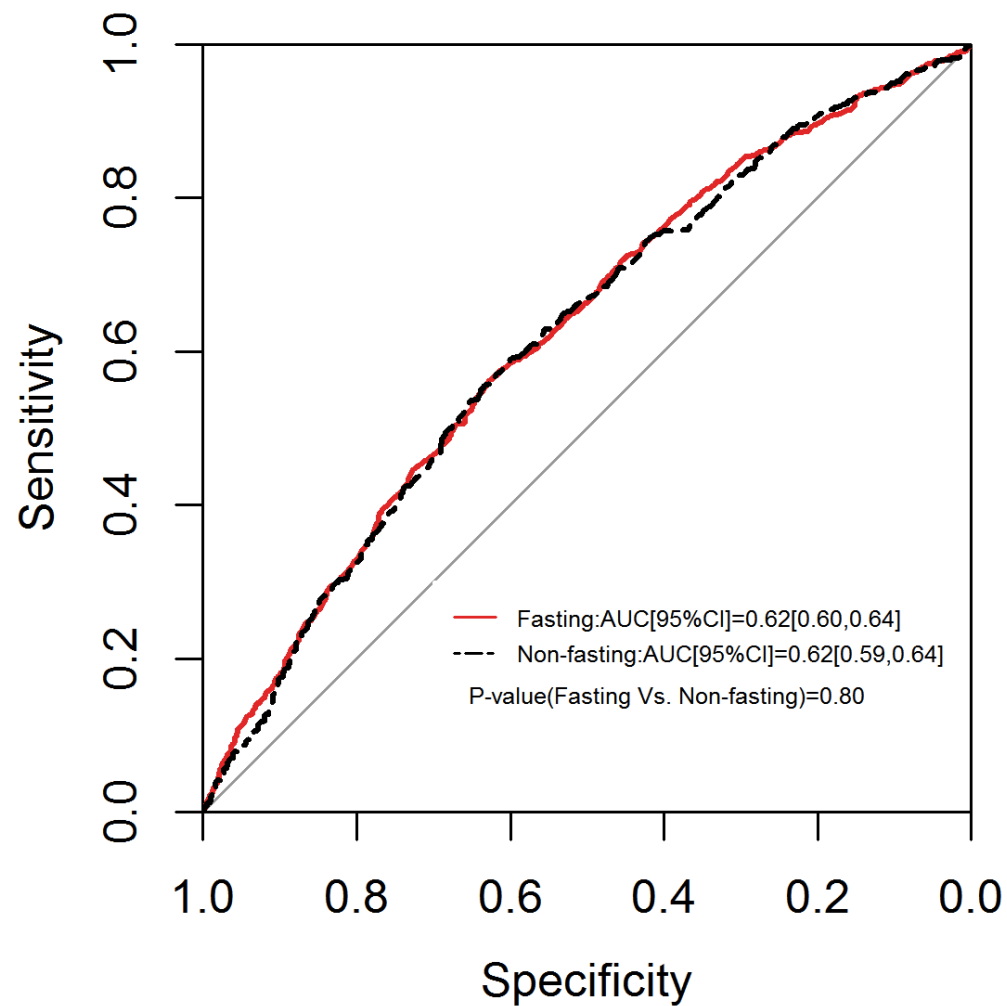
Supplemental Figure 7 –Prognostic value of fasting vs. non-fasting triglyceride level on all-cause mortality in the unmatched cohort



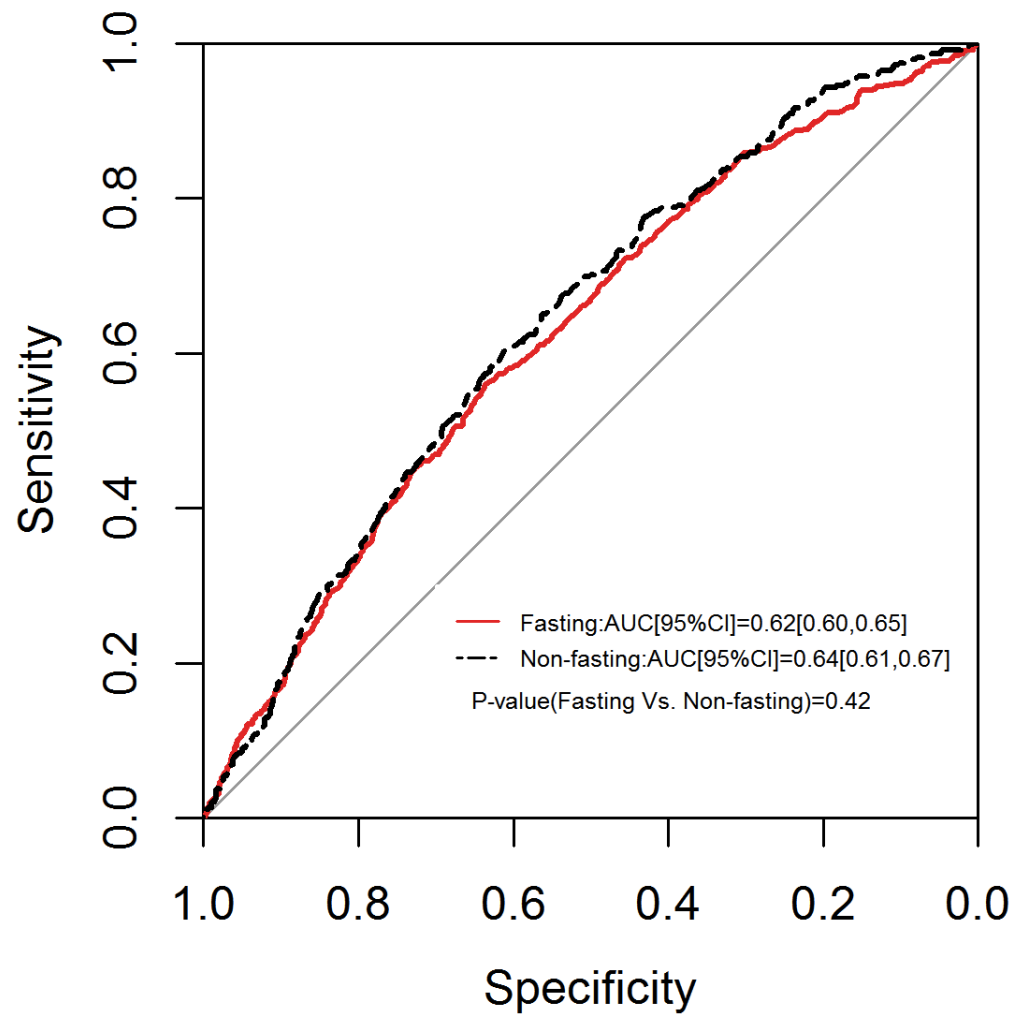
Supplemental Figure 8 –Prognostic value of fasting vs. non-fasting total cholesterol level on all-cause mortality in the unmatched cohort



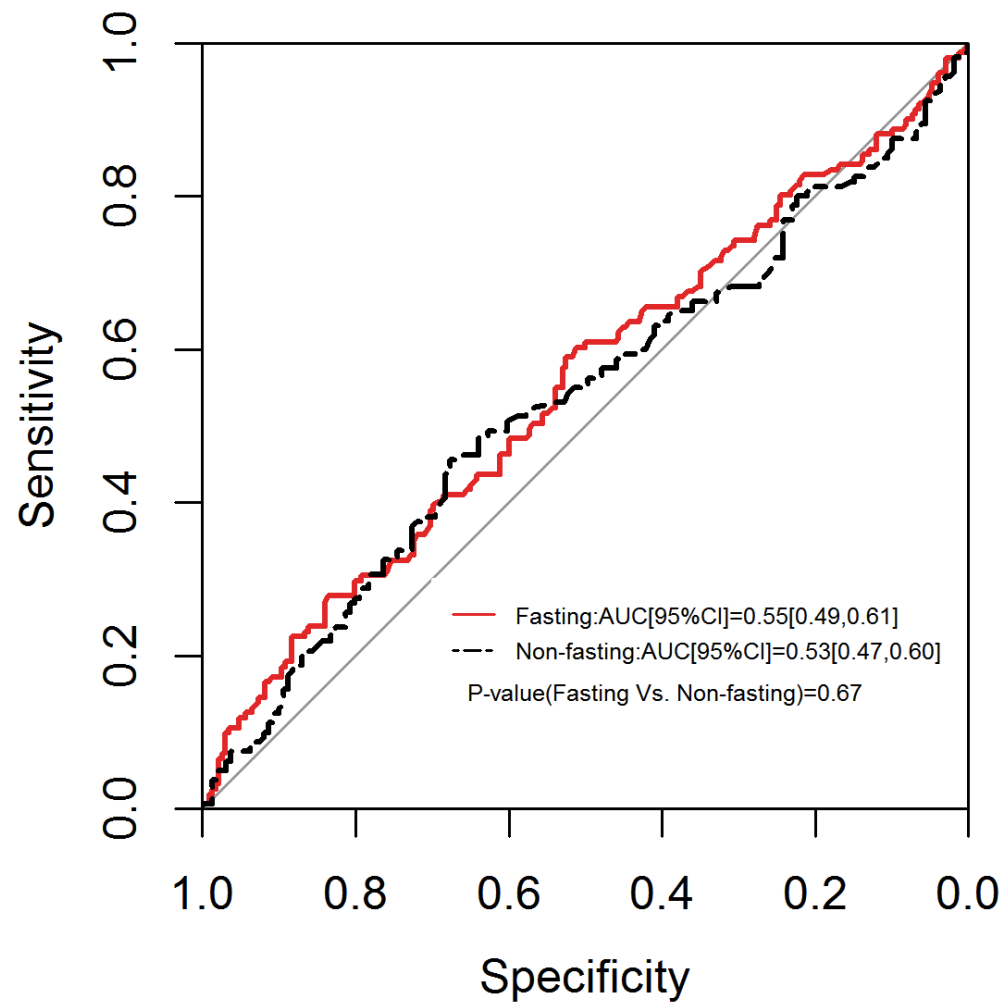
Supplemental Figure 9 – Prognostic value of fasting vs. non-fasting LDL-C level
on cardiovascular mortality in the unmatched cohort



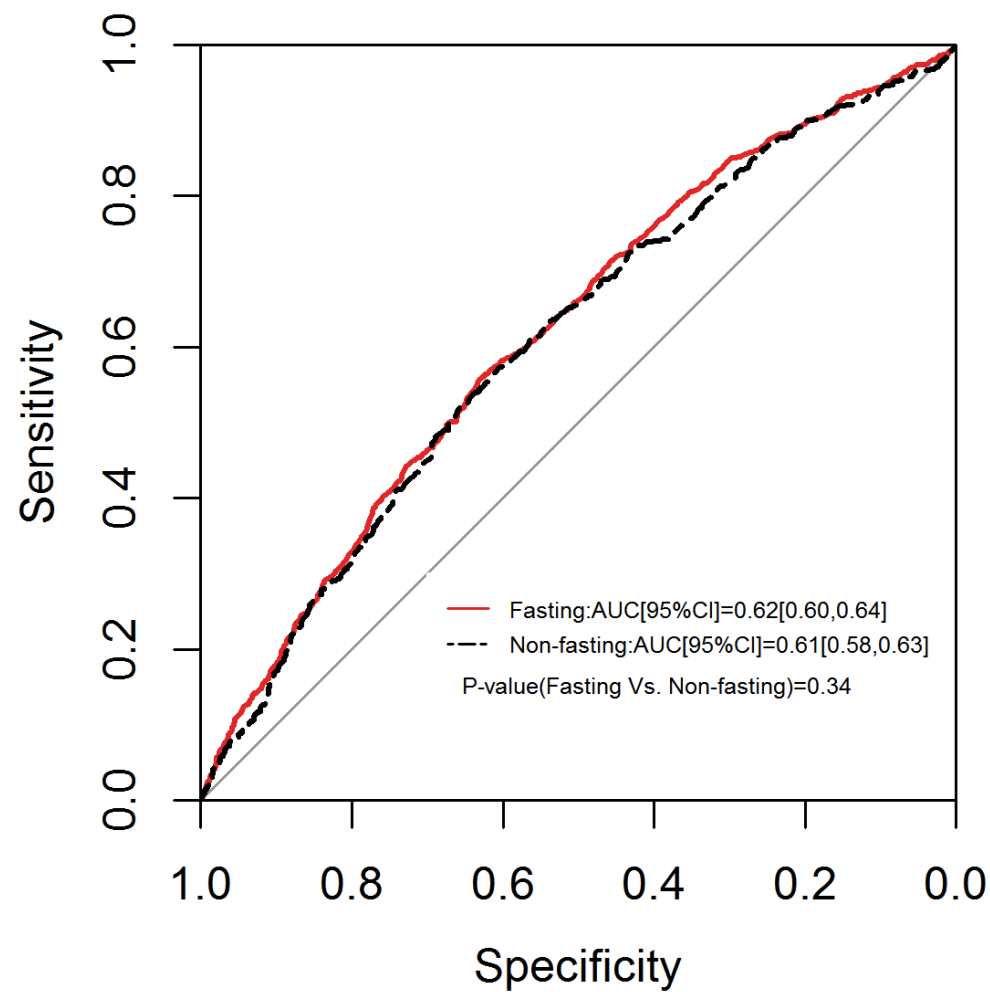
Supplemental Figure 10 – Prognostic value of fasting vs. non-fasting LDL-C level on cardiovascular mortality in patients without diabetes in the unmatched cohort



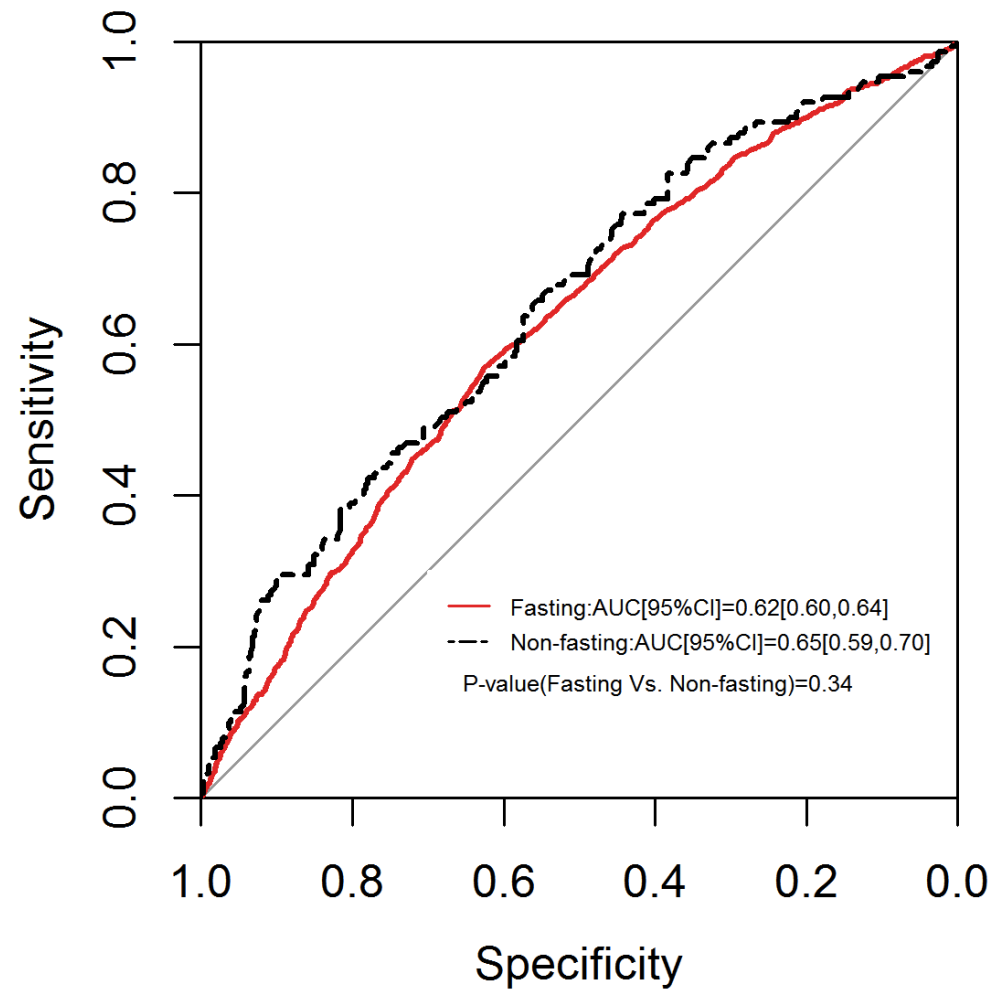
Supplemental Figure 11 – Prognostic value of fasting vs. non-fasting LDL-C level on cardiovascular mortality in diabetic patients in the unmatched cohort



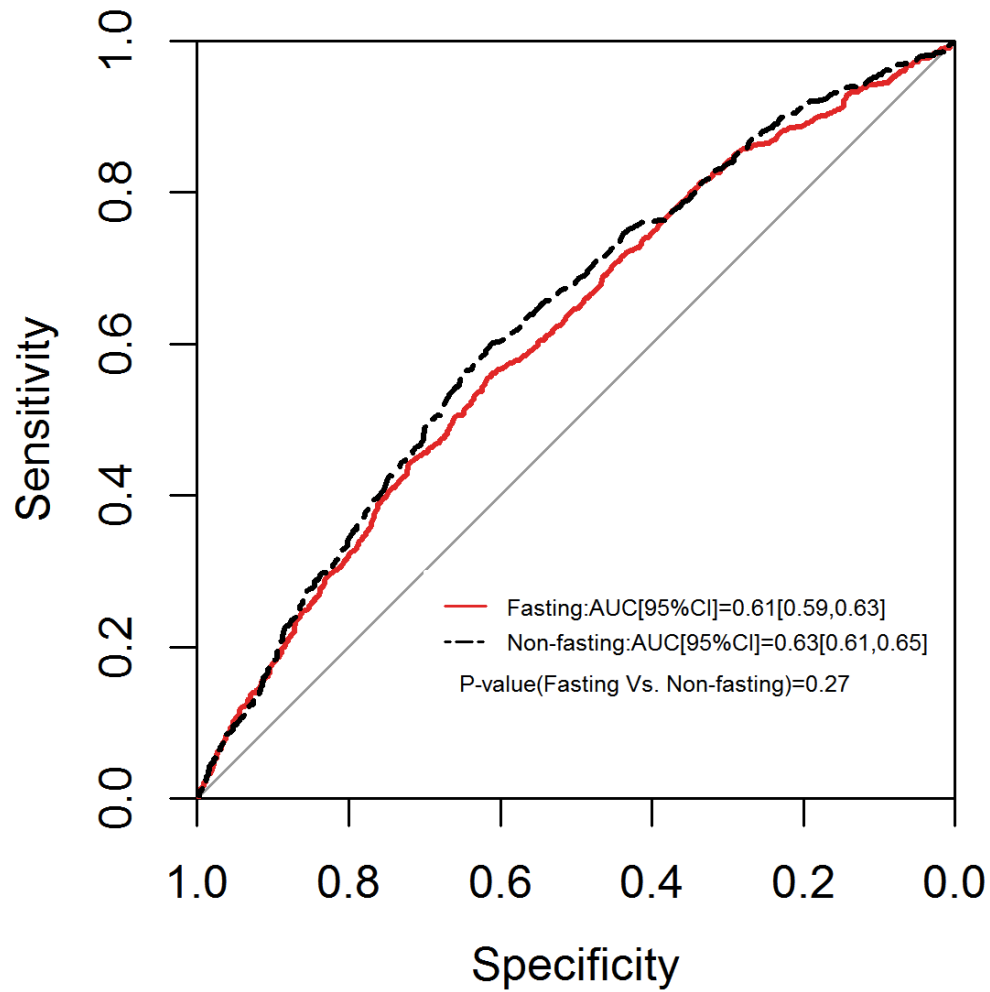
Supplemental Figure 12 - Sensitivity analysis: Prognostic value of fasting vs. non-fasting LDL-C level including those with triglycerides ≥ 400 mg/dL on cardiovascular mortality in the unmatched cohort



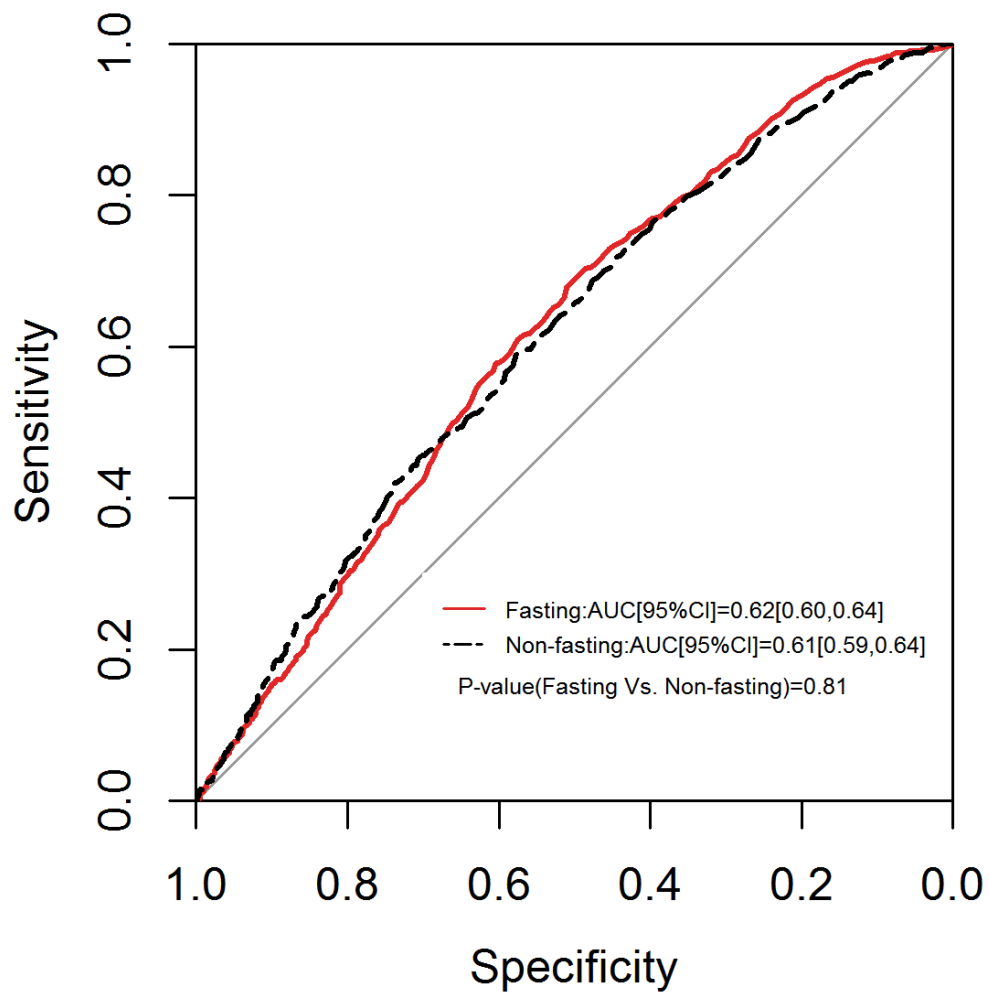
Supplemental Figure 13 – Sensitivity Analysis: Prognostic value of fasting (<4 hours) vs. non-fasting (≥ 4 hours) LDL-C level on cardiovascular mortality in the unmatched cohort



Supplemental Figure 14 – Sensitivity Analysis: Prognostic value of fasting (<12 hours) vs. non-fasting (≥ 12 hours) LDL-C level on cardiovascular mortality in the unmatched cohort



Supplemental Figure 15 –Prognostic value of fasting vs. non-fasting triglyceride level on cardiovascular mortality in the unmatched cohort



Supplemental Figure 16 –Prognostic value of fasting vs. non-fasting total cholesterol level on cardiovascular mortality in the unmatched cohort

