Lipoprotein(a) and Risk of Type 2 Diabetes

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BACKGROUND: Previous studies have demonstrated that cardiovascular risk is higher with increased lipoprotein(a) [Lp(a)]. Whether Lp(a) concentration is related to type 2 diabetes is unclear.

METHODS: In 26 746 healthy US women (mean age 54.6 years), we prospectively examined baseline Lp(a) concentrations and incident type 2 diabetes (n = 1670) for a follow-up period of 13 years. We confirmed our findings in 9652 Danish men and women with prevalent diabetes (n = 419). Analyses were adjusted for risk factors that included age, race, smoking, hormone use, family history, blood pressure, body mass index, hemoglobin A_{1c} (Hb A_{1c}), C-reactive protein, and lipids.

RESULTS: Lp(a) was inversely associated with incident diabetes, with fully adjusted hazard ratios (HRs) and 95% CIs for quintiles 2–5 vs quintile 1 of 0.87 (0.75–1.01), 0.80 (0.68–0.93), 0.88 (0.76–1.02), and 0.78 (0.67–0.91); *P* for trend 0.002. The association was stronger in nonfasting women, for whom respective HRs were 0.79 (0.58–1.09), 0.78 (0.57–1.08), 0.66 (0.46–0.93), and 0.56 (0.40–0.80); *P* for trend 0.001; *P* for interaction with fasting status 0.002. When we used Lp(a) ≥10 mg/L and Hb A_{1c} <5% as reference values, the adjusted HRs were 1.62 (0.91–2.89) for Lp(a) <10 mg/L and Hb A_{1c} <5%, 3.50 (3.06–4.01) for Lp(a)≥10 mg/L and Hb A_{1c} 5%–<6.5%, and 5.36 (4.00–7.19) for Lp(a) <10 mg/L and Hb A_{1c} 5%–<6.5%. Results were similar in nonfasting Danish men and women, for whom adjusted odds ratios were 0.75 (0.55–1.03), 0.64 (0.46–0.88), 0.74 (0.54–1.01), and 0.58 (0.42–0.79) for Lp(a) quintiles 2–5 vs quintile 1; *P* for trend 0.002.

CONCLUSIONS: Our results indicated that Lp(a) was associated inversely with risk of type 2 diabetes independently of risk factors, in contrast to prior findings of positive associations of Lp(a) with cardiovascular risk.

Lipoprotein(a) [Lp(a)],[7] a subtype of LDL that carries apolipoprotein(a) [apo(a)], has been associated with risk of cardiovascular disease (CVD) *(1)*, but the role of Lp(a) in type 2 diabetes is unclear. Since the discovery of Lp(a) by Berg in 1963, increased Lp(a) concentrations have been associated with a higher risk of CVD in most studies *(2)*. Also, increased concentrations of Lp(a) have been associated with higher risk of CVD in diabetic patients *(3–5)*. However, it is unclear if Lp(a) concentrations are related to risk of type 2 diabetes or insulin resistance *(6)*. It has been suggested that hyperinsulinemia lowers Lp(a) concentrations *(7, 8)*, but results of prior case-control studies have been inconclusive *(6)*. Some of these studies found no change in Lp(a) concentrations in patients with type 2 diabetes *(9)*, whereas others found either higher or lower Lp(a) concentrations *(10, 11)*.

Case-control studies are susceptible to bias, because the disease (e.g., diabetes) may alter lipoprotein concentrations; thus, prospective studies are better for determining risk-factor associations. Therefore, we conducted the first prospective study of Lp(a) concentration and risk of type 2 diabetes in a cohort of healthy US women. Based on prior work involving this cohort, which suggested that nonfasting concentrations of certain lipids may be superior to fasting concentrations for risk prediction *(12, 13)*, we also examined whether fasting status modified the association of Lp(a) with type 2 diabetes. Finally, we replicated our findings in a general population of men and women from Denmark *(14)*.

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[7] Nonstandard abbreviations: Lp(a), lipoprotein(a); apo(a), apolipoprotein(a); CVD, cardiovascular disease; WHS, Women's Health Study; Hb A_{1c}, hemoglobin A_{1c}; CCHS, Copenhagen City Heart Study; hsCRP, high-sensitivity C-reactive protein; BMI, body mass index; HR, hazard ratio; OR, odds ratio.

Materials and Methods

STUDY POPULATIONS

The Women's Health Study (WHS) is a completed randomized, double-blinded, placebo-controlled clinical trial of low-dose aspirin and vitamin E in US female health-care professionals *(15)*. Eligible participants were apparently healthy women, ages 45 years or older, who were free of self-reported CVD or cancer at study entry (1992–1995). At the time of enrollment, participants gave written informed consent and completed questionnaires on demographics, medical history, medications, and lifestyle factors. They were also asked to provide a blood sample, if they were willing. Participants were requested, but not required, to have the sample drawn in the morning before eating, and sample donors reported the number of hours since their last meal before the blood draw. For the present analysis, we excluded women with prevalent diabetes (n = 770), baseline hemoglobin A_{1c} (Hb A_{1c}) ≥6.5% (n = 270), or missing lipid measurements (n = 237), resulting in 26 746 women for analysis. We also repeated the analyses after excluding the 164 women with Hb A_{1c} ≥6.0% and <6.5%. The study was approved by the institutional review boards of the Brigham and Women's Hospital (Boston, MA). We replicated our findings in a general population of 9652 men and women [Copenhagen City Heart Study (CCHS)] *(14)* in relation to prevalent type 2 diabetes (n = 419).

LABORATORY MEASUREMENTS

EDTA blood samples were obtained from WHS participants at the time of enrollment and stored in vapor-phase liquid nitrogen (−170 °C). Samples from participants whose last meal was 8 h or more before their blood draw comprised the fasting sample (n = 19 292), and samples from those who had eaten within 8 h comprised the nonfasting sample (n = 6100). In a laboratory (N. Rifai) certified by the National Heart, Lung and Blood Institute/Centers for Disease Control and Prevention Lipid Standardization program, baseline Lp(a) was measured by using a commercially available immunoturbidimetric assay that is not affected by the number of kringle-IV type-2 repeats *(16)*, with reagents and calibrators from Denka Seiken. There was no interference of this Lp(a) assay with triglycerides. The CVs at Lp(a) concentrations of 176 and 581 mg/L were 3.6% and 1.5%, respectively. Total, LDL, and HDL cholesterol were assayed directly. Hb A_{1c} was measured with turbidimetric immunoinhibition using hemolyzed whole blood or packed red cells (Roche Diagnostics). High-sensitivity C-reactive protein (hsCRP) was measured by using a high-sensitivity immunoturbidimetric assay with reagents and calibrators from Denka Seiken.

For CCHS participants, Lp(a) concentrations were measured at the 1991–1994 examination with a well-characterized inhouse immunoturbidimetric assay using a Technicon Axon autoanalyser (Miles), rabbit antihuman lipoprotein polyclonal antibodies (Q023, Dako), and a human serum lipoprotein calibrator (Dako) *(14)*. There was no interference from triglycerides up to 8 mmol/L (708 mg/dL). Samples with a concentration of Lp(a) above 850 mg/L or of triglycerides above 8 mmol/L were diluted 1:5. The CVs at Lp(a) concentrations of 90, 300, 420, 660, 1000, and 1270 mg/L and at triglyceride concentrations of 1–2 mmol/L were 11%, 3%, 2%, 2%, 5%, and 4%, respectively. Enzymatic assays were used to measure total and HDL cholesterol and triglycerides. LDL cholesterol was measured directly at triglycerides >400 mg/dL (4.52 mmol/L) and otherwise calculated according to Friedewald. hsCRP was measured by using a high-sensitivity immunoturbidimetric assay (Dako).

ASCERTAINMENT OF TYPE 2 DIABETES

Incident type 2 diabetes in WHS participants was ascertained by self-report on annual follow-up questionnaires through March 2008 as previously described *(17, 18)*. Screening rates for diabetes were high (85%–90%). All self-reported cases of type 2 diabetes were validated by using a supplemental questionnaire based on diagnostic criteria recommended by the American Diabetes Association, additional information from the participants obtained by telephone interview, or review of medical records, with a positive predictive value for incident type 2 diabetes validation of 91% *(17)*. Only confirmed cases of incident type 2 diabetes were included in this analysis.

In the CCHS, prevalent type 2 diabetes was ascertained by self-report at the 1991–1994 examination, use of hypoglycemic drugs, or a nonfasting plasma glucose >200 mg/dL (11.1 mmol/L).

STATISTICAL ANALYSIS

Statistical analyses were performed using STATA version 10.1 (STATA Corporation).

For WHS analyses, statistical comparisons were obtained from Student *t*-tests for continuous variables expressed as means, from Kruskal–Wallis tests for variables expressed as medians, and χ^2 tests for categorical variables. We calculated Pearson correlation coefficients for Lp(a) with select covariates in fasting and nonfasting participants. Following guidelines from the Department of Health and Human Services, Lp(a) concentrations were divided into quintiles based on the distribution among women not taking hormone replacement. Quintile cutpoints were defined separately for the fasting and nonfasting groups.

Next, cumulative probabilities of incident type 2 diabetes were calculated for WHS participants stratified by baseline Lp(a) quintiles and fasting status. Cox proportional hazard regression models were used to calculate the hazard ratios (HRs) and 95% CIs according to these quintiles. Incidence rates and regression models were examined for thresholds. To examine the extent to which Lp(a) was associated with incident events, we considered 3 levels of adjustment: (*a*) age, race, and randomized treatment assignment; (*b*) covariates in model 1 plus baseline smoking status, menopausal status, postmenopausal hormone use, family history of diabetes, blood pressure, body mass index (BMI), and baseline Hb A_{1c}; (*c*) covariates in model 2 plus hsCRP, LDL cholesterol, HDL cholesterol, and triglycerides. Further adjustment for exercise, alcohol use, and education level, as well as adjustment for time of blood draw resulted in almost identical findings. The *P* value for trend was obtained by using quintile number as a predictor. All *P* values were 2-tailed. Statistical tests for interaction between fasting status and Lp(a) concentration in relation to incident type 2 diabetes were obtained by using likelihood ratio tests.

We repeated the analyses after we excluded the 164 women with Hb A_{1c} ≥6.0% and <6.5%. Given prior reports of modification of Lp(a)-related CVD risk in the presence of high LDL cholesterol concentrations, we also examined this phemonenon in relation to diabetes. We also repeated the analyses according to time of diabetes diagnosis (<6 and ≥6 years) to assess for potential confounding by participants who may have had subclinical preexisting diabetes at baseline. We analyzed risk of type 2 diabetes in participants based on baseline concentrations of Lp(a) and Hb A_{1c} to examine additive effects of these 2 biomarkers. Finally, we repeated the analysis in women according to baseline hormones use.

For CCHS analyses, Lp(a) concentrations were divided into quintiles and logistic-regression models were used to calculate odds ratios (ORs) and 95% CIs according to these quintiles. Three levels of adjustment were considered, as described for the WHS.

Results

Baseline characteristics of participants according to diabetes are shown in Table 1. Lp(a) concentrations in the WHS and CCHS were significantly lower in diabetes patients compared with individuals without diabetes, although the medians differed according to study population (WHS 95 vs 107 mg/L, $P < 0.001$; CCHS 157 vs 174 mg/L, $P = 0.006$). As reflected in their risk factors, the WHS participants were generally healthier and at lower risk than the CCHS population, because they were selected after we excluded baseline CVD, cancer, and diabetes, unlike the CCHS population, which was a general Danish population.

Pearson correlation coefficients showed low correlation of Lp(a) with other risk factors for diabetes in the WHS, including blood pressure, BMI, lipids, Hb A_{1c} and hsCRP (data not shown). Although some correlations were statistically significant given the large sample size, the magnitude of the correlation was small (all coefficients <0.2).

Cumulative event probabilities for incident diabetes in WHS during a median follow-up of 13.3 years (interquartile range 12.3–13.8 years) analyzed according to baseline Lp(a) quintiles demonstrated a significant inverse association overall as well as by fasting status (Fig. 1). Associations of Lp(a) concentrations with incident type 2 diabetes were examined by fasting status in the WHS (Fig. 1 and Table 2). Incidence rates were significantly lower in quintiles 2–5 compared with quintile 1. In fasting participants, there was a threshold effect of approximately 20% lower relative risk in quintiles 2–5 compared to quintile 1. In nonfasting participants, there was a more linear effect, with up to 50% lower relative risk in quintile 5 compared with quintile 1. Notably, the inverse association of Lp(a) with diabetes remained significant and minimally attenuated after full adjustment for covariates, including LDL cholesterol, triglycerides, and Hb A_{1c}. Overall, nonfasting Lp(a) concentrations were more strongly associated with risk of incident diabetes (*P* for interaction 0.002) compared with fasting.

We repeated our analyses and adjusting additionally for time of blood draw, with no change in results. Almost identical results were also obtained when we added exercise, alcohol use, and education to the models. We also examined the association of Lp(a) with diabetes in the WHS participants who were not taking hormones at baseline (n = 14 825). Similar results were obtained for participants who did not use hormones. For example, the fully adjusted HRs and 95% CIs for quintiles 2–5 vs quintile 1 in non–hormone users were: 0.90 (0.74–1.10), 0.86 (0.70–1.05), 0.91 (0.75–1.11), and 0.76 (0.61–0.93); *P* for trend 0.02.

The association of Lp(a) with diabetes was also similar in participants stratified by LDL cholesterol [below or above median, 121 mg/dL (3.13 mmol/L)] or by year of study follow-up (<6 or ≥6 years). The results were essentially unchanged when we additionally excluded the 164 women with baseline Hb A_{1c} ≥6.0%.

We further investigated the threshold effect of Lp(a) on incident diabetes that was suggested for the lowest quintile concentration (<40 mg/L), using lower cutpoints of 30, 20, and 10 mg/L (Table 3). The incidence rates increased by approximately 1.5- to 2-fold

Table 1. Baseline characteristics according to incident (WHS) or prevalent (CCHS) type 2 diabetes.[a]

	WHS			CCHS		
	No diabetes n = 25 076	Diabetes n = 1670	*P*	No diabetes n = 9233	Diabetes n = 419	*P*
Men, %	0	0		42.9	60.4	<0.001
Age, mean (SD), years	54.6 (7.1)	54.6 (6.5)	0.93	58.0 (15.4)	65.9 (10.5)	<0.001
Current smoking, %	11.5	13.0	0.06	49.2	43.5	0.02
Hypertension, %	22.4	47.1	<0.001	54.5	76.3	<0.001
Postmenopausal status in women, %	53.9	55.6	<0.001	73.0	93.9	<0.001
Postmenopausal hormone use in women, %	44.2	40.4	0.002	19.2	9.7	0.003
Fasting, %	75.8	78.6	0.01	0	0	
BMI, mean (SD), kg/m^2	25.4 (4.6)	30.6 (6.0)	<0.001	25.5 (4.3)	28.5 (5.3)	<0.001
Family history of diabetes, %	23.4	43.6	<0.001	12.9	33.8	<0.001
Plasma concentrations, median (25th to 75th percentile)						
Lp(a), mg/L	107 (45–331)	95 (36–293)	<0.001	174 (57–399)	157 (30–380)	0.006
Total cholesterol, mg/dL[b]	208 (183–235)	213 (187–242)	<0.001	236 (205–271)	240 (205–271)	0.30
LDL cholesterol, mg/dL[b]	121 (100–144)	126 (104–152)	<0.001	142 (115–173)	139 (110–171)	0.13
HDL cholesterol, mg/dL[b]	53 (44–63)	42 (36–50)	<0.001	58 (46–74)	46 (39–58)	<0.001
Triglycerides, mg/dL[c]	115 (82–167)	174 (126–247)	<0.001	134 (96–193)	204 (137–317)	<0.001
Hb A_{1c},%	4.98 (4.83–5.15)	5.28 (5.07–5.53)	<0.001	—	—	
hs-CRP, mg/L	1.83 (0.74–3.98)	4.22 (2.26–7.33)	<0.001	1.72 (1.25–2.92)	2.88 (1.65–5.37)	<0.001

[a] *P* values were obtained from Student *t*-tests for continuous variables expressed as means, Kruskal-Wallis tests for variables expressed as medians, and χ^2 tests for categorical variables.
[b] To convert cholesterol concentrations in mg/dL to mmol/L, multiply by 0.0259.
[c] To convert triglyceride concentrations in mg/dL to mmol/L, multiply by 0.0113.

for Lp(a) concentrations <10 mg/L compared with higher cutpoints. With Lp(a) ≥10 mg/L used as the reference, the age- and treatment-adjusted HR for Lp(a) <10 mg/L was 1.74 (95% CI 1.37–2.21), and the fully adjusted HR was 1.57 (95% CI 1.23–2.01), $P < 0.001$ for both.

Next, we examined whether baseline Lp(a) concentrations <10 and ≥10 mg/L provided additive risk information to Hb A_{1c} concentrations within the reference interval (<5% and 5% to <6.5%, Fig. 2). With the use of the reference group of Lp(a) ≥10 mg/L and Hb A_{1c} <5%, participants with Lp(a) <10 mg/L and Hb A_{1c} <5% had a fully adjusted HR (95% CI) of 1.62 (0.91–2.89), whereas those with Lp(a) ≥10 mg/L and Hb A_{1c} 5 to <6.5% had an adjusted HR of 3.50 (3.06–4.01), and those with Lp(a) <10 mg/L and Hb A_{1c} 5 to <6.5% had an adjusted HR of 5.36 (4.00–7.19); *P* for trend <0.001.

As a final step, we replicated our findings in 2 settings. First, we internally validated the findings in a case-control analysis of 797 WHS women with baseline prevalent diabetes or Hb A_{1c} ≥6.5% (cases) who were excluded from the prospective WHS study. We used as controls the 25 076 women who remained free of diabetes during the 13-year follow-up period. With the Lp(a) quintile 1 used as the reference, the adjusted ORs (95% CIs) for quintiles 2–5 were 0.75 (0.59–0.94), 0.67 (0.52–0.85), 0.72 (0.56–0.91), and 0.74 (0.58–0.93), respectively; *P* for trend 0.01. Lp(a) <10 vs ≥10 mg/L was associated with an adjusted OR of 2.29 (1.59–3.28); $P < 0.001$.

Second, we externally validated the findings in relation to prevalent type 2 diabetes in 9652 nonfasting men and women enrolled in the CCHS (Table 4) with adjusted ORs of 0.75 (0.55–1.03), 0.64 (0.46–0.88), 0.74 (0.54–1.01), and 0.58 (0.42–0.79), respectively, for quintiles 2–5 vs 1; *P* for trend 0.002. Lp(a) <10 mg/L (vs ≥10 mg/L) was associated with an adjusted OR of 1.54 (1.14–2.08); $P = 0.005$. When stratified by sex, risk estimates appeared stronger in men. However, tests for interaction of sex and Lp(a) concentration in relation to diabetes were nonsignificant.

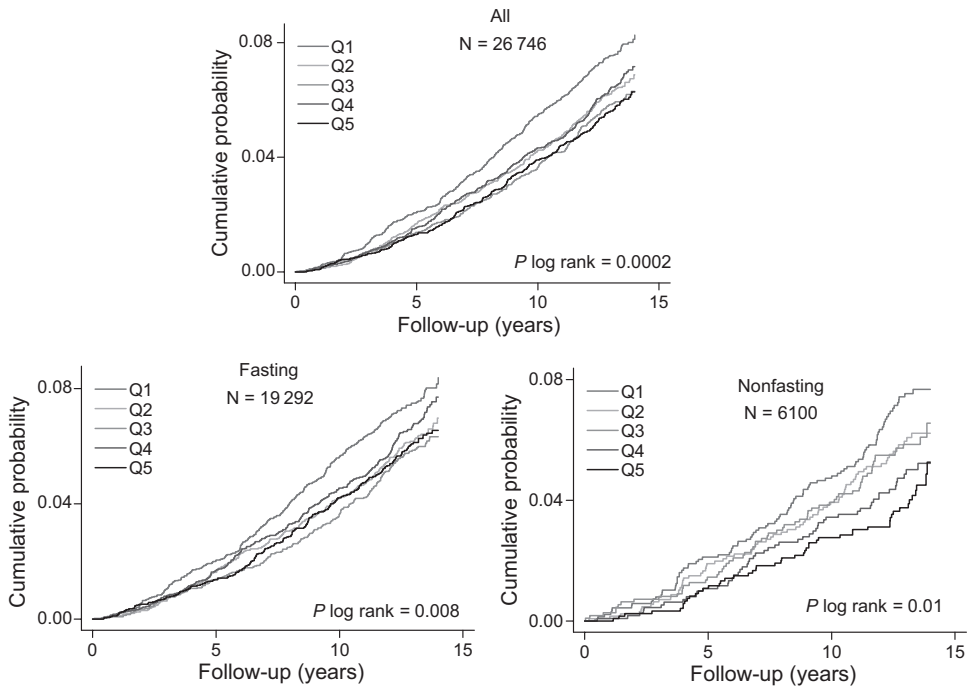

Fig. 1. Cumulative probability of incident type 2 diabetes according to quintiles (Q) of Lp(a) concentration in the WHS, stratified by nonfasting or fasting state at the time of the blood draw.

Discussion

In this prospective study of 26 746 initially healthy US women with 13-year follow-up, we found an inverse association of Lp(a) with risk of type 2 diabetes, with approximately 20%–50% lower relative risk in quintiles 2–5 compared with quintile 1. Lp(a) concentrations showed low correlation with other risk factors, and full adjustment for these risk factors resulted in almost no attenuation of the association. We externally validated these findings in a general population of 9652 Danish men and women with prevalent diabetes, confirming the inverse association of Lp(a) with diabetes with nearly identical results.

To our knowledge, this is the first prospective study that examines the association of Lp(a) with type 2 diabetes. Predicting risk of diabetes has focused largely on glycemic factors *(19)*, with fewer studies on lipoprotein factors. Our finding of an inverse association between Lp(a) concentration and risk of incident diabetes stands in marked contrast to prior studies that have shown a positive association of Lp(a) with CVD *(2)*, including prior findings from the same 2 cohorts in this study *(14, 20)*. Risk factors for diabetes may differ from those for CVD *(21)*. For example, LDL cholesterol is a strong risk factor for CVD and atherosclerosis, but most prior studies have shown no independent association for LDL cholesterol with diabetes *(21)*.

Although increased concentrations of Lp(a), in particular >300 mg/L, have been associated with higher risk of CVD *(20)*, little is known about the association of Lp(a) with diabetes in the absence of CVD. Small case-control studies examining Lp(a) with type 2 diabetes have shown mixed results *(6)*. In 1 small case-control study of Mexican-American individuals, lower concentrations of Lp(a) were found in diabetic patients compared with controls *(11)*. The present finding of an inverse association of Lp(a) with diabetes after adjustment for other risk factors deserves investigation in other prospective study populations for replication of findings and determination of potential clinical utility.

The physiological function and exact mechanisms that may underlie the role of Lp(a) in CVD remain unclear, and even less is known about the role of Lp(a) in diabetes. The independence from known risk factors of the association of Lp(a) with diabetes suggests another mechanism. It is possible that low Lp(a) concentrations may be markers of insulin resistance. However, we adjusted for correlates of insulin resistance, such as triglycerides, HDL cholesterol, Hb A_{1c} and hsCRP, as well as BMI and family history of diabetes, although we did not have insulin concentrations or more sophisticated measures of insulin resistance.

Table 2. Association of Lp(a) with incident type 2 diabetes in the WHS according to fasting status.

		Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P* for trend[a]	$P_{Interaction}$ for fasting status[b]
Range, mg/L								
Fasting	n = 19 292	<39	39–82	83–165	166–466	>466		
Nonfasting	n = 6100	<39	39–85	86–169	170–433	>433		
All	n = 26 746	<39	39–84	85–166	167–453	>453		
Incidence rate (95% CI) per 1000 person-years								
Fasting		6.02 (5.39–6.72)	4.88 (4.30–5.53)	4.55 (3.98–5.20)	5.36 (4.73–6.08)	4.75 (4.16–5.43)	0.008	
Nonfasting		5.69 (4.67–6.94)	4.59 (3.65–5.77)	4.57 (3.58–5.84)	3.74 (2.86–4.90)	3.24 (2.45–4.27)	0.01	
All		5.97 (5.43–6.55)	4.87 (4.39–5.42)	4.50 (4.01–5.06)	5.03 (4.50–5.61)	4.43 (3.94–4.97)	<0.001	
Model 1, HR (95% CI)[c]								
Fasting		Reference	0.80 (0.68–0.95)	0.73 (0.61–0.87)	0.86 (0.72–1.01)	0.77 (0.65–0.92)	0.01	
Nonfasting		Reference	0.81 (0.59–1.09)	0.78 (0.57–1.07)	0.64 (0.46–0.90)	0.56 (0.40–0.79)	<0.001	0.004
All		Reference	0.81 (0.70–0.94)	0.73 (0.63–0.85)	0.82 (0.71–0.95)	0.73 (0.63–0.85)	<0.001	
Model 2, HR (95% CI)[d]								
Fasting		Reference	0.88 (0.74–1.05)	0.76 (0.64–0.92)	0.86 (0.72–1.02)	0.80 (0.66–0.95)	0.01	
Nonfasting		Reference	0.82 (0.60–1.13)	0.81 (0.58–1.11)	0.66 (0.47–0.94)	0.54 (0.38–0.76)	<0.001	0.003
All		Reference	0.89 (0.77–1.03)	0.78 (0.67–0.91)	0.86 (0.74–1.00)	0.75 (0.65–0.88)	<0.001	
Model 3, HR (95% CI)[e]								
Fasting		Reference	0.86 (0.72–1.02)	0.78 (0.65–0.94)	0.87 (0.73–1.04)	0.84 (0.70–1.01)	0.09	
Nonfasting		Reference	0.79 (0.58–1.09)	0.78 (0.57–1.08)	0.66 (0.46–0.93)	0.56 (0.40–0.80)	0.001	0.002
All		Reference	0.87 (0.75–1.01)	0.80 (0.68–0.93)	0.88 (0.76–1.02)	0.78 (0.67–0.91)	0.005	

[a] *P* for trend for event rates obtained from log-rank tests for equality of survivor functions and *P* for trend for HRs from Cox regression models with quintile number used as the predictor.
[b] *P* for interaction with fasting status obtained from likelihood ratio tests for interaction with fasting/nonfasting status and the Lp(a) concentration as a continuous variable, in relation to incident type 2 diabetes.
[c] Model 1 was adjusted for age, race, and randomized treatment assignment.
[d] Model 2 was adjusted for model 1 variables plus smoking status, menopausal status, postmenopausal hormone use, family history of diabetes, blood pressure, BMI, and Hb A_{1c}.
[e] Model 3 was adjusted for model 2 variables plus hsCRP, LDL cholesterol, HDL cholesterol, and triglycerides.

Table 3. Incidence rates and hazard ratios in the WHS according to Lp(a) thresholds.

Lp(a), mg/L	n	Incident diabetes, n	Incidence rate per 1000 person-years (95% CI)	Adjusted HR[a] (95% CI)	*P*
≥10	26 063	1599	4.90 (4.66–5.14)	Reference	
<10	683	71	8.40 (6.66–10.61)	1.57 (1.23–2.01)	<0.001
≥20	23 968	1456	4.85 (4.60–5.10)	Reference	
<20	2778	214	6.17 (5.40–7.06)	1.19 (1.02–1.38)	0.02
≥30	22 173	1329	4.78 (4.53–5.04)	Reference	
<30	4573	341	5.97 (5.37–6.64)	1.17 (1.03–1.32)	0.01
≥40	20 767	1230	4.72 (4.47–4.99)	Reference	
<40	5979	440	5.90 (5.37–6.48)	1.18 (1.05–1.32)	0.004

[a] Adjusted for age, race, randomized treatment assignment, smoking status, menopausal status, postmenopausal hormone use, blood pressure, BMI, Hb A_{1c}, family history of diabetes, hsCRP, LDL cholesterol, HDL cholesterol, and triglycerides.

Lp(a) has been associated inversely with insulin and 2-h glucose *(7)*, consistent with our finding of an inverse association with diabetes. Insulin suppressed apo(a) function in hepatocytes at the posttranscriptional level of apo(a) *(8)*, which may account for lower concentrations of Lp(a) found in type 2 diabetes (hyperinsulinemia and insulin resistance) and higher concentrations in type 1 diabetes (insulin deficiency). In addition, there is hormonal regulation of Lp(a), including lowering of Lp(a) by testosterone *(22)* and insulinlike growth factor 1 *(23)*, and a stimulatory effect of growth hormone *(24)*, all of which may be implicated in glucose and lipid metabolism *(25)*. The role of Lp(a) in insulin resistance and glucose metabolism deserves further investigation for clarification of mechanisms.

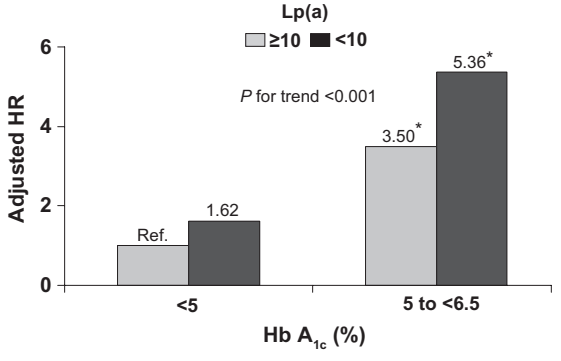

Fig. 2. Additive association of Lp(a) (mg/L) and Hb A_{1c} (%) concentrations with incident type 2 diabetes in the WHS.

HRs were adjusted for age, race, randomized treatment assignment, smoking status, menopausal status, postmenopausal hormone use, blood pressure, BMI, family history of diabetes, hs-CRP, LDL cholesterol, HDL cholesterol, and triglycerides. *$P < 0.001$ compared with reference (Ref.).

It is unclear whether the relative deficiency of Lp(a) promotes the development of diabetes or whether increased concentrations of Lp(a) may be protective. The increase in incidence rates at an Lp(a) concentration cutpoint of <10 mg/L compared to higher cutpoints suggests that the relative deficiency of Lp(a) may be involved in risk. Although Lp(a) concentrations <10 mg/L had the highest relative risk, concentrations <40 mg/L were associated with approximately 20% to 50% higher relative risk in both study populations. The WHS and CCHS participants differed with respect to Lp(a) concentrations (higher in CCHS) and other risk factors, but the association of Lp(a) with diabetes was consistent and similar in magnitude in the 2 studies. Moreover, Lp(a) concentrations <40 mg/L represented the bottom quintile of both populations. Lp(a) was better for predicting incident diabetes when measured in nonfasting samples, consistent with prior data from the WHS in relation to certain lipids, in particular triglycerides, and incident cardiovascular events *(12, 13)*.

A potential limitation of this study was that ascertainment of type 2 diabetes was by self-report. However, all self-reports were confirmed, and this approach has been demonstrated to be valid in these female healthcare professionals *(17)*. Lp(a) measurements were available only once at baseline and results could not be corrected for potential regression dilution bias. Although we measured standard and emerging risk factors for diabetes, including BMI, triglycerides, Hb A_{1c} and hsCRP, we did not have a more specific measure of insulin resistance. Strengths of the present study include the large sample size of both cohorts, the prospective design of the WHS cohort, confirmation of the WHS

Table 4. Association of Lp(a) with prevalent type 2 diabetes in the CCHS (nonfasting samples).

	Quintile 1[a]	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P* for trend[b]	$P_{interaction\ for\ sex}$[c]
Range, mg/L							
Women N = 5441	<44	44–130	131–255	256–540	>540		
Men N = 4211	<33	33–105	106–227	228–464	>464		
All N = 9652	<39	39–117	118–241	242–498	>498		
Model 1, OR (95% CI)[d]							
Women	Reference	0.69 (0.41–1.17)	0.97 (0.61–1.55)	0.75 (0.46–1.23)	0.94 (0.59–1.50)	0.90	
Men	Reference	0.65 (0.44–0.94)	0.43 (0.28–0.66)	0.65 (0.45–0.94)	0.49 (0.33–0.74)	0.001	0.16
All	Reference	0.65 (0.48–0.88)	0.59 (0.44–0.81)	0.68 (0.50–0.91)	0.63 (0.46–0.85)	0.005	
Model 2, OR (95% CI)[e]							
Women	Reference	0.71 (0.42–1.20)	0.89 (0.55–1.44)	0.74 (0.45–1.22)	0.87 (0.54–1.40)	0.64	
Men	Reference	0.67 (0.46–0.99)	0.43 (0.28–0.65)	0.66 (0.45–0.97)	0.53 (0.35–0.80)	0.003	0.38
All	Reference	0.66 (0.48–0.90)	0.57 (0.42–0.78)	0.68 (0.50–0.92)	0.63 (0.46–0.86)	0.007	
Model 3, OR (95% CI)[f]							
Women	Reference	0.89 (0.51–1.54)	1.03 (0.62–1.71)	0.94 (0.55–1.59)	0.85 (0.51–1.41)	0.61	
Men	Reference	0.75 (0.51–1.12)	0.48 (0.31–0.75)	0.70 (0.47–1.04)	0.49 (0.32–0.74)	0.001	0.28
All	Reference	0.75 (0.55–1.03)	0.64 (0.46–0.88)	0.74 (0.54–1.01)	0.58 (0.42–0.79)	0.002	

[a] Quintiles were defined based on the distribution among women not taking hormone replacement, among men, or among the entire cohort, respectively.
[b] *P* for trend for OR obtained from logistic regression models using quintile number as predictor.
[c] *P* for interaction with sex obtained from likelihood ratio tests for interaction with sex and the Lp(a) concentration as a continuous variable, in relation to prevalent type 2 diabetes.
[d] Model 1 was adjusted for age and sex.
[e] Model 2 was adjusted for model 1 variable plus smoking status, menopausal status (women only), postmenopausal hormone use (women only), family history of diabetes, hypertension, and BMI.
[f] Model 3 was adjusted for model 2 variables plus hsCRP, LDL cholesterol [corrected for the Lp(a) contribution *(14)*], HDL cholesterol, and triglycerides.

findings in a second population of Danish men and women, and replication of the findings by using 2 different Lp(a) assays, including the use in WHS of a previously validated immunoassay that is independent of kringle-IV type-2 repeats *(16)*. Finally, the finding that Lp(a) concentration predicted incident diabetes similarly both early (years <6) and late (years ≥ 6) in follow-up makes reverse causality seem an unlikely explanation for our findings.

In summary, we found an inverse association for Lp(a) with risk of incident type 2 diabetes in women, with external confirmation of this finding in a general population of Danish men and women with respect to prevalent diabetes. Lp(a) was associated with diabetes independent of other risk factors, including BMI, Hb A_{1c}, or triglycerides, a finding that deserves further investigation.

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