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Original Article

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Discrepant Effect of High-Density Lipoprotein Cholesterol on the Hematologic Malignancy Risk: A Nationwide Cohort Study

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ABSTRACT

Objective: Although high-density lipoprotein cholesterol (HDL-C) is inversely associated with hematologic malignancies, modification by smoking has not been reported. We investigated how smoking and menopausal status modify these association.
Methods: This population-based cohort study enrolled cancer-free individuals who underwent a national cancer screening in 2010 and followed up until December 2017. HDL-C levels were classified into eight groups based on 10 mg/dL intervals: (<30, 30–39, 40–49, 50–59, 60–69, 70–79, 80–89, or ≥90 mg/dL).
Results: Among 4,517,892 participants, 5887 had lymphoma, 3348 had leukemia, and 12151 had unspecified hematologic malignancies. The adjusted hazard ratios (aHRs) for the lowest HDL-C levels compared to the 70–79 mg/dL range were 1.83 (1.45–2.31) for lymphoma, 3.14 (2.41–4.08) for leukemia, and 2.34 (2.01–2.72) for unspecified hematologic malignancy. The effects of low HDL-C levels on hematologic malignancies were similar in both men and women. Low HDL-C levels were associated with a higher risk of leukemia regardless of smoking status, but extremely high HDL-C levels were linked to a higher risk of leukemia (aHR, 2.32; 95% confidence interval [95% CI], 1.18–4.55) only in current smokers.The hazardous effect of low HDL-C levels on lymphoma was significant only in never smokers (aHR, 2.01; 95% CI, 1.51–2.68). Hazardous effects of low HDL-C levels on leukemia were observed only in post-menopausal women (aHR, 2.94; 95% CI, 1.69–5.11).
Conclusion: Low HDL-C levels were associated with a higher risk of leukemia and lymphoma, with discrepancies based on smoking and menopausal status.

Keywords: High density lipoprotein cholesterol; Lymphoma; Leukemia; Smoking; Menopause

INTRODUCTION

Hematologic malignancies such as non-Hodgkin's lymphoma, Hodgkin's lymphoma, lymphoid leukemia, myeloid leukemia, and multiple myeloma, are relatively rare[1] High-density lipoprotein cholesterol (HDL-C) can regulate immune responses and exhibit anti-oxidative, anti-apoptotic, and anti-inflammatory properties.[2-4] Epidemiologic studies

the manuscript. Funding source provided the cost for the use of big data.

Conflict of Interest

The authors have no conflicts of interest to declare.

Data Availability Statement

The datasets were derived from sources in the public domain: National Health Insurance Service System, https://nhiss.nhis.or.kr/bd/ay/bdaya001iv.do.

Author Contributions

Conceptualization: Nam SY; Data curation: Nam SY, Jo J, Lee WK; Formal analysis: Nam SY, Jo J; Funding acquisition: Nam SY; Investigation: Nam SY, Jo J, Lee WK; Methodology: Nam SY, Jo J, Lee WK; Project administration: Nam SY; Resources: Nam SY; Supervision: Nam SY; Validation: Nam SY; Visualization: Nam SY; Writing - original draft: Nam SY; Writing - review & editing: Nam SY, Jo J, Lee WK.

suggested that low HDL-C levels are associated with a higher risk of several types of cancers.[5-7] Some studies have found no significant associations,[8] while others have reported a positive correlation between HDL-C levels and breast cancer risk.[9] Recent research suggested that low HDL-C levels are associated with overall hematologic malignancy, lymphoma, and leukemia.[10-12] Sex-specific discrepancies have been suggested in the risk of some cancers.[13,14] A previous study found that HDL-C levels are inversely associated with overall hematologic malignancies in both premenopausal and postmenopausal women.[12] However, effect modification by smoking status has been extremely rarely reported for the effect of HDL-C levels on cancer risk. One study conducted a subgroup analysis for the association between HDL-C levels and lung cancer risk.[15] To the best of our knowledge, no previous studies have investigated the effect of smoking status on the association between HDL-C levels and the risk of hematologic malignancy.

We aimed to investigate the impact of HDL-C level on the risk of individual hematologic malignancy in various models and to assess effect modification by important individual factors such as sex, smoking, and menopausal status using data from the National Health Insurance Service System (NHISS).

MATERIALS AND METHODS

1. Data source and extraction

This is a large population-based cohort study using data from the NHISS, covering approximately 98% of the Korean population aged ≥40 years every 2 years. The NHISS provides the Base One Foundation Component Library (BFC), T20, National General Health Examination (NGHE), and National Cancer Screening Data. The BFC includes basic individual information. We extracted sex, age, and economic status (twentiles of house incomes) from the BFC, disease codes of the International Classification of Diseases, 10th revision (ICD-10) from the T20 data, and demographic and laboratory data from the NGHE. The NGHE questionnaire included questions on chronic disease, medication, smoking status, alcohol consumption frequency, physical activity, and family history. Questionnaires on women-specific factors (age at menarche, menstrual status, parity, breastfeeding duration, use of oral contraceptive pills, and estrogen replacement therapy) were extracted from the National Cancer Screening Data. Questionnaires for chronic diseases included those for hypertension, diabetes mellitus, cerebrovascular disease, and ischemic heart disease. Missing values for diabetes and hypertension were defined as fasting glucose (higher than 126 mg/dL) and blood pressure (systolic >140 mmHg or diastolic >90 mmHg) measured using the NGHE. Missing values for cerebrovascular disease and ischemic heart disease within 1 year were defined using the ICD-10 code. Menstrual status was classified as premenopausal, hysterectomy-treated, and postmenopausal. Parity was classified as 1, >2, or never. Breastfeeding duration was classified as <6 months, ≥6 to <12 months, ≥12 months, or never. Use of oral contraceptive pills was categorized as never, <1 year, ≥1 year, and unknown. Smoking status was classified into none, past, and current smoker. Alcohol consumption frequency was classified into none, 1/week, 2–3/week, 4–5/week, and ≥ 6/week. Moderate physical activity was defined as physical activity with light sweating for over 30 minutes/day. The body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Blood lipid and glucose levels were measured after 12 hours of fasting. The NGHE provided serum lipid tests to all populations aged >40 years every two years from 2009–2016. Therefore, the missing rates of lipids and glucose were extremely low during this period.

2. Baseline enrollment and follow-up

The NHISS provided NGHE and national gastric cancer screening data from 2008, after excluding common cancers from 2004 to 2007. Participants who underwent both the NGHE and gastric cancer screening in 2010 were enrolled in this study (**Fig. 1A**). We further excluded participants diagnosed with cancer before 2010, those with cancer detected during cancer screening, those with pre-existing cancer based on questionnaires, and all individuals who died or were diagnosed with any cancer within 1 year of baseline enrollment. The outcomes included lymphoma (C81–C86), leukemia (C91–C95), and unspecified hematologic malignancy (C96), with the first sensing date until December 2017. The NHISS provides data after excluding identifying information. Therefore, the requirement for informed consent was waived. This study was approved by the Institutional Review Board of Kyungpook National University Hospital, Chilgok, Korea (KNUCH 2017-12-022).

3. Statistical analysis

We did not determine the sample size because the number of participants was fixed. However, we performed calculations for the primary analysis with a specified power (**Supplementary Data 1**). Categorical variables were presented as numbers (percentages) and continuous variables were presented as means ± standard deviations, respectively. We calculated person-years from baseline to the first date of cancer diagnosis, death, or December 31, 2017. We tested the linear relationship between HDL-C levels and

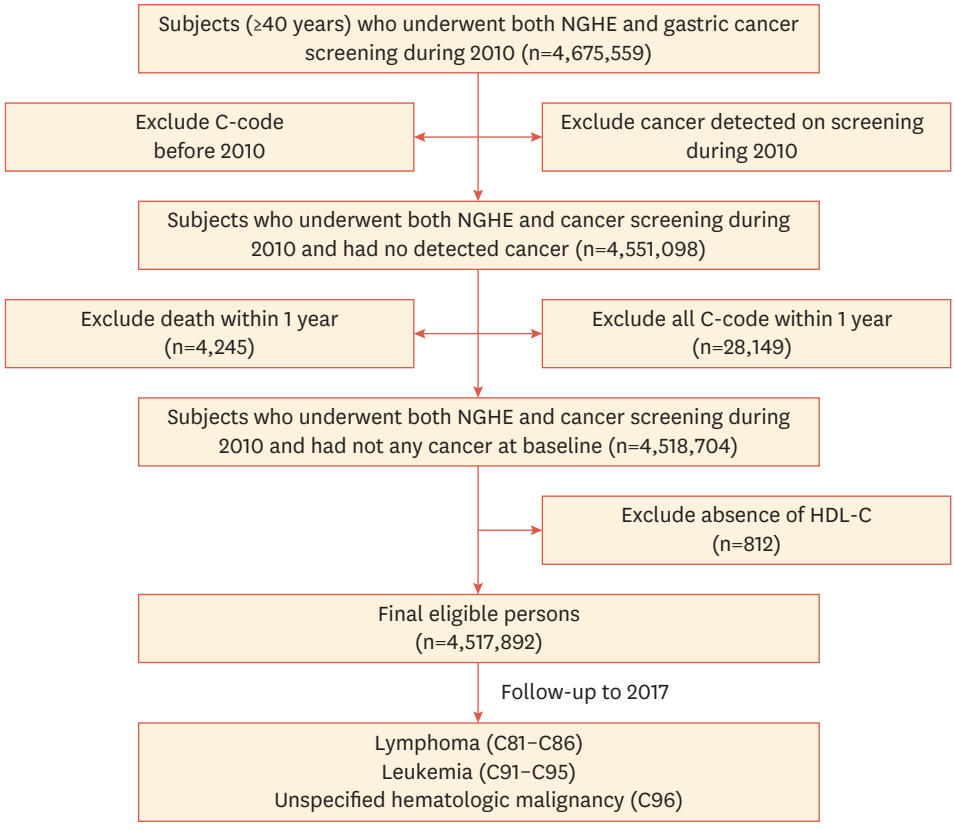

Fig. 1. Study overview. Eligible participants underwent national cancer screening and a general health examination from January to December 2010. Patients diagnosed with cancer before study enrollment and in 2010 were excluded. Individuals who were diagnosed with cancer or died from any cause within 1 year of enrollment were also excluded.
NGHE, National General Health Examination; HDL-C, high density lipoprotein cholesterol.

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hematologic malignancy (**Supplementary Table 1**). The main exposure, baseline HDL-C level, was categorized as <30, 30–39, 40–49, 50–59, 60–69, 70–79, 80–89, or ≥90 mg/dL. We set a reference for the lowest risk group for hematologic malignancy in overall population. Triglyceride was classified as normal (<150 mg/dL) and high (≥150 mg/dL), and low-density lipoprotein cholesterol was classified as normal (<130 mg/dL) and high (≥130 mg/dL) for adjusted analysis. The risk of each cancer according to the HDL-C level was assessed using Cox proportional regression analysis with hazard ratios (HRs) and 95% confidence intervals (CIs). A directed acyclic graph provided an assumed causal framework for covariate adjustment (**Supplementary Fig. 1**). Multivariate analyses were adjusted for age, sex, economic status, BMI, hypertension, diabetes, cerebrovascular disease, heart disease, physical activity,[16] smoking status, alcohol consumption, triglyceride, low-density lipoprotein, and use of lipid-lowering drugs (Model I). An interaction analysis (joint test) was conducted between the important cofactors (sex, smoking, menopausal status, and BMI) and HDL-C levels for hematologic malignancy risk (**Supplementary Table 2**). Subgroup analyses were also conducted based on sex and smoking status. Subgroup analysis by menopausal status was performed in women based on previous evidence of different effects of HDL-C in some cancers.[17] Women's factors (parity, breastfeeding duration, and oral pills) were further adjusted for in the women's sub-analysis. The missing rate of serologic covariates was <0.02%, and that of smoking (missing number=11,692) and drinking status (missing number=11,780) was 0.26% in the final eligible population. Therefore, we deleted missing data list-wise in the adjusted analysis.

To conduct a sensitivity analysis of the impact of exposure duration, we excluded any cancer that developed within 24 months of the baseline HDL-C measurement (Model II, **Fig. 1B**). We performed another analysis adjusted for covariates, excluding economic status, triglyceride, low-density lipoprotein, and lipid-lowering drug levels, to conduct a sensitivity analysis for baseline imbalance (Model III). For additional analysis, we classified HDL-C as low (<40 mg/dL in men and <50 mg/dL in women) or normal (≥40 mg/dL in men and ≥50 mg/dL in women) based on Adult Treatment Panel III (ATP III).[18] All analyses were conducted using SAS software (version 9.4; SAS Institute). The statistical tests were two-sided, and values of $p<0.05$ were considered statistically significant.

RESULTS

1. Baseline characteristics and cancer development

Among the 4,675,559 individuals, those with previous cancers and cancer detected on screening (n=124,461), those who died (n=4,245) or those diagnosed with any cancer (n=28,149) within 1 year of baseline enrollment were excluded. A total of 4,517,892 individuals were eligible (2,019,651 men; mean age, 55 years), and 5,887 lymphoma, 3,348 leukemia, and 12,151 unspecified hematologic malignancies developed during the 8-year follow-up period (**Fig. 1A**). The total person-years were 32,634,890. We provided the baseline characteristics of the sex-common variables (**Table 1**) and women-specific variables by baseline HDL-C levels (**Supplementary Table 3**). Age and BMI were inversely associated with HDL-C levels. Men had lower HDL-C levels than women. The TG levels were high in the low and extremely high HDL-C groups.

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Table 1. Baseline characteristics

Variables	HDL-C (mg/dL)							
	<30 (n=41,057)	30–39 (n=444,909)	40–49 (n=1,229,664)	50–59 (n=1,323,011)	60–69 (n=877,920)	70–79 (n=382,121)	80–90 (n=141,112)	≥90 (n=78,098)
Person year from baseline HDL-C measurement to end of follow-up								
Total person years	295,130	3,210,376	8,884,860	9,566,101	6,341,793	2,757,170	1,016,877	562,583
Age (yr)	58.2±11.4	56.7±11.1	55.7±10.9	55.0±10.6	54.4±10.6	53.6±10.3	53.4±10.2	53.6±10.2
Men	27,088 (66.0)	276,300 (62.1)	665,840 (54.2)	559,623 (42.3)	308,935 (35.2)	115,442 (30.2)	40,406 (28.6)	26,017 (33.3)
BMI (kg/m^2)	24.9±3.1	24.9±5.5	24.5±3	24.0±3.6	23.5±3.0	23.0±3.0	22.8±3.0	22.8±3.1
Economic status*	12.1±5.8	12.5±5.8	12.3±5.8	12.1±5.9	11.9±5.9	11.7±6.0	11.6±6.0	11.7±5.9
Serologic test								
High-density lipoprotein (mg/dL)	26.0±4.2	35.8±2.6	44.8±2.8	54.28±2.9	63.9±2.8	73.7±2.8	83.6±2.8	163.3±193.9
Total cholesterol (mg/dL)	189.2±166.5	186.4±37.9	194.9±37.8	200.2±37.7	204.3±37.3	210.1±36.9	215.6±37.2	220.2±46.4
Triglyceride (mg/dL)	246.5±228.7	197.4±137.2	156.3±98.7	127.7±79.3	109.7±68.2	98.3±63.7	93.5±67.1	274.6±579.4
Low density lipoprotein (mg/dL)	118.3±190.9	114.1±79.6	121.0±66.5	121.3±50.9	118.8±45.4	116.8±38.6	113.5±37.9	128±167.4
Fasting glucose (mg/dL)	105.6±32.3	103.1±27.9	101.4±25.6	99.5±23.5	98.1±22.1	97.2±21.3	97.1±21.4	98.2±23.3
Chronic disease								
Hypertension	15,452 (37.6)	150,239 (33.8)	368,539 (30.0)	351,052 (26.5)	210,292 (24.0)	83,636 (21.9)	30,349 (21.5)	17,655 (22.6)
Heart disease	2,337 (5.7)	20,978 (4.7)	47,980 (3.9)	42,576 (3.2)	25,105 (2.9)	9,578 (2.5)	3,278 (2.3)	1,960 (2.5)
Cerebrovascular disease	1,083 (2.6)	9,586 (2.2)	21,163 (1.7)	18,088 (1.4)	10,926 (1.2)	4,110 (1.1)	1,509 (1.1)	837 (1.1)
Diabetes mellitus	7,769 (18.9)	63,372 (14.2)	134,188 (10.9)	108,869 (8.2)	57,089 (6.5)	20,594 (5.4)	7,066 (5.0)	4,585 (5.9)
Lipid lowering drug	1,246 (3.0)	12,496 (2.8)	34,159 (2.8)	36,302 (2.7)	22,972 (2.6)	9,805 (2.6)	3,650 (2.6)	2,158 (2.8)
Alcohol consumption								
None	26,939 (65.7)	280,433 (63.2)	748,950 (61.1)	810,724 (61.5)	532,098 (60.8)	222,604 (58.4)	78,781 (56.0)	40,931 (52.6)
1/wk	9,056 (22.1)	114,183 (25.7)	320,639 (26.1)	328,163 (24.9)	215,948 (24.7)	96,877 (25.4)	36,522 (26.0)	20,588 (26.5)
2–3/wk	2,843 (6.9)	33,046 (7.4)	104,294 (8.5)	117,348 (8.9)	80,013 (9.1)	38,007 (10.0)	15,392 (10.9)	9,477 (12.2)
4–5/wk	1,104 (2.7)	9,442 (2.1)	31,694 (2.6)	37,933 (2.9)	28,192 (3.2)	13,895 (3.7)	5,867 (4.2)	4,023 (5.2)
≥ 6/wk	1,052 (2.6)	6,864 (1.6)	21,127 (1.7)	25,197 (1.9)	19,222 (2.2)	9,683 (2.5)	4,138 (2.9)	2,823 (3.6)
Smoking status								
No smoker	21,530 (52.5)	246,457 (55.5)	749,115 (61.1)	906,825 (68.7)	642,331 (73.4)	289,546 (76.0)	107,681 (76.5)	56,702 (72.8)
Past smoker	7,539 (18.4)	84,134 (19.0)	214,466 (17.5)	192,564 (14.6)	108,231 (12.4)	41,960 (11.0)	14,625 (10.4)	9,379 (12.0)
Current smoker	11,916 (29.1)	113,330 (25.5)	263,124 (21.5)	219,939 (16.7)	124,877 (14.3)	49,572 (13.0)	18,502 (13.1)	11,855 (15.2)
Moderate physical activity† (day/week)	1.1±1.8	1.1±1.8	1.2±1.8	1.2±1.9	1.2±1.9	1.3±1.9	1.3±1.9	1.3±1.9

Missing rate is 0.26% (n=11,780) in smoking status and 0.26% (n=11,692) in alcohol drinking status. Percent is after excluding missing data. Categorical variables were presented as numbers (percentages) and continuous variables were presented as means ± standard deviations, respectively.
HDL-C, high density lipoprotein cholesterol; SD, standard deviation; BMI, body mass index.
*Economic status measured using annual national health insurance paid by individuals categorized from 1 to 20. One is the lowest level and 20 is highest level.
†Moderate activity was defined as physical activity with light sweating over 30 minutes per day.

2. Effect of HDL-C on the risk of hematologic malignancy

In the adjusted analysis, low HDL-C levels were associated with a higher risk of lymphoma, leukemia, and unspecified hematologic malignancies in a dose-dependent manner. The adjusted HR (aHR) for the lowest HDL-C level was 1.83 (1.45–2.31) for lymphoma, 3.14 (2.41–4.08) for leukemia, and 2.34 (2.01–2.72) for unspecified hematologic malignancy, compared to the reference group 70-79 mg/dL of HDL-C (**Table 2**).

3. Subgroup analysis by sex and smoking status

Significant interactions between HDL-C levels and cofactors (sex and smoking status) on the risk of hematologic malignancies were observed (**Supplementary Table 2**). The hazardous effect of low HDL-C levels on lymphoma, leukemia, and unspecified hematologic malignancy was similarly observed in both men and women, even though the effect size was larger in women for lymphoma risk (p interaction=0.002) and in men for leukemia risk (**Table 2**). The optimal HDL-C range to prevent hematologic malignancy is ≥40 mg/dL in men and ≥50 mg/dL in women for lymphoma and ≥60 mg/dL in men and ≥40 mg/dL in women for leukemia.

The impact of HDL-C levels on hematologic malignancy differed according to smoking status (**Fig. 2** and **Supplementary Table 4**). The hazardous effect of low HDL-C levels on lymphoma was observed only in never smokers (**Fig. 2A**). Low HDL-C levels markedly were

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Table 2. Impact of HDL-C on the risk of hematologic malignancy

HDL-C (mg/dL)	Total number (n=4,517,892)	Number of cancer	Total		Men		Women	
			aHR (95% CI)*	*p*-value	aHR (95% CI)*	*p*-value	aHR (95% CI)†	*p*-value
Lymphoma (C81–C86)								
<30	41,057	101	1.83 (1.45–2.31)	**<0.001**	1.55 (1.16–2.07)	**0.003**	2.02 (1.38–2.97)	**<0.001**
30–39	444,909	734	1.39 (1.21–1.58)	**<0.001**	1.21 (1.01–1.46)	**0.038**	1.39 (1.15–1.68)	**0.001**
40–49	1,229,664	1,717	1.20 (1.07–1.35)	**0.002**	1.08 (0.91–1.28)	0.400	1.24 (1.06–1.44)	**0.008**
50–59	1,323,011	1,681	1.17 (1.04–1.31)	0.008	1.16 (0.97–1.37)	0.081	1.13 (0.97–1.31)	0.130
60–69	877,920	1,027	1.10 (0.97–1.24)	0.134	1.08 (0.90–1.30)	0.392	1.10 (0.94–1.29)	0.252
70–79	382,121	396	1		1		1	
80–89	141,112	148	1.03 (0.85–1.25)	0.761	0.81 (0.58–1.13)	0.211	1.20 (0.94–1.53)	0.144
≥90	78,098	83	1.00 (0.78–1.28)	0.993	0.85 (0.57–1.25)	0.402	1.14 (0.83–1.57)	0.413
Leukemia (C91–C95)								
<30	41,057	84	3.14 (2.41–4.08)	**<0.001**	3.39 (2.41–4.76)	**<0.001**	2.13 (1.31–3.45)	**0.002**
30–39	444,909	500	1.70 (1.43–2.03)	**<0.001**	1.87 (1.45–2.42)	**<0.001**	1.46 (1.15–1.85)	**0.002**
40–49	1,229,664	1,008	1.34 (1.15–1.57)	**0.001**	1.46 (1.15–1.87)	**0.002**	1.19 (0.97–1.46)	0.091
50–59	1,323,011	881	1.16 (0.99–1.35)	0.061	1.33 (1.04–1.71)	**0.025**	1.01 (0.82–1.23)	0.962
60–69	877,920	549	1.10 (0.93–1.30)	0.250	1.20 (0.92–1.57)	0.170	1.04 (0.84–1.28)	0.741
70–79	382,121	204	1		1		1	
80–89	141,112	75	1.00 (0.76–1.31)	0.991	1.33 (0.88–1.99)	0.170	0.81 (0.56–1.16)	0.251
≥90	78,098	47	1.17 (0.85–1.60)	0.353	1.35 (0.83–2.17)	0.221	1.03 (0.67–1.58)	0.902
Unspecified hematologic malignancy (C96)								
<30	41,057	248	2.34 (2.01–2.72)	**<0.001**	2.09 (1.73–2.53)	**<0.001**	2.24 (1.75–2.88)	**<0.001**
30–39	444,909	1,647	1.55 (1.41–1.70)	**<0.001**	1.44 (1.26–1.64)	**<0.001**	1.44 (1.27–1.64)	**<0.001**
40–49	1,229,664	3,621	1.28 (1.18–1.39)	**<0.001**	1.20 (1.06–1.36)	**0.004**	1.26 (1.13–1.40)	**<0.001**
50–59	1,323,011	3,385	1.17 (1.08–1.27)	**0.001**	1.20 (1.06–1.35)	**0.005**	1.10 (0.99–1.23)	0.071
60–69	877,920	2,027	1.08 (0.99–1.17)	0.091	1.09 (0.96–1.25)	0.182	1.06 (0.94–1.18)	0.340
70–79	382,121	783	1		1		1	
80–89	141,112	278	0.98 (0.85–1.13)	0.782	0.94 (0.75–1.18)	0.583	1.01 (0.85–1.21)	0.902
≥90	78,098	162	1.02 (0.85–1.21)	0.853	0.92 (0.70–1.21)	0.531	1.08 (0.86–1.35)	0.501

The *p*-values marked with bold indicate statistically significant.
HDL-C, high density lipoprotein cholesterol; aHR, adjusted hazard ratio; CI, confidence interval.
*Adjusted for age, sex, economic status, body mass index, hypertension, diabetes, cerebrovascular disease, heart disease, smoking status, drinking status, triglyceride, Low density lipoprotein cholesterol, physical activity, and use of lipid lowering drug.
†Women analysis was additionally adjusted for menopausal status, breast feeding, parity, and use of oral contraceptive pill. Reference group of HDL-C is the lowest risk group.

associated with a higher risk of leukemia regardless of smoking status, while extremely high HDL-C levels were associated with a higher risk of leukemia only in current smokers (aHR, 2.32; 95% CI, 1.18–4.55) (**Fig. 2B**). The hazardous effects of low HDL-C levels on unspecified hematologic malignancies were consistent in terms of effect direction and effect size, regardless of smoking status (**Fig. 2C**).

4. Subgroup analysis by menopausal status

The effect of HDL-C levels on the subtype of hematologic malignancy differed according to the menopausal status (**Fig. 3** and **Supplementary Table 5**). Low HDL-C levels were associated with a higher risk of leukemia in both premenopausal and postmenopausal women (**Fig. 3A**). The hazardous effect of low HDL-C levels on leukemia was significant only in postmenopausal women (**Fig. 3B**). Although the trend was similar, the effect size of the hazardous impact of low HDL-C levels on unspecified hematologic malignancies was more prominent in postmenopausal women (**Fig. 3C**).

5. Sensitivity analysis

Our main results were robust to various sensitivity analyses (**Supplementary Table 6**) for the hematologic malignancy subtypes; the estimated effect sizes and CI were similar to those of the main analysis. **Fig. 4** shows the overlapping aHRs from the three models. In the adjusted analysis using binary HDL-C, normal HDL-C levels were associated with a reduced risk of lymphoma

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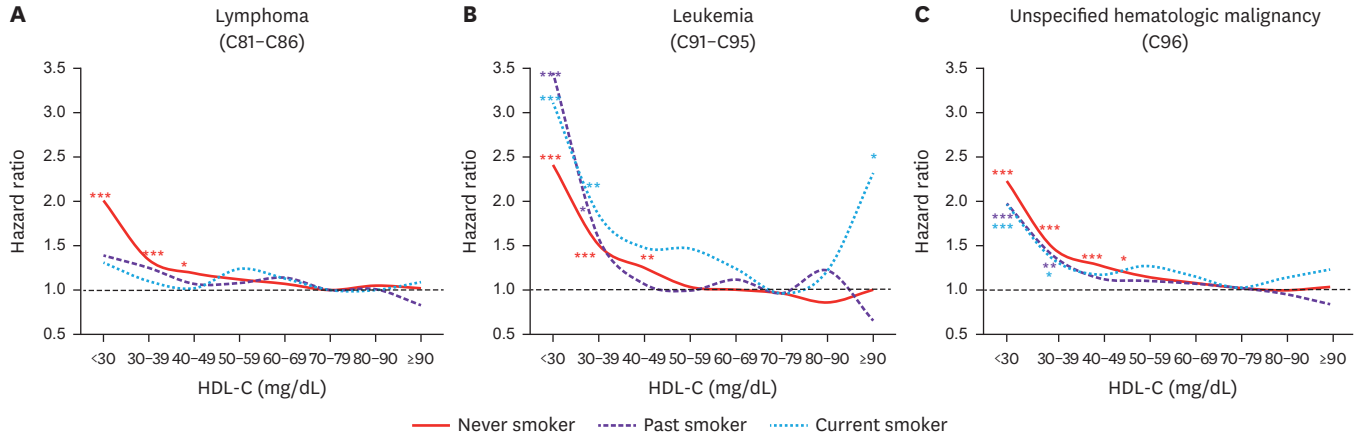

Fig. 2. Effect of HDL-C on cancer by smoking status. aHRs for lymphoma (A), leukemia (B), and unspecified hematologic malignancy (C). HRs were adjusted for age, sex, economic status, body mass index, hypertension, diabetes, cerebrovascular and heart disease, drinking status, triglyceride, low-density lipoprotein, physical activity, and use of lipid-lowering drugs. Exact aHR and confidence interval are provided in **Supplementary Table 4**.
HDL-C, high density lipoprotein cholesterol; aHR, adjusted hazard ratio.
*p<0.5; **p<0.01; ***p<0.001.

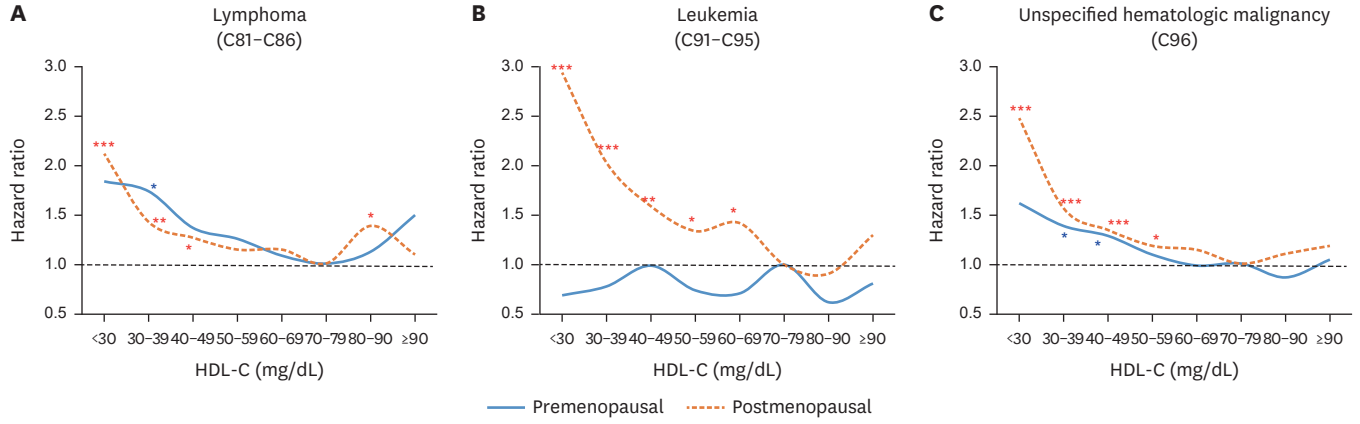

Fig. 3. Effect of HDL-C on cancer by menopausal status. aHRs for lymphoma (A), leukemia (B), and unspecified hematologic malignancy (C). HRs were adjusted for age, economic status, body mass index, hypertension, diabetes, cerebrovascular disease, heart disease, smoking status, drinking status, triglyceride, Low density lipoprotein, physical activity, use of lipid lowering drug, parity, breast feeding duration, and use of oral contraceptive pills. The blue solid (premenopausal) and red dot line (postmenopausal) represents the adjusted hazard ratio. Exact aHR and confidence intervals are provided in **Supplementary Table 5**.
HDL-C, high density lipoprotein cholesterol; aHR, adjusted hazard ratio.
*p<0.5; **p<0.01; ***p<0.001.

and leukemia (12%–25%) compared with low HDL-C levels (**Supplementary Table 7**). These associations were similarly observed in both men and women in the sex-specific analysis.

DISCUSSION

To the best of our knowledge, this is the first study to investigate the effect of smoking status on the association between serum HDL-C levels and the risk of hematologic malignancy. Low HDL-C levels increase the risk of lymphoma, leukemia, and unspecified hematologic malignancies. These hazardous effects remained robust across various sensitivity analyses. An unfavorable effect of low HDL-C levels on lymphoma risk was observed only in never-smokers, while low HDL-C levels were associated with a higher risk of leukemia and unspecified hematologic malignancies, regardless of smoking status. However, extremely

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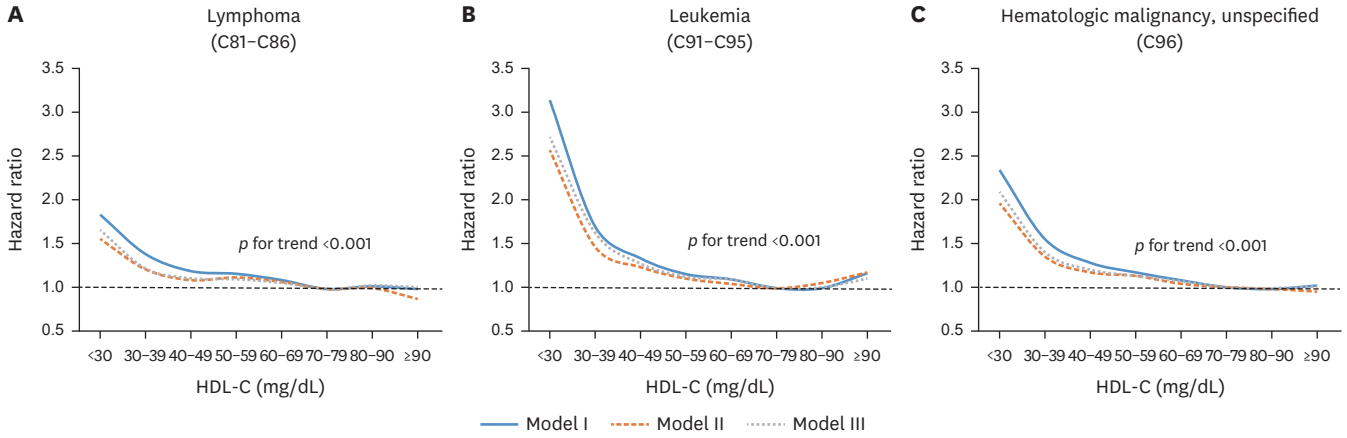

Fig. 4. Sensitivity analysis by exposure duration and adjusted variables. aHRs for lymphoma (A), leukemia (B), and unspecified hematologic malignancy (C). Blue lineaHR of model I (main model: exclusion of any cancer developed within 1 year from baseline HDL-C measurement); red line: aHR of model II (exclusion of any cancer developed within 2 years from baseline HDL-C measurement); gray line: aHR of mode III. Models I and II: HRs were adjusted for age, sex, economic status, body mass index, hypertension, diabetes, cerebrovascular and heart disease, drinking status, smoking status, triglyceride, low-density lipoprotein, physical activity, and use of lipid-lowering drugs. Model III: HRs were adjusted for age, sex, body mass index, hypertension, diabetes, cerebrovascular disease and heart disease, drinking status, smoking status, and physical activity. Exact aHR and confidence intervals are provided in **Table 2** and **Supplementary Table 6**.
aHR, adjusted hazard ratio; HDL-C, high density lipoprotein cholesterol.

high HDL-C levels was associated with a higher risk of leukemia in current smokers. The hazardous effect of low HDL-C levels on cancer risk was more prominent in postmenopausal women than in premenopausal women.

Several plausible mechanisms have been proposed to explain the role of HDL-C in cancer development. HDL-C has anti-atherosclerotic, anti-oxidative, anti-inflammatory, anti-thrombotic, anti-apoptotic, immune-modulating, and endothelium protective effects.[2,19] This protective role of HDL-C in several pathological processes may also relate to the interaction between lipid metabolism and cancer biology.[20] The antioxidative properties of HDL-C may contribute to its protective effects on cancer development. Oxidizing agents attack the DNA and transform normal cells into neoplastic cells. Additionally, the antioxidative properties of HDL-C are also related to its capacity to limit oxidized low-density lipoprotein formation.[21] HDL-C mediates anti-inflammatory reprogramming of macrophages in mouse models and cell lines.[22] It also has anti-apoptotic properties, as HDL-C inhibits endothelial cell death by interacting with caspase-3, a key regulator of apoptosis.[23] Apolipoprotein M may further contribute to the anti-apoptotic properties of HDL-C.[24]

Previous studies have analyzed the relationship between HDL-C level and cancer risk using the highest or lowest quartile [or quintile] of HDL-C level as a reference (**Supplementary Table 8**). However, when the lowest risk group for cancer is at a middle HDL-C level, such an analysis may not accurately reflect these relationships. Our study estimated cancer risk using HDL-C levels at 10 mg/dL intervals from <30 mg/dL to ≥90 mg/dL and set the lowest-risk group as the reference. This study explored the association between HDL-C levels and hematologic malignancy risk and conducted a sub-analysis based on individual factors. Here, we characterized the association between HDL-C levels and hematologic cancers more comprehensively than previously conducted studies. Low HDL-C levels (70–79 mg/dL) markedly was associated with a higher risk of lymphoma, leukemia, and unspecified hematologic malignancies in a dose-dependent manner. The hazardous effects of low HDL-C levels were robust across various sensitivity analyses. This association was compatible with previous studies (HR [lowest vs. highest quartile or quintile of HDL-C level], 1.35–2.61).[10,11]

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The harmful effects of low HDL-C levels on lymphoma, leukemia, and unspecified hematologic malignancy were similar in both men and women with different effect size by sex. A previous study showed that the effect of HDL-C level on overall hematologic malignancy risk was similar in men and women.[10] Our study suggests that optimal HDL-C ranges to prevent overall hematologic malignancy are ≥60 mg/dL in men and ≥50 mg/dL in women.

To the best of our knowledge, this study is the first subgroup analysis by smoking status regarding HDL-C and the risk of hematologic malignancy. The harmful effects of low HDL-C levels on lymphoma were observed only in never smokers, suggesting that the protective role of HDL-C against lymphoma is attenuated in smokers. The hazardous effect of low HDL-C levels on leukemia was constant regardless of smoking status, but an unfavorable effect of extremely high HDL-C levels on leukemia was observed only in current smokers. The findings that extremely high HDL-C levels was associated with a higher risk of leukemia in current smokers may be partially explained by the anti-apoptotic property of HDL-C.[23] A previous small study using binary HDL-C showed that the harmful effects of low HDL-C levels on lung cancer were observed only in past smokers (HR, 1.77; 95% CI, 1.05–2.97).[15] Another study suggested no difference according to the smoking status in the association between HDL-C level and overall cancers.[10] However, the exact mechanism for the discrepant effect of HDL-C levels on hematologic malignancy according to smoking status is unknown and should be further investigated in the future.

We also explored the risk of hematologic malignancy according to the menopausal status. The hazardous effect of low HDL-C levels on leukemia was significant only in postmenopausal women. Although the trends were similar, the effect size on the risk of unspecified hematologic malignancies was more prominent in postmenopausal women. Cohort studies on the association of HDL-C levels with cancer risk by menopausal status have rarely been reported.[12,17] A previous study (1.19 million participants) showed a consistent association of HDL-C levels with overall hematologic malignancy in premenopausal and postmenopausal women (aHR [highest vs. lowest quartile], 0.80 in premenopausal and 0.70 in postmenopausal women).[12] In subtype analysis, low HDL-C levels were associated with the risk of non-Hodgkin's lymphoma, lymphocytic leukemia, and myeloid leukemia regardless of menopausal status, but low HDL-C levels were associated with Hodgkin's lymphoma only in post-menopausal women.[12] However, our large cohort study (4.52 million participants) showed a hazardous effect of low HDL-C levels on lymphoma regardless of menopausal status, but low HDL-C levels markedly was associated with a higher risk of leukemia only among postmenopausal women. In our study, the effect size (HR) of HDL-C levels on leukemia in postmenopausal women was similar to that in men. These findings suggest that sex hormones such as estrogen may attenuate the inflammatory, oxidative, and cancerous processes caused by low HDL-C levels during the development or progression of leukemia. However, it remains unclear how sex hormones and menopausal status affect the development of hematologic malignancies.

This study has several strengths. First, the large population-based cohort study enabled us to investigate the risk of hematologic malignancy by HDL-C levels at 10 mg/dL intervals and showed nonlinear associations. Second, we used high-quality data from the NHISS which includes direct measurement of lipids and BMI, detailed information on many covariates, and nearly complete sensing of cancer detection. Third, the analytical model was adjusted for several potential covariates. Furthermore, the women's analyses were adjusted for women-specific factors. Fourth, this is the first study to investigate the effect modification

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by smoking status in the association between HDL-C level and hematologic malignancy risk. Subgroup analyses according to sex, smoking status, and menopausal status clarified these associations. Fifth, our results were robust to sensitivity analyses. Finally, the NHISS data represent the general Korean population aged over 40 years.

This study has some limitations. First, it has the potential for residual confounding factors. Although the risk was adjusted for smoking status, it was probably confounded by smoking amount. Second, we used baseline HDL-C levels to investigate the association between HDL-C levels and the risk of hematologic cancer. Therefore, this cohort study could not confirm causality, which should be confirmed by investigating the effect of HDL-C level modification on the risk of cancer development. Third, unmeasured confounding variables that may be associated with hematologic malignancies, such as radiation or heavy metal exposure, were not adjusted for. Finally, the study focused only on Koreans, limiting the generalizability of the findings.

In this large cohort study, the effects of HDL-C levels on the risk of hematologic malignancies were similar in both men and women. Low HDL-C levels was associated with a higher risk of lymphoma, leukemia, and unspecified hematologic malignancies, and these associations were robust in various sensitivity analyses. This study is the first subgroup analysis by smoking status regarding HDL-C levels and hematologic malignancy risk. The harmful effects of low HDL-C levels on lymphoma were observed only in never smokers. Low HDL-C levels were associated with a higher risk of leukemia regardless of smoking status, but extremely high HDL-C levels were associated with a higher risk of leukemia in current smokers. Furthermore, the hazardous effect of low HDL-C levels on leukemia was significant only in post-menopausal women. Therefore, we can consider modest HDL-C levels in current smokers and stricter control of HDL-C levels in postmenopausal women.

SUPPLEMENTARY MATERIALS

Supplementary Data 1
Supplementary methods

Supplementary Table 1
Linearity with hematologic malignancy risk by HDL-C

Supplementary Table 2
Interaction analysis (Joint test)

Supplementary Table 3
Baseline women factors by HDL-C

Supplementary Table 4
Subgroup analysis by smoking status (adjusted analysis)

Supplementary Table 5
Sub-analysis by menopausal status (adjusted analysis)

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Supplementary Table 6

Sensitivity analysis for the exposure duration impact (model II) and baseline imbalance (model III)

Supplementary Table 7

Adjusted hazard ratio for each cancer by binary HDL-C

Supplementary Table 8

Comparison of HDL-C–cancer association with those from current study and literature review

Supplementary Fig. 1

Simplified directed acyclic graph showing assumed causal structure in our adjusted models. Directed acyclic graph were constructed at website (http://www.dagitty.net/dags.html#). Women factors (mentation status, delivery frequency, breast feeding duration, use of oral pills, and estrogen replacement therapy) were considered to estimate the cancer risk in women sub-analysis.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209-249. PUBMED | CROSSREF
2. Catapano AL, Pirillo A, Bonacina F, Norata GD. HDL in innate and adaptive immunity. Cardiovasc Res 2014;103:372-383. PUBMED | CROSSREF
3. Kuvin JT, Karas RH. The effects of LDL reduction and HDL augmentation on physiologic and inflammatory markers. Curr Opin Cardiol 2003;18:295-300. PUBMED | CROSSREF
4. Yvan-Charvet L, Pagler T, Gautier EL, Avagyan S, Siry RL, Han S, et al. ATP-binding cassette transporters and HDL suppress hematopoietic stem cell proliferation. Science 2010;328:1689-1693. PUBMED | CROSSREF
5. Furberg AS, Veierød MB, Wilsgaard T, Bernstein L, Thune I. Serum high-density lipoprotein cholesterol, metabolic profile, and breast cancer risk. J Natl Cancer Inst 2004;96:1152-1160. PUBMED | CROSSREF
6. Cust AE, Kaaks R, Friedenreich C, Bonnet F, Laville M, Tjønneland A, et al. Metabolic syndrome, plasma lipid, lipoprotein and glucose levels, and endometrial cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC). Endocr Relat Cancer 2007;14:755-767. PUBMED | CROSSREF
7. Ahn J, Lim U, Weinstein SJ, Schatzkin A, Hayes RB, Virtamo J, et al. Prediagnostic total and high-density lipoprotein cholesterol and risk of cancer. Cancer Epidemiol Biomarkers Prev 2009;18:2814-2821. PUBMED | CROSSREF
8. Kucharska-Newton AM, Rosamond WD, Mink PJ, Alberg AJ, Shahar E, Folsom AR. HDL-cholesterol and incidence of breast cancer in the ARIC cohort study. Ann Epidemiol 2008;18:671-677. PUBMED | CROSSREF
9. Martin LJ, Melnichouk O, Huszti E, Connelly PW, Greenberg CV, Minkin S, et al. Serum lipids, lipoproteins, and risk of breast cancer: a nested case-control study using multiple time points. J Natl Cancer Inst 2015;107:107. PUBMED | CROSSREF
10. Pedersen KM, Çolak Y, Bojesen SE, Nordestgaard BG. Low high-density lipoprotein and increased risk of several cancers: 2 population-based cohort studies including 116,728 individuals. J Hematol Oncol 2020;13:129. PUBMED | CROSSREF
11. Jeong SM, Choi T, Kim D, Han K, Kim SJ, Rhee SY, et al. Association between high-density lipoprotein cholesterol level and risk of hematologic malignancy. Leukemia 2021;35:1356-1364. PUBMED | CROSSREF
12. Jung W, Jeon KH, Kang J, Choi T, Han K, Jin SM, et al. Association between cholesterol level and the risk of hematologic malignancy according to menopausal status: a Korean nationwide cohort study. Biomedicines 2022;10:1617. PUBMED | CROSSREF
13. Costa AR, Lança de Oliveira M, Cruz I, Gonçalves I, Cascalheira JF, Santos CR. The sex bias of cancer. Trends Endocrinol Metab 2020;31:785-799. PUBMED | CROSSREF

14. Bhaskaran K, Douglas I, Forbes H, dos-Santos-Silva I, Leon DA, Smeeth L. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5·24 million UK adults. Lancet 2014;384:755-765. PUBMED | CROSSREF
15. Kucharska-Newton AM, Rosamond WD, Schroeder JC, McNeill AM, Coresh J, Folsom AR, et al. Communities (ARIC) study. Lung Cancer 2008;61:292-300. PUBMED | CROSSREF
16. Tu H, Wen CP, Tsai SP, Chow WH, Wen C, Ye Y, et al. Cancer risk associated with chronic diseases and disease markers: prospective cohort study. BMJ 2018;360:k134. PUBMED | CROSSREF
17. Lim JH, Shin CM, Han K, Yoo J, Jin EH, Choi YJ, et al. Nationwide cohort study: cholesterol level is inversely related with the risk of gastric cancer among postmenopausal women. Gastric Cancer 2022;25:11-21. PUBMED | CROSSREF
18. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 2001;285:2486-2497. PUBMED | CROSSREF
19. Lupattelli G, Marchesi S, Lombardini R, Siepi D, Bagaglia F, Pirro M, et al. Mechanisms of high-density lipoprotein cholesterol effects on the endothelial function in hyperlipemia. Metabolism 2003;52:1191-1195. PUBMED | CROSSREF
20. Beloribi-Djefaflia S, Vasseur S, Guillaumond F. Lipid metabolic reprogramming in cancer cells. Oncogenesis 2016;5:e189. PUBMED | CROSSREF
21. Heinecke JW. Oxidants and antioxidants in the pathogenesis of atherosclerosis: implications for the oxidized low density lipoprotein hypothesis. Atherosclerosis 1998;141:1-15. PUBMED | CROSSREF
22. De Nardo D, Labzin LI, Kono H, Seki R, Schmidt SV, Beyer M, et al. High-density lipoprotein mediates anti-inflammatory reprogramming of macrophages via the transcriptional regulator ATF3. Nat Immunol 2014;15:152-160. PUBMED | CROSSREF
23. Sugano M, Tsuchida K, Makino N. High-density lipoproteins protect endothelial cells from tumor necrosis factor-alpha-induced apoptosis. Biochem Biophys Res Commun 2000;272:872-876. PUBMED | CROSSREF
24. Ruiz M, Okada H, Dahlbäck B. HDL-associated ApoM is anti-apoptotic by delivering sphingosine 1-phosphate to S1P1 & S1P3 receptors on vascular endothelium. Lipids Health Dis 2017;16:36. PUBMED | CROSSREF