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High-Density Lipoprotein Cholesterol and Cause-Specific Mortality in Individuals Without Previous Cardiovascular Conditions

The CANHEART Study

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ABSTRACT

BACKGROUND The prognostic importance of high-density lipoprotein cholesterol (HDL-C) as a specific risk factor for cardiovascular (CV) disease has been challenged by recent clinical trials and genetic studies.

OBJECTIVES This study sought to reappraise the association of HDL-C level with CV and non-CV mortality using a "big data" approach.

METHODS An observational cohort study was conducted using the CANHEART (Cardiovascular Health in Ambulatory Care Research Team) dataset, which was created by linking together 17 different individual-level data sources. People were included if they were between 40 and 105 years old on January 1, 2008, living in Ontario, Canada, without previous CV conditions or severe comorbidities, and had an outpatient fasting cholesterol measurement in the year prior to the inception date. The primary outcome was cause-specific mortality.

RESULTS A total of 631,762 individuals were included. The mean age of our cohort was 57.2 years, 55.4% were women, and mean HDL-C level was 55.2 mg/dl. There were 17,952 deaths during a mean follow-up of 4.9 ± 0.4 years. The overall all-cause mortality rate was 8.1 per 1,000 person-years for men and 6.6 per 1,000 person-years for women. Individuals with lower HDL-C levels were more likely to have low incomes, unhealthy lifestyle, higher triglycerides levels, other cardiac risk factors, and medical comorbidities. Individuals with lower HDL-C levels were independently associated with higher risk of CV, cancer, and other mortality compared with individuals in the reference ranges of HDL-C levels. In addition, individuals with higher HDL levels (>70 mg/dl in men, >90 mg/dl in women) had increased hazard of non-CV mortality.

CONCLUSIONS Complex associations exist between HDL-C levels and sociodemographic, lifestyle, comorbidity factors, and mortality. HDL-C level is unlikely to represent a CV-specific risk factor given similarities in its associations with non-CV outcomes. (J Am Coll Cardiol 2016;68:2073–83) © 2016 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CCHS = Canadian Community Health Survey

CI = confidence interval

CV = cardiovascular

HDL-C = high-density lipoprotein cholesterol

HR = hazard ratio

ICD = International Classification of Diseases

LDL-C = low-density lipoprotein cholesterol

For the past several decades, it has been widely accepted that high-density lipoprotein cholesterol (HDL-C) plays an important role in the development of cardiovascular (CV) mortality and morbidity (1–4). Early epidemiological studies consistently demonstrated a linear inverse relationship between HDL-C levels and CV events. For example, studies have shown that each 1 mg/dl increase in HDL-C level was associated with 3% to 4% lower rates of death from cardiac causes (2,5,6), suggesting that attainment of higher levels of HDL-C may reduce the risk of CV events. However, the inability of recent randomized trials to improve clinical outcomes by attempting to increase HDL-C level has challenged this conventional wisdom (7–11). Newer epidemiological and genetics studies have suggested that HDL-C level may not be predictive of CV outcomes in all subjects (12–15). Moreover, associations are known between HDL-C level and other demographic and lifestyle factors, such as smoking, obesity, and limited physical activity (2). These data suggest that HDL-C level may be a confounded variable, and thereby question the plausibility of HDL-C level as a specific risk factor for CV disease (16).

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To the best of our knowledge, no large population-based study has evaluated the association between the full range of HDL-C levels and CV and non-CV deaths in individuals living in the same environment and exposed to the same health care system. To achieve our objectives, we used the CANHEART (Cardiovascular Health in Ambulatory Care Research Team) cohort, which is a novel "big data" research database created by linking together multiple individual-level population-based datasets on sociodemographics, cardiac risk factors and comorbidities, laboratory values, health services, medications, and clinical outcomes in Ontario, Canada (17,18).

METHODS

The CANHEART cohort used in this study was created by merging 17 different individual-level data sources using encoded identifiers to ensure patient confidentiality (17,18). This big data source is described in detail elsewhere (17,18). Specific data sources essential to this current study included: 1) the Ontario Registered Persons Database, a registry of all Ontario residents with health insurance coverage; 2) the Canadian Institute for Health Information Discharge Abstract Database, the Ontario Diabetes Database, the Ontario Hypertension Database, and the Ontario Cancer Registry, which were used to identify previous cardiac risk factors and comorbidities; 3) the Ontario Drug Benefit prescription database, which was used to determine outpatient prescription drug use for patients 65 years or older; 4) the Gamma-Dynacare Medical Laboratory database, which captures 25% to 30% of all outpatient laboratory testing in Ontario, was used to determine cholesterol levels; 5) the Registrar General of Ontario Vital Statistics Database, which was used to determine cause of death of all Ontarians; and 6) the Canadian Community Health Survey (CCHS), an ongoing Canada-wide population-based survey that collected information on self-reported health status, health determinants, and health care utilization. This study was approved by the Sunnybrook Health Sciences Center Ethics Board. Consent was obtained by Statistics Canada from respondents to link the CCHS database to administrative databases.

STUDY SAMPLE. Ontario residents who were alive on January 1, 2008, were 40 to 105 years of age, and had a valid Ontario Health Insurance Plan number were eligible for inclusion in the study cohort. The inception year of 2008 was chosen to allow at least 4 years of follow-up on every individual. We excluded individuals who had lived in Ontario for <2 years prior to the inception date because they may represent temporary residents of the province. To construct a cohort of individuals without pre-existing CV disease,

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we excluded patients who had a history of myocardial infarction, heart failure, stroke, and coronary revascularization (percutaneous coronary intervention or coronary artery bypass graft surgery). Individuals who were long-term nursing home residents were excluded. We also excluded conditions that may reduce life expectancy such as a history of cancer, dementia, peripheral vascular disease, abdominal aortic aneurysm, and venous thrombosis (deep vein thrombosis and pulmonary embolism). Identification of these conditions was based on International Classification of Diseases (ICD)-9th and -10th revisions (17).

EXPOSURES AND OUTCOMES. Individuals who had a fasting HDL-C measurement performed in the outpatient setting in the year prior to the inception date (i.e., January 1, 2007 to December 31, 2007) were included in the study cohort. Cholesterol results closest to January 1, 2008, were used as the exposure measurement. HDL-C levels were determined by homogenous assay. Low-density lipoprotein cholesterol (LDL-C) levels were calculated by the Friedewald equation. In Canada, national practice guidelines recommend screening with full fasting lipid profile every 1 to 3 years for all men older than 40 years of age and women who are post-menopausal or older than 50 years of age (19). Lipid testing is also recommended for individuals at any age with CV risk factors, renal insufficiency, or evidence of atherosclerosis (19).

The primary outcome of our study was cause-specific mortality. Information on cause of death was obtained from the Ontario Vital Statistics Database, which categorizes cause of death using ICD codes (17). Deaths from CV causes were identified with ICD-10-CA I00 to I99, deaths from cancer causes were identified using C00 to D48, and the remaining codes were used to identify non-CV, noncancer causes of death. Complete follow-up data were available for each patient through December 31, 2012.

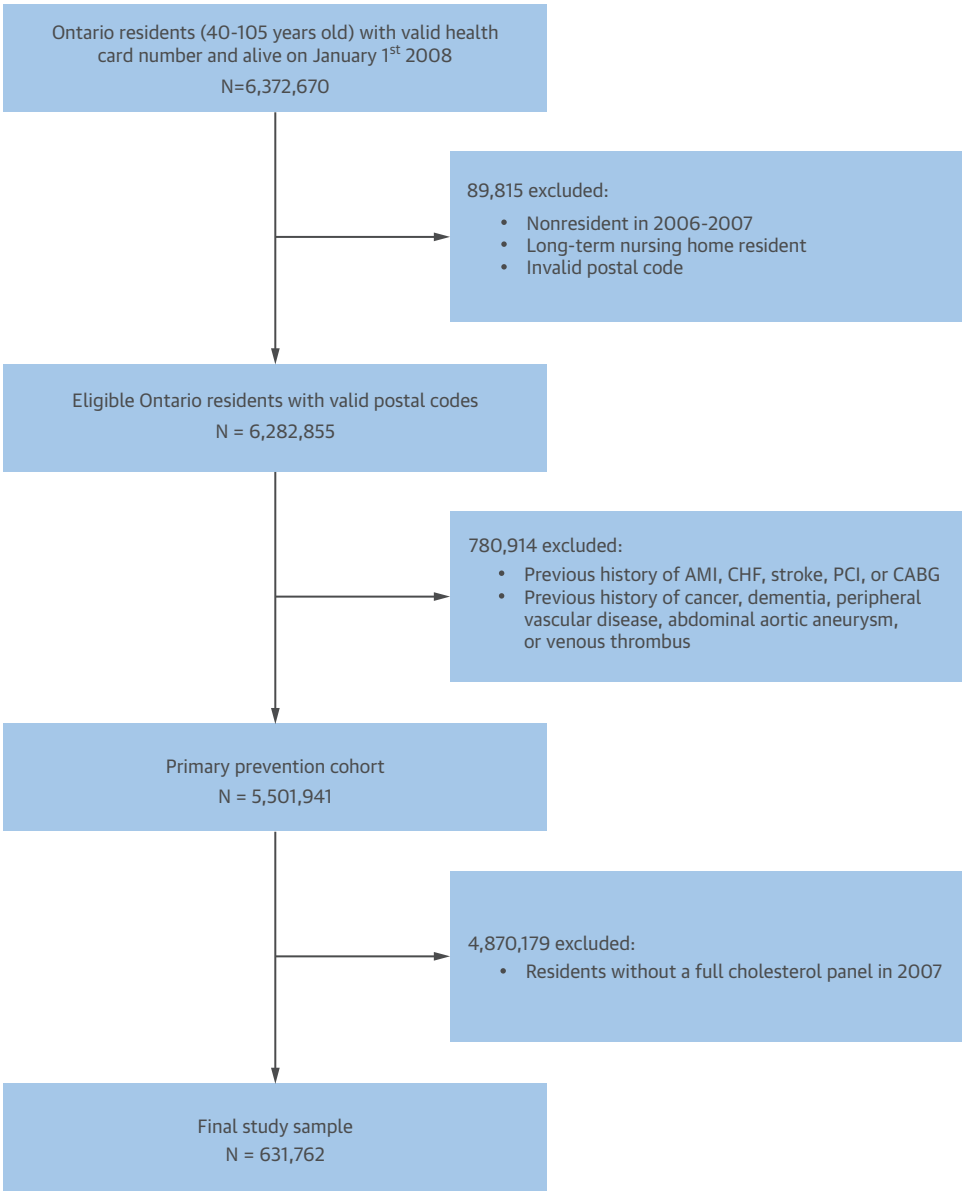
STATISTICAL ANALYSIS. The study cohort was stratified into pre-determined groups based on HDL-C levels in mg/dl (≤30, 31 to 40, 41 to 50, 51 to 60, 61 to 70, 71 to 80, 81 to 90, and >90) to allow examination of the relationship between HDL-C levels and mortality. Overall cause-specific mortality rates were standardized by age and sex, calculated by direct standardization using the 2006 Canadian population as the reference population. Based on previous studies, the HDL-C strata 41 to 50 mg/dl in men and 51 to 60 mg/dl in women were selected as the reference ranges for comparison (20). Analyses were stratified by sex because HDL-C levels differ in men and women in the general population. Tests of differences in characteristics across strata were performed using 1-way analysis of variance for comparing mean values of continuous variables and chi-square test for categorical variables.

Cause-specific hazard models were used to estimate the association of HDL-C levels on each of the 3 causes of death, after accounting for the other 2 causes of death as competing risks because individuals who died of a specific cause were no longer at risk of other causes of death (21,22). Hazard models were constructed separately in men and women. In the final cause-specific hazard model, we adjusted for the following factors: age, neighborhood income, hypertension, diabetes, smoking, cholesterol levels (non-HDL, triglyceride with logarithmic transformation), previous comorbidities (chronic obstructive pulmonary disease, hemiplegia or paraplegia, renal disease, liver disease, rheumatologic disorder, bleeding, major psychiatric disorder, pneumonia, respiratory failure, sepsis, and trauma), and the Johns Hopkins' Aggregated Diagnosis Groups, which has been shown to accurately predict mortality in the general ambulatory population (23). Alcohol use was also included in the adjustment model for non-CV, noncancer death. We imputed smoking status and alcohol use for those with missing data based on the characteristics of the respondents to CCHS surveys (additional details can be found in the Online Appendix) (17). Analyses were conducted in 10 imputed datasets and the validity of these databases was checked by examining the distribution of the observed and imputed values.

A series of additional analyses were performed to enhance our findings. First, we performed covariate adjustment starting with age, adding other variables sequentially (cardiac risk factors, neighborhood income, cholesterol levels, medical comorbidities, and smoking) to ensure consistent results. Second, we explored the association of HDL-C and cause-specific mortality in individuals with different LDL-C levels (≤100 mg/dl and >100 mg/dl). Third, we examined the potential impact of statins in a selected subgroup of individuals older than 66 years of age who were eligible for prescription drug benefits and stratified them based on the presence or absence of statin prescriptions within a year prior to cohort inception. Finally, we examined the potential impact of obesity by incorporating imputed body mass index (BMI) to the adjustment model and stratified individuals by BMI (more or less than 25 kg/m^2) among those who completed the CCHS.

Two-tailed p values <0.05 were considered significant. Analyses were performed with the use of SAS

FIGURE 1 Study Cohort



More than 6.3 million Ontario residents 40 to 105 years of age were initially considered in the study cohort. After inclusion and exclusion, our final study sample included 631,762 individuals who had cholesterol measurement within 12 months of the cohort inception. AMI = acute myocardial infarction; CABG = coronary artery bypass graft; CHF = coronary heart failure; PCI = percutaneous coronary intervention.

software (version 9.3, SAS Institute Inc., Cary, North Carolina).

RESULTS

To create the study cohort (Figure 1), we began with more than 6.3 million Ontario residents 40 to 105 years of age, with a valid health card number, and who were alive on January 1, 2008. From this study sample, 870,729 were excluded for demographic or medical conditions as described previously. Of the 5.5 million eligible individuals, cholesterol measurements were available in 631,762 patients within 12 months prior to the date of cohort inception; these individuals formed the study cohort.

BASELINE CHARACTERISTICS. The mean age of the study cohort was 57.2 years; 55.4% were women.

TABLE 1 Baseline Characteristics

		HDL-C (mg/dl)							
	Overall (N = 631,762)	**≤30 (n = 12,542)**	**31–40 (n = 91,932)**	**41–50 (n = 171,043)**	**51–60 (n = 155,845)**	**61–70 (n = 102,045)**	**71–80 (n = 54,459)**	**81–90 (n = 25,952)**	**>90 (n = 17,944)**
Age, yrs	57.2 ± 11.3	55.4 ± 10.9	56.1 ± 11.1	56.9 ± 11.2	57.5 ± 11.4	57.7 ± 11.5	57.9 ± 11.5	58.1 ± 11.4	58.7 ± 11.1
Female	55.4	20.1	28.1	43.5	59.6	71.7	79.8	84.4	86.4
Income quintiles									
1 (lowest)	16.2	20.4	18.4	17.0	15.9	15.1	14.0	13.2	13.3
2	20.1	21.9	21.0	20.8	20.2	19.4	18.6	18.0	17.3
3	20.6	20.8	21.1	21.1	20.7	20.2	19.7	19.6	18.7
4	21.4	19.7	20.7	21.2	21.5	21.7	22.1	22.0	21.7
5 (highest)	21.6	16.9	18.5	19.7	21.5	23.4	25.5	26.9	28.8
Hypertension	43.1	49.4	47.8	46.4	43.2	39.6	36.3	34.7	35.5
Diabetes	19.6	38.0	29.6	23.6	17.8	13.5	10.8	9.1	9.0
Smoker	16.6	25.4	21.7	18.0	13.9	15.3	12.6	16.8	12.8
COPD	8.8	11.2	9.6	9.1	8.5	8.3	8.1	8.3	9.2
Heavy alcohol consumption*	12.5	12.1	13.6	11.5	12.7	12.1	9.8	16.2	19.9
Aggregated diagnosis groups	9.6 ± 3.7	9.4 ± 3.8	9.3 ± 3.8	9.4 ± 3.7	9.6 ± 3.7	9.7 ± 3.7	9.8 ± 3.6	9.8 ± 3.6	9.9 ± 3.7
Lipid profile									
HDL-C, mg/dl	55.2 ± 15.8	27.4 ± 3.3	36.4 ± 2.7	45.6 ± 2.9	55.2 ± 2.9	65.1 ± 2.9	75.0 ± 2.9	85.0 ± 2.8	101.6 ± 11.1
LDL-C, mg/dl	119.2 ± 36.1	93.4 ± 37.2	112.5 ± 36.6	120.8 ± 36.5	122.9 ± 35.9	121.8 ± 35.2	119.4 ± 33.9	116.6 ± 33.1	112.5 ± 33.0
Triglycerides, mg/dl	134.2 ± 84.3	261.9 ± 167.4	194.7 ± 111.2	151.2 ± 79.8	121.8 ± 60.2	102.4 ± 48.8	89.8 ± 41.1	81.1 ± 36.0	74.6 ± 33.4
Triglyceride	113 (81–163)	219 (151–318)	169 (123–234)	134 (99–182)	109 (81–147)	92 (70–123)	81 (62–107)	74 (58–95)	67 (53–87)
Non-HDL-C, mg/dl	146.0 ± 40.4	144.0 ± 44.0	151.1 ± 42.4	151.1 ± 41.4	147.3 ± 39.8	142.2 ± 38.3	137.3 ± 36.3	132.8 ± 35.1	127.4 ± 34.6
Total cholesterol, mg/dl	201.1 ± 41.2	171.4 ± 44.2	187.6 ± 42.6	196.6 ± 41.4	202.5 ± 39.8	207.3 ± 38.3	212.4 ± 36.3	217.8 ± 35.1	228.9 ± 35.4
Lifestyle factors, n	5,108	103	737	1,352	1,211	814	478	248	165
Ideal BMI (<25 kg/m^2)	37.0	13.6	19.9	25.4	38.8	48.4	53.3	62.1	67.9
Moderate physical activity†	47.8	40.8	41.0	45.9	46.9	50.7	54.0	59.7	54.5
Ideal fruit and vegetable consumption‡	37.9	26.2	30.8	33.1	39.2	44.6	43.7	46.8	41.8

Values are mean ± SD, %, or median (interquartile range), unless otherwise indicated. *Heavy alcohol consumption defined as ≥5 drinks on 12 or more occasions per year. †Moderate physical activity defined as ≥30 min walking/day. ‡Ideal fruit and vegetable consumption defined as ≥5 servings/day.

BMI = body mass index; COPD = chronic obstructive pulmonary disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

The mean HDL-C level was 55.2 mg/dl, mean non-HDL-C level was 146.0 mg/dl, and the mean triglyceride level was 134.2 mg/dl. **Table 1** shows the baseline characteristics in all individuals as well as by HDL-C strata. The proportion of elderly and women was higher with increased HDL-C levels. Conversely, individuals with lower HDL-C levels had progressively higher rates of lower income, hypertension, diabetes, smoking, and chronic obstructive pulmonary disease. LDL-C levels did not have a consistent relationship with HDL-C levels, whereas triglyceride levels were lower in individuals with higher HDL-C levels. Heavy alcohol consumption was more frequently observed among individuals with very high HDL-C levels. The mean HDL-C level was 48.9 mg/dl in men and 60.2 mg/dl in women. The relationship between lower HDL-C levels and higher rates of cardiac risk factors and comorbidities were similarly observed in men and women.

There were 5,108 individuals who also completed the CCHS survey, which allowed us to examine lifestyle factors by HDL-C levels (**Table 1**). There was a strong relationship between healthier lifestyle factors with increasing HDL-C levels. Individuals with increasing HDL-C levels had progressively higher prevalence of lower BMI (<25 kg/m^2), moderate physical activity (≥30 min walking/day), and fruit and vegetable consumptions (≥5 servings/day).

MORTALITY AND HDL-C LEVELS. There were 17,952 deaths observed during a mean follow-up period of 4.9 ± 0.4 years, of which 4,658 were due to cardiac causes, 6,850 were cancer-related, and 6,444 deaths due to noncardiac/noncancer causes. The overall age- and sex-standardized mortality rate was 2.0 per 1,000 person-years for CV deaths, 2.5 per 1,000 person-years for cancer deaths, and 2.7 per 1,000 person-years for other deaths (Online Table 1). Age-standardized mortality rates for men and women according to HDL-C levels are shown in **Table 2** and **Figure 2**. In men, the age-standardized mortality rate was 8.1 per 1,000 person-years. Individuals at the

TABLE 2 Age-Standardized Cause-Specific Mortality*

		HDL-C (mg/dl)							
	Overall	≤30	31–40	41–50	51–60	61–70	71–80	81–90	>90
Men	281,973	10,025	66,121	96,645	62,887	28,838	10,987	4,037	2,433
All-cause mortality	8.1 (7.9–8.3)	14.7 (13.4–16.2)	9.3 (8.9–9.8)	7.5 (7.2–7.8)	7.2 (6.8–7.5)	7.2 (6.7–7.7)	8.0 (7.2–8.8)	9.2 (7.9–10.7)	12.1 (10.2–14.4)
Cardiovascular mortality	2.2 (2.2–2.3)	4.0 (3.3–4.8)	2.8 (2.5–3.0)	2.2 (2.0–2.3)	1.9 (1.8–2.1)	1.9 (1.6–2.2)	1.9 (1.5–2.4)	1.8 (1.2–2.5)	2.8 (1.9–4.0)
Cancer mortality	2.8 (2.7–2.9)	4.9 (4.1–5.7)	3.3 (3.0–3.5)	2.7 (2.5–2.8)	2.6 (2.4–2.8)	2.5 (2.2–2.8)	2.6 (2.2–3.0)	3.3 (2.6–4.2)	3.4 (2.5–4.6)
Other mortality	3.0 (2.9–3.1)	5.9 (5.1–6.8)	3.3 (3.0–3.6)	2.7 (2.5–2.9)	2.7 (2.5–2.9)	2.8 (2.5–3.2)	3.5 (3.0–4.1)	4.1 (3.3–5.2)	5.9 (4.5–7.5)
Women	349,789	2,517	25,811	74,398	92,958	73,207	43,472	21,915	15,511
All-cause mortality	6.6 (6.4–6.7)	19.1 (15.7–23.1)	9.0 (8.4–9.6)	7.5 (7.1–7.8)	6.2 (5.9–6.5)	5.6 (5.3–5.9)	5.8 (5.4–6.2)	5.8 (5.2–6.4)	6.8 (6.1–7.5)
Cardiovascular mortality	1.9 (1.8–1.9)	5.1 (3.3–7.5)	2.7 (2.3–3.1)	2.2 (2.0–2.4)	1.8 (1.6–2.0)	1.6 (1.4–1.8)	1.6 (1.3–1.8)	1.7 (1.4–2.0)	1.6 (1.3–2.0)
Cancer mortality	2.3 (2.2–2.3)	5.1 (3.6–7.0)	3.0 (2.7–3.4)	2.5 (2.3–2.7)	2.2 (2.0–2.3)	2.0 (1.8–2.2)	2.2 (2.0–2.4)	2.0 (1.7–2.3)	2.2 (1.8–2.6)
Other mortality	2.4 (2.3–2.5)	8.9 (6.6–11.8)	3.3 (2.9–3.7)	2.9 (2.6–3.1)	2.2 (2.1–2.4)	2.0 (1.9–2.2)	2.1 (1.9–2.4)	2.1 (1.8–2.5)	3.0 (2.5–3.5)

Values are n or incidence rate (95% confidence interval). *Age-standardized mortality rate per 1,000 person-years calculated using the 2006 Canadian population as the standard population.
HDL-C = high-density lipoprotein cholesterol.

lowest 2 strata of HDL-C levels (≤30 mg/dl and 31 to 40 mg/dl) had significantly higher overall mortality rates at 14.7 per 1,000 person-years, and 9.3 per 1,000-person years, respectively. Furthermore, individuals at the highest HDL-C stratum (>90 mg/dl) also had a higher than average mortality rate at 12.1 per 1,000-person years. In women, a similar pattern was observed where individuals with lower HDL-C levels had significantly higher age-standardized all-cause mortality and cause-specific mortality compared with the overall rate. Also, a higher than overall age-standardized mortality rate was observed for noncardiac/noncancer mortality in individuals with very high HDL-C levels (>90 mg/dl).

Adjusted hazard ratios (HR) of cause-specific mortality in different cholesterol strata compared with pre-specified reference ranges (41 to 50 mg/dl in men and 51 to 60 mg/dl in women) are shown in the **Central Illustration**. Men in the lowest HDL-C category (≤30 mg/dl) had increased cause-specific HR for CV mortality (HR: 1.81; 95% confidence interval [CI]: 1.45 to 2.25), cancer mortality (HR: 1.61; 95% CI: 1.32 to 1.97), and other mortality (HR: 2.01; 95% CI: 1.63 to 2.47) as compared to individuals with HDL-C of 41 to 50 mg/dl. Men with HDL-C levels from 31 to 40 mg/dl had increased relative hazard that ranged from 15% to 29% for cause-specific mortality. For men with high HDL-C levels (>90 mg/dl), increased hazards for noncardiac/noncancer mortality were also observed (**Central Illustration**).

Women with low HDL-C levels ≤30 mg/dl also demonstrated significantly higher cause-specific hazards of CV mortality (HR: 2.26; 95% CI: 1.56 to 3.29), cancer mortality (HR: 1.96; 95% CI: 1.43 to 2.69), and other mortality (HR: 2.86; 95% CI: 2.17 to 3.76) compared with women with cholesterol of 51 to 60 mg/dl. Individuals with HDL-C levels 31 to 40 mg/dl and 41 to 50 mg/dl had significantly higher relative hazard for cause-specific mortality that ranged from 7% to 43%. Women in the highest cholesterol category (>90 mg/dl) had significantly increased hazard of non-CV/noncancer deaths (HR: 1.32; 95% CI: 1.01 to 1.71).

ADDITIONAL ANALYSES. Among 149,348 individuals (61,343 men; 88,005 women) who were older than 66 years, 31,507 men and 44,399 women were prescribed statin therapy prior to cohort inception. The relationship between HDL-C cause-specific outcomes for statin users (**Figure 3**) was similar to our overall cohort in that we observed those with lower HDL-C had higher HR for cause-specific mortality. Subjects with very high HDL-C levels were not associated with significantly higher risk of mortality. For 29,836 men and 43,606 women older than 66 years who were not prescribed statins, the relationship was similar with those prescribed statins (Online Figure 1).

The results of additional analyses for patients with LDL-C <100 mg/dl or ≥100 mg/dl (Online Figures 2 and 3) were consistent with the previous analysis that lower HDL-C levels were associated with higher HR for cause-specific mortality and subjects with very high HDL-C levels also were associated with higher risk. Additionally, we evaluated the impact of BMI, but it did not alter our overall results, as shown in Online Figure 4.

DISCUSSION

In combining multiple clinical and administrative databases in Canada, we were able to create a

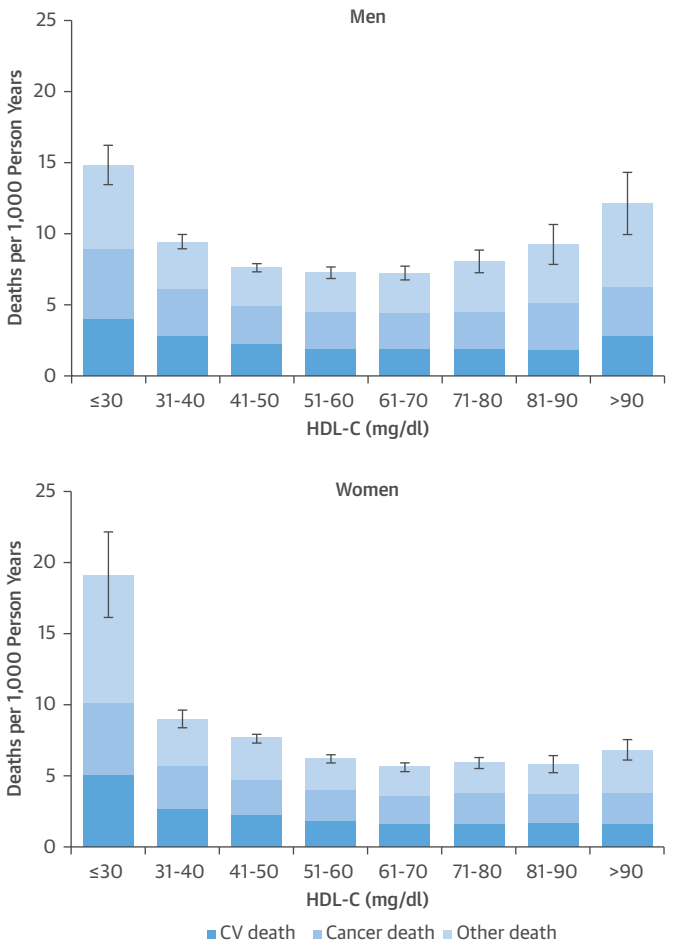
CANHEART "big data" cohort to examine the relationship of HDL-C levels and cause-specific mortality in more than 630,000 individuals without previous CV conditions. This afforded a unique opportunity to extend previous knowledge by evaluating the entire spectrum of HDL-C levels in an unselected population. We found that lower HDL-C levels were associated with a progressively higher proportion of individuals who were socioeconomically disadvantaged and had less healthy lifestyle behaviors, more cardiac risk factors, and a greater burden of medical comorbidities. Even adjusting for a comprehensive list of potential confounding factors, we found that the relationship between HDL-C levels and outcomes were not linear. Instead, we found lower HDL-C levels had increased hazard of both CV and non-CV mortality, and individuals who had very high HDL-C levels also demonstrated increased hazard of non-CV mortality. This suggested that HDL-C level is a marker of poor general health and may not be an independent modifiable risk factor specifically for CV disease.

Recent studies have cast doubts about the prognostic importance of HDL-C level as a modifiable risk factor (3,16,24). Trials of niacin and cholesteryl ester transfer protein inhibitors have clearly demonstrated their ability to increase HDL-C substantially (7–11). However, none of these trials exhibited improved clinical outcomes compared with the placebo arms. Several contemporary studies have shown a lack of significant association of HDL-C levels and outcomes for patients on higher-intensity statins, with coronary artery disease, or who had undergone coronary artery bypass graft surgery (12,13,15). Genetic studies using Mendelian randomization to examine the effect of very low HDL-C levels found no association with premature coronary heart disease (14). Accordingly, the current focus of the HDL-C hypothesis has shifted away from absolute HDL concentrations and toward the function of HDL-C. For example, HDL-C efflux capacity has been shown to be less confounded than HDL-C levels and a strong independent marker of CV events (25).

Our finding that lower HDL-C levels were associated with higher risk of CV death was consistent with other observational studies. However, our study was among the first to describe a similar relationship with cancer death and other causes of death. Wilson et al. (26) examined 2,748 Framingham Heart Study participants and found no conclusive relationship between HDL-C levels and cancer deaths. The study was likely underpowered because it was based only on 100 cancer deaths in men and 76 cancer deaths in women, whereas our study included 6,850 cancer deaths, and 6,444 non-CV/noncancer deaths. Wilkins et al. (27) conducted the Lifetime Risk Pooling Project, which included a community-based cohort of 24,440 participants, also found an association between HDL-C and total mortality in men. However, in contrast to our findings, that association was attenuated after adjustment for traditional CV risk factors and alcohol consumption.

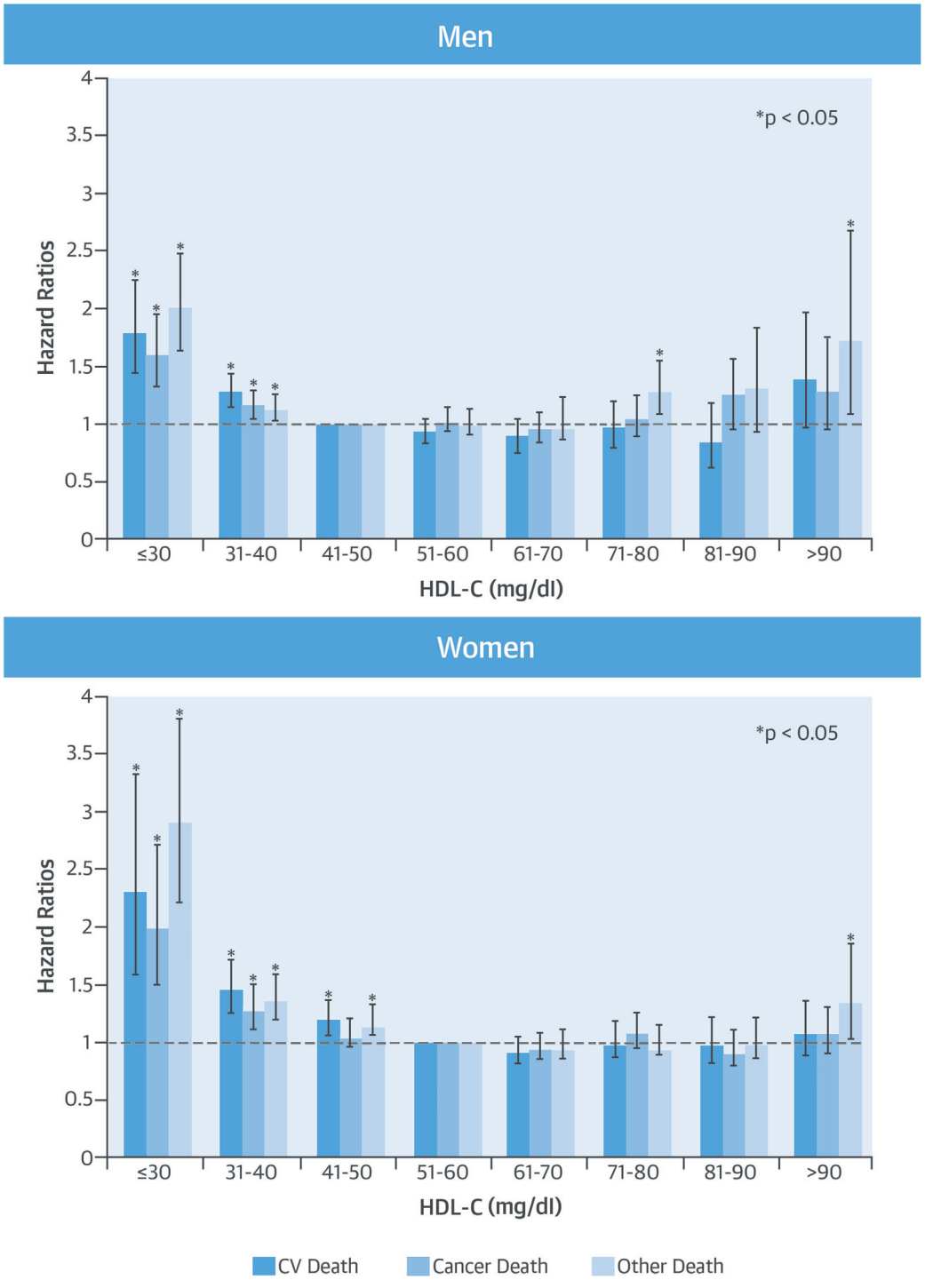
The majority of previous observational studies likely lacked sufficient sample sizes to explore outcomes at a full range of HDL-C levels. The Emerging

FIGURE 2 Age-Standardized Cause-Specific Mortality



Both men and women demonstrated a similar pattern in which lower levels of high-density lipoprotein cholesterol (HDL-C) levels were associated with significantly higher age-standardized all-cause mortality and cause-specific mortality. Mortality also rose with higher HDL-C levels, particularly in men. Error bars = 95% confidence intervals of the total mortality rates. CV = cardiovascular.

CENTRAL ILLUSTRATION **HDL-C and Cause-Specific Mortality in Individuals Without Prior CV Conditions**



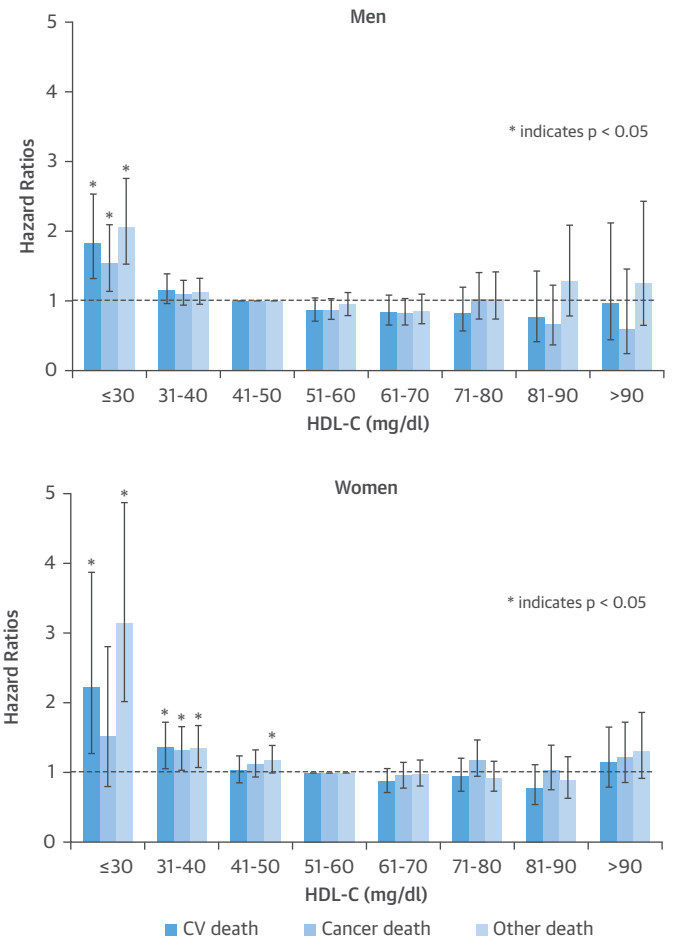
Ko, D.T. et al. J Am Coll Cardiol. 2016;68(19):2073–83.

In this observational cohort study, we examined the association of high-density lipoprotein cholesterol (HDL-C) level with cardiovascular (CV) and non-CV mortality using a "big data" set created by linking together 17 different individual-level data sources. Lower HDL-C levels were independently associated with higher risk of CV, cancer, and other mortality compared with individuals in the reference ranges of HDL-C levels (men: 41 to 50 mg/dl; women: 51 to 60 mg/dl). Additionally, individuals with higher HDL levels had increased hazard of non-CV mortality. Given the similarities in associations with CV and non-CV outcomes, it is not likely that HDL-C level represents a CV-specific risk factor.

Risk Factors Collaboration was able to examine the impact of cholesterol levels and outcomes on 302,430 subjects, but the data were merged from 68 long-term prospective studies from different time periods and different countries. A major strength of our study was the ability to examine a large population-based cohort of individuals living in a similar environment, under the care of the same health care system, with complete follow-up for a host of mortality outcomes. We observed a dose-response association between HDL-C levels and cause-specific mortality outcomes that was "U-shaped," rather than linear, as it is traditionally described. Patients whose HDL-C levels were very low (<50 mg/dl in women and <40 mg/dl in men) and very high (>80 to 90 mg/dl) experienced a greater hazard of death compared with individuals who had HDL-C levels that fell within intermediate ranges.

We are uncertain as to why higher hazard of noncardiac/noncancer mortality was observed among individuals with very high HDL-C levels. A previous study from Finland has suggested that the increased risk associated with high HDL-C levels in men might be related to increased alcohol intake (28). However, similar increased hazard was observed in our study even after adjusting for heavy alcohol use. The relationship of HDL-C levels and mortality may be mediated through complex relationships of many factors as we observed a pervasive pattern that individuals with low cholesterol levels had lower income; worse lifestyle factors in terms of ideal BMI, smoking status, physical activity, and fruit and vegetable consumption; and more comorbidities with higher prevalence of hypertension, diabetes, pulmonary disease, and unfavorable lipid profiles. Each of these factors is known to be associated with increased risk of morbidity and mortality.

FIGURE 3 Statin Therapy and Cause-Specific Mortality



Use of statin therapy did not change the relationship of HDL-C levels and cause-specific outcomes from those seen in the overall cohort in patients older than 65 years. Abbreviations as in Figure 2.

STUDY LIMITATIONS. First, our study focused on HDL-C because it is commonly performed in routine clinical practice to assess CV risk. We were unable to examine other potentially important aspects of HDL-C such as the relationship of HDL particle sizes, subclasses, or function with CV or non-CV mortality because these data are not available at the population level. Second, our laboratory data source included approximately 25% to 30% of all outpatient laboratory test results in Ontario. However, we have previously found that individuals included in our dataset are representative of those in the entire province (17). Third, information on cause-specific mortality may be subject to misclassification because we relied on vital statistics data, which classify causes of death on the basis of death certificate reports. However, such misclassification is likely nondifferential and unlikely to influence our results substantially. Fourth, we did not have smoking status or alcohol use in the entire population. Using data from individuals in our study cohort who also completed the CCHS survey, we imputed smoking status and alcohol use for those with missing data to facilitate additional analyses. We analyzed the relationship of HDL-C and outcomes with and without imputed values and found the results were unchanged. Finally, although we did not have physical measures of obesity beyond

BMI, our overall cohort included individuals with and without obesity, and the inclusion of BMI did not alter our finding between HDL-C levels and outcomes. This additional analysis reinforces the fact that our associations were not just driven by patients with increased adiposity.

CONCLUSIONS

In a large population-based cohort of individuals without pre-existing cardiovascular conditions, low and very high HDL-C levels were associated with a higher risk of CV mortality as well as non-CV mortality. HDL-C levels were highly correlated with many factors such as sociodemographic, lifestyle, and comorbidity factors, all of which increase the risk of adverse outcomes. These findings suggested that HDL-C level is unlikely to represent a cardiovascular-specific risk factor or a target for intervention given similarities in its associations with noncardiovascular outcomes.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The association of HDL-C levels with conditions that increase the risk of both cardiovascular and non-CV mortality cast doubt on its role as an independently modifiable risk factor.

TRANSLATIONAL OUTLOOK: Future studies should examine specific aspects of HDL-C, such as HDL particle size, subclasses, and function to identify correlates of cardiovascular risk that may be amenable to therapeutic intervention.

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KEY WORDS cardiac and noncardiac death, epidemiology, outcomes, risk factor, sociodemographic

APPENDIX For supplemental methods as well as a table and figures, please see the online version of this paper.