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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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