High-density lipoprotein cholesterol and cause-specific mortality: A population-based study of more than 630,000 individuals without prior cardiovascular conditions

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for the Canadian Cardiovascular Health in Ambulatory Care Research Team

CANHEART

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Epidemiological data have suggested a protective dose-response relationship between HDL cholesterol levels and cardiovascular outcomes.

More recently, the importance of HDL cholesterol as a modifiable risk factor for heart disease has come under debate.

Niacin and cholesteryl ester transfer protein (CETP) inhibitors have shown an ability to raise HDL cholesterol levels substantially, but have not improved clinical outcomes.

Mendelian randomization studies have demonstrated some genetic mechanisms that raise HDL cholesterol levels are not associated with lower risk of myocardial infarction.
Background

- Conventional knowledge on the relationship between HDL cholesterol levels and cardiovascular events has primarily come from observational studies such as the Framingham Heart study.

- Potential limitations:
  - Smaller numbers of patients that precluded evaluation of the full spectrum of HDL levels.
  - Few studies evaluated the relationship of HDL with non-cardiac events.
  - Relationship may have changed because of contemporary treatment.
To reappraise the epidemiological relationship of HDL cholesterol levels with mortality in a large unselected population without preexisting cardiovascular conditions

- A “big data” approach to examine the full spectrum of HDL cholesterol levels and cause-specific mortality
CANHEART cohort data sources

**Socio-demographics**
- Registered Persons Database (RPDB)
- Citizenship & Immigration Canada Permanent Resident DB
- Ontario Visible Minority Database

**CV Risk Factors and Co-morbidities**
- Canadian Community Health Survey (CCHS)
- Gamma-Dynacare Medical Laboratories (GDML)
- Ontario Diabetes Database (ODD)
- Ontario Hypertension Database (OHD)
- EMRALD (EMR)
- Ontario Chronic Obstructive Pulmonary Disease Database (COPD)
- Ontario Asthma Database (ASTHMA)
- Ontario Cancer Registry (OCR)

**Health Care Services and Medications**
- ON Health Insurance Plan Physician Claims Database (OHIP)
- ICES Physician Database (IPDB)
- Ontario Drug Benefit Database (ODB)

**Clinical Outcomes**
- CIHI Discharge Abstract Database (CIHI DAD)
- CIHI National Amb. Care Reporting System (NACRS)
- Registrar General of Ontario Vital Statistics (ORGD)

GDML performs ~ 1/3 of all Ontario’s outpatient laboratory testing

Linked with encoded personal identifiers
CIHI=Canadian Institute for Health Information
EMRALD=Electronic Medical Record Administrative Data Linked Database

Tu JV et al. Circ Cardiovasc Qual Outcomes. 2015:204-12
Study sample

- **Inclusions:**
  - Ontario residents on January 1\textsuperscript{st}, 2008, 40 to 105 years old, valid health card number
  - Outpatient cholesterol level in the year prior to the cohort inception (i.e., Jan 1 to Dec 31, 2007)

- **Exclusions:**
  - Cardiovascular disease (myocardial infarction, heart failure, stroke, coronary revascularization)
  - Comorbidities (cancer, dementia, peripheral vascular disease, abdominal aortic aneurysm, venous thrombosis)
  - Nursing home residents

- **Sample size = 631,762**
Methods

- Outcomes
  - Cardiovascular mortality
  - Cancer mortality
  - Other (non-cardiovascular, non-cancer) mortality

- Cause-specific Cox proportional hazard models that accounted for the competing risk of other types of cause-specific deaths
  - Final model adjusted for age, income, smoking, hypertension, diabetes, non-HDL, triglyceride, medical comorbidities (respiratory, neurological, renal, rheumatologic, bleeding disorder, sepsis, major psychiatric disorder, history of respiratory failure/shock, trauma), and the Aggregated Diagnosis Groups
## Baseline characteristics

<table>
<thead>
<tr>
<th>HDL Cholesterol (mg/dL)</th>
<th>≤30</th>
<th>31-40</th>
<th>41-50</th>
<th>51-60</th>
<th>61-70</th>
<th>71-80</th>
<th>81-90</th>
<th>&gt;90</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=12,542</td>
<td>N=91,932</td>
<td>N=171,043</td>
<td>N=155,845</td>
<td>N=102,045</td>
<td>N=54,459</td>
<td>N=25,952</td>
<td>N=17,944</td>
<td></td>
</tr>
<tr>
<td>Mean age, years</td>
<td>55.4</td>
<td>56.1</td>
<td>56.9</td>
<td>57.5</td>
<td>57.7</td>
<td>57.9</td>
<td>58.1</td>
<td>58.7</td>
</tr>
<tr>
<td>Female, %</td>
<td>20.1</td>
<td>28.1</td>
<td>43.5</td>
<td>59.6</td>
<td>71.7</td>
<td>79.8</td>
<td>84.4</td>
<td>86.4</td>
</tr>
<tr>
<td>Low income, %</td>
<td>20.4</td>
<td>18.4</td>
<td>17.0</td>
<td>15.9</td>
<td>15.1</td>
<td>14.0</td>
<td>13.2</td>
<td>13.3</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>49.4</td>
<td>47.8</td>
<td>46.4</td>
<td>43.2</td>
<td>39.6</td>
<td>36.3</td>
<td>34.7</td>
<td>35.5</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>38.0</td>
<td>29.6</td>
<td>23.6</td>
<td>17.8</td>
<td>13.5</td>
<td>10.8</td>
<td>9.1</td>
<td>9.0</td>
</tr>
<tr>
<td>Smoker, %</td>
<td>25.2</td>
<td>21.6</td>
<td>18.0</td>
<td>14.0</td>
<td>16.0</td>
<td>12.5</td>
<td>16.9</td>
<td>13.0</td>
</tr>
<tr>
<td>COPD, %</td>
<td>11.2</td>
<td>9.6</td>
<td>9.1</td>
<td>8.5</td>
<td>8.3</td>
<td>8.1</td>
<td>8.3</td>
<td>9.2</td>
</tr>
<tr>
<td>Total cholesterol, mean (mg/dL)</td>
<td>171.4</td>
<td>187.6</td>
<td>196.6</td>
<td>202.5</td>
<td>207.3</td>
<td>212.4</td>
<td>217.8</td>
<td>228.9</td>
</tr>
</tbody>
</table>
Age-standardized mortality in women

- Deaths per 1000 person years

<table>
<thead>
<tr>
<th>HDL-C (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>31-40</td>
</tr>
<tr>
<td>*</td>
</tr>
</tbody>
</table>

* P < 0.05 compared with average mortality

Average mortality = 6.6/1000 person-yr

8,613 deaths during follow-up of 4.9 years. Error bars correspond to 95% CI. Rate standardized to the 2006 Ontario census.
Adjusted hazard ratios in women

* P < 0.05 compared with reference group

Hazard ratios

CV death  Cancer death  Other death

REF

HDL-C (mg/dL)

≤30  31-40  41-50  51-60  61-70  71-80  81-90  >90

0  0.5  1  1.5  2  2.5  3  3.5  4
9,339 deaths during follow-up of 4.9 years. Error bars correspond to 95% CI. Rate standardized to the 2006 Ontario census.
Adjusted hazard ratios in men

Hazard ratios

HDL-C (mg/dL)

≤30 31-40 41-50 51-60 61-70 71-80 81-90 >90

CV death Cancer death Other death

* P < 0.05 compared with reference group

REF
Subgroup analyses stratified by i) LDL cholesterol levels (< 100 mg/dL, > 100 mg/dL), ii) statin user and nonusers for individuals older than 65 years showed similar results.

5,108 participants in the detailed Canadian Community Health Survey showed higher HDL cholesterol levels associated with lifestyle:
- Lower BMI (<25 kg/m²)
- Moderate physical activity (≥30 minutes walking/day)
- Fruit and vegetable consumptions (≥5 servings/day)
- Heavy alcohol use (≥5 drinks per occasion at least once a month during the year preceding the survey)
Limitations

- Did not have the ability to examine other aspects of HDL cholesterol such as particle sizes, subclasses, or function.

- Laboratory data source included approximately one third of all outpatient cholesterol tests in Ontario. We have demonstrated that data are representative of the overall Ontario population.

- Causes of death are based on death certificates which have not been independently adjudicated.
Conclusions

- HDL cholesterol levels are associated with many socioeconomic, lifestyle, and comorbidity factors.
- "U-shaped" response between HDL cholesterol levels and outcomes were observed particularly in men where individuals had higher risks of death at low and very high HDL cholesterol levels.
- Similar relationship between HDL cholesterol levels and the risk of both cardiac and non-cardiac deaths.
- HDL is unlikely to represent a cardiovascular specific risk-factor given similarities in its associations with non-cardiovascular outcomes.