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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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CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

Sunnybrook Health Sciences Centre

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Background

- 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

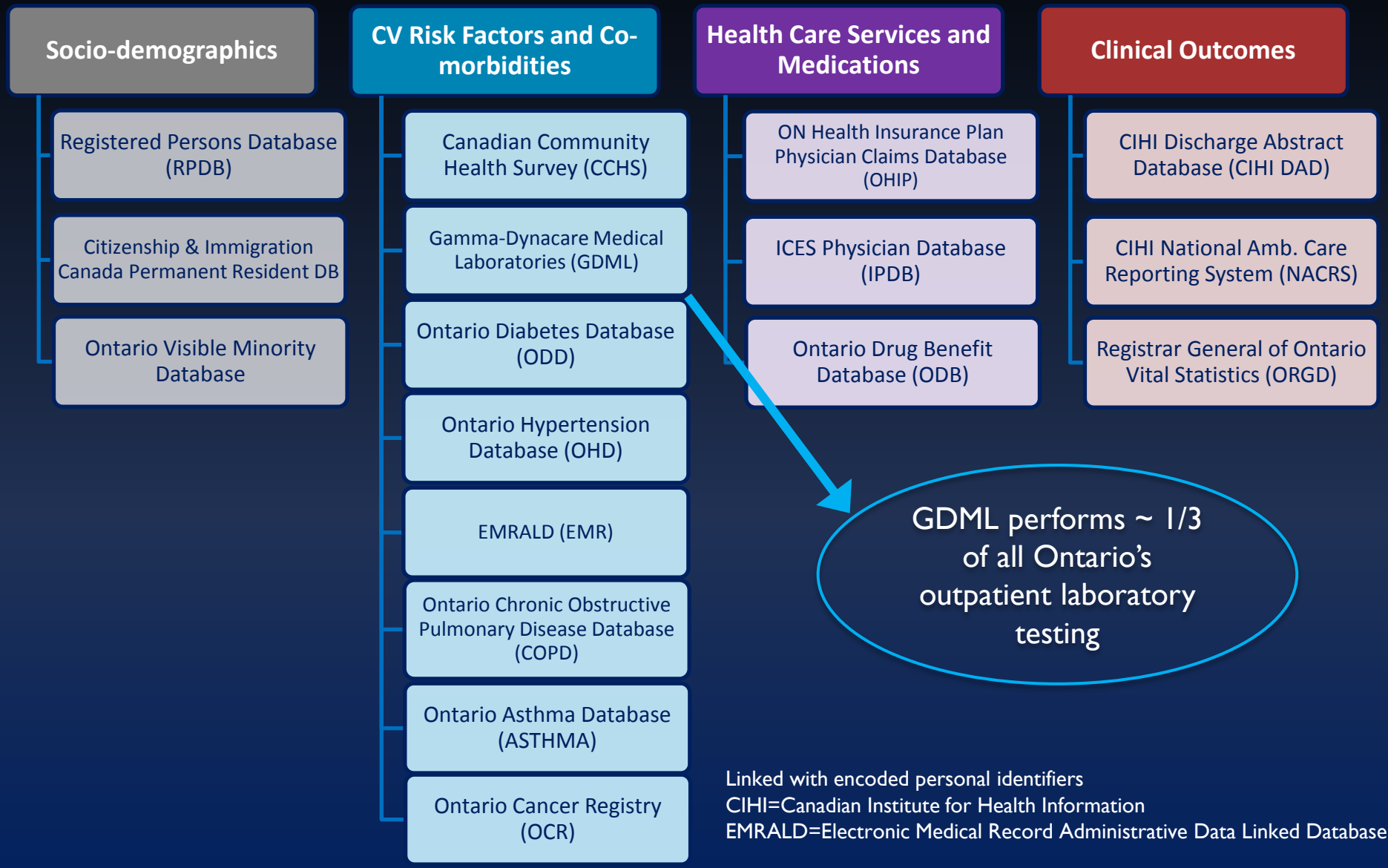
- Conventional knowledge on the relationship between HDL cholesterol levels and cardiovascular events has primarily come from observational studies such as the Framingham Heart study
- Potential limitations:
  - Smaller numbers of patients that precluded evaluation of the full spectrum of HDL levels
  - Few studies evaluated the relationship of HDL with non-cardiac events
  - Relationship may have changed because of contemporary treatment

Study objective

- 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



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 1st, 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**

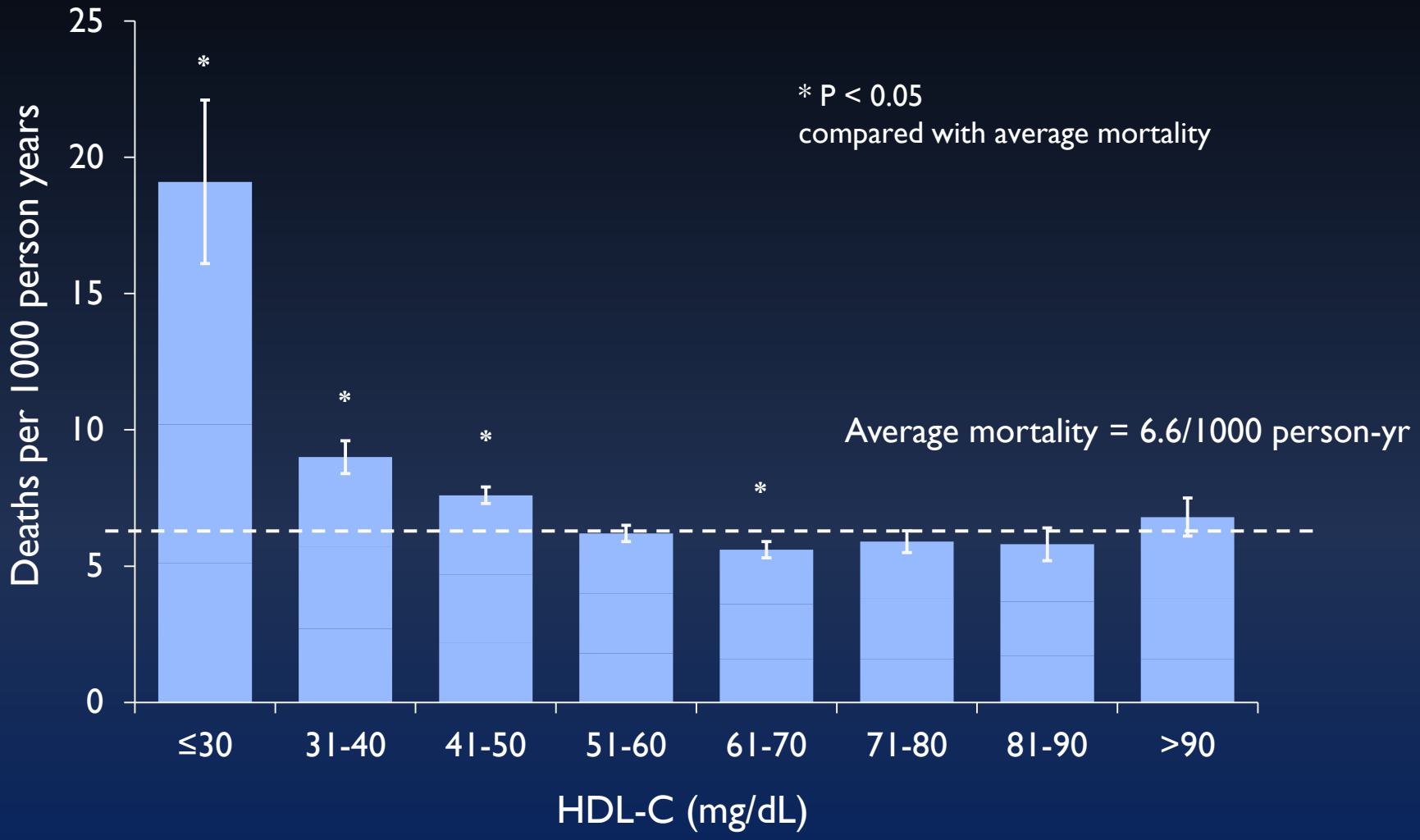
Methods

- 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

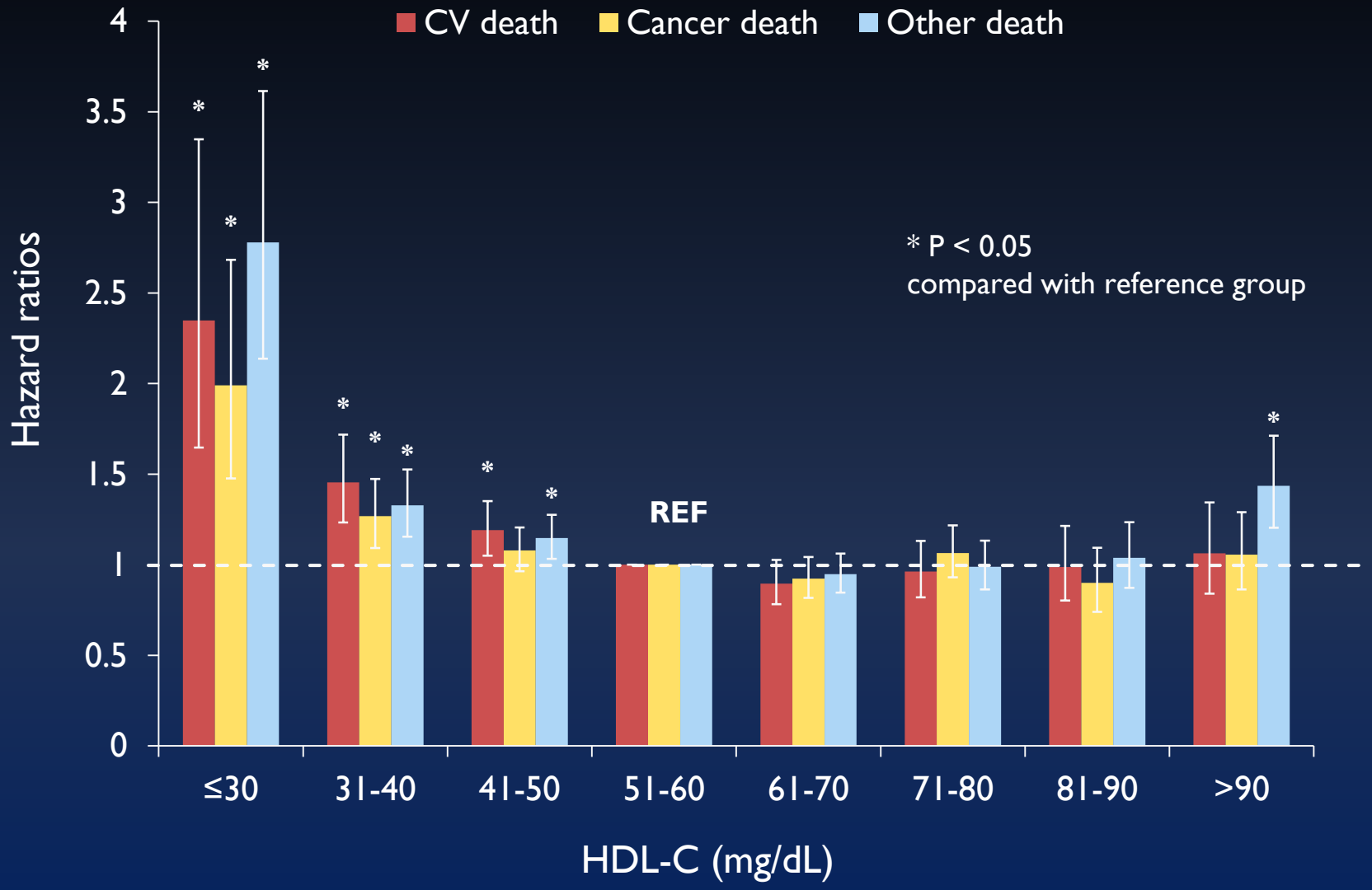
	HDL Cholesterol (mg/dL)							
	≤30	31-40	41-50	51-60	61-70	71-80	81-90	>90
	N=12,542	N=91,932	N=171,043	N=155,845	N=102,045	N=54,459	N=25,952	N=17,944
Mean age, years	55.4	56.1	56.9	57.5	57.7	57.9	58.1	58.7
Female, %	20.1	28.1	43.5	59.6	71.7	79.8	84.4	86.4
Low income, %	20.4	18.4	17.0	15.9	15.1	14.0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

Age-standardized mortality in women

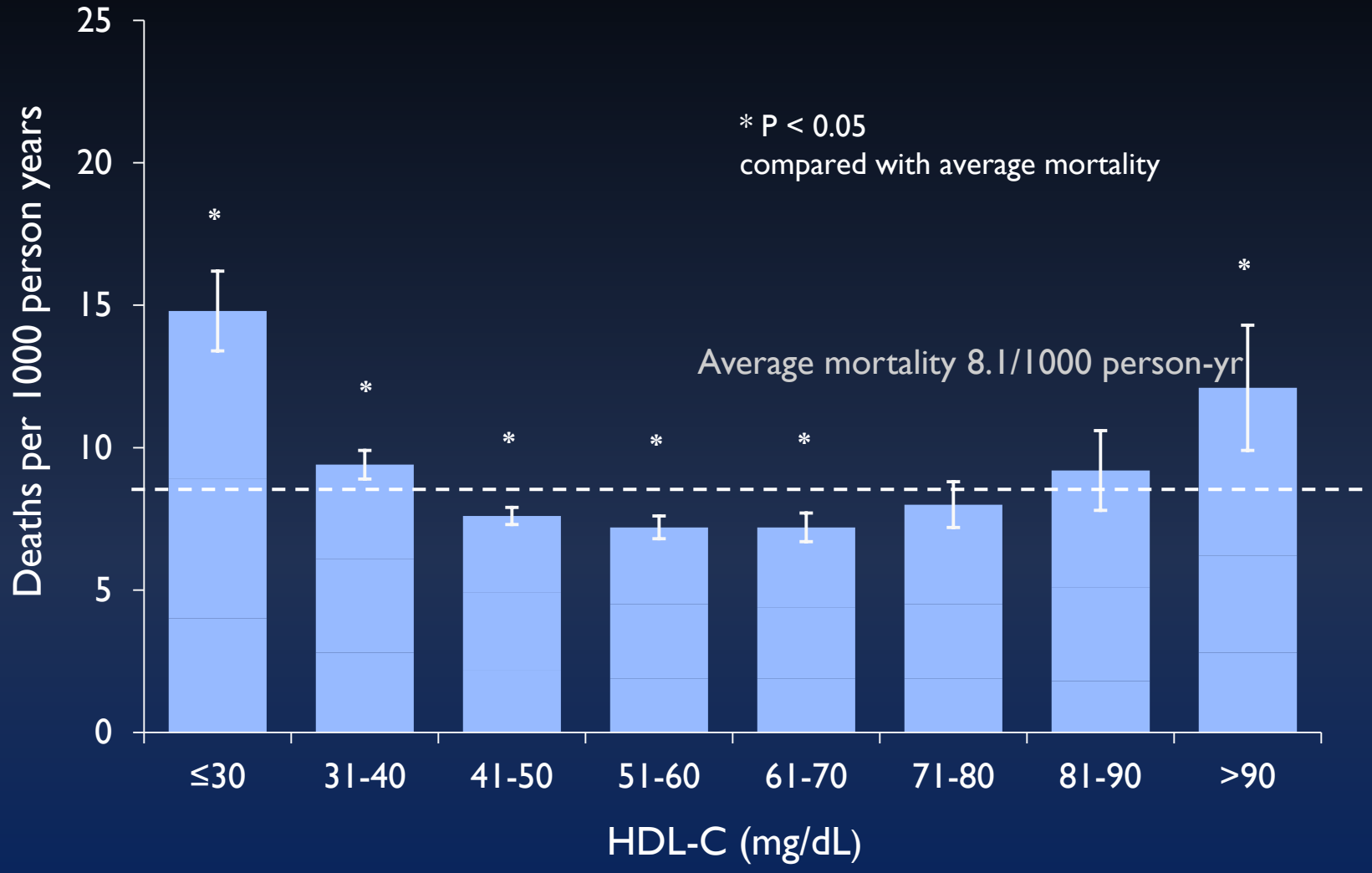


8,613 deaths during follow-up of 4.9 years. Error bars correspond to 95% CI. Rate standardized to the 2006 Ontario census.

Adjusted hazard ratios in women

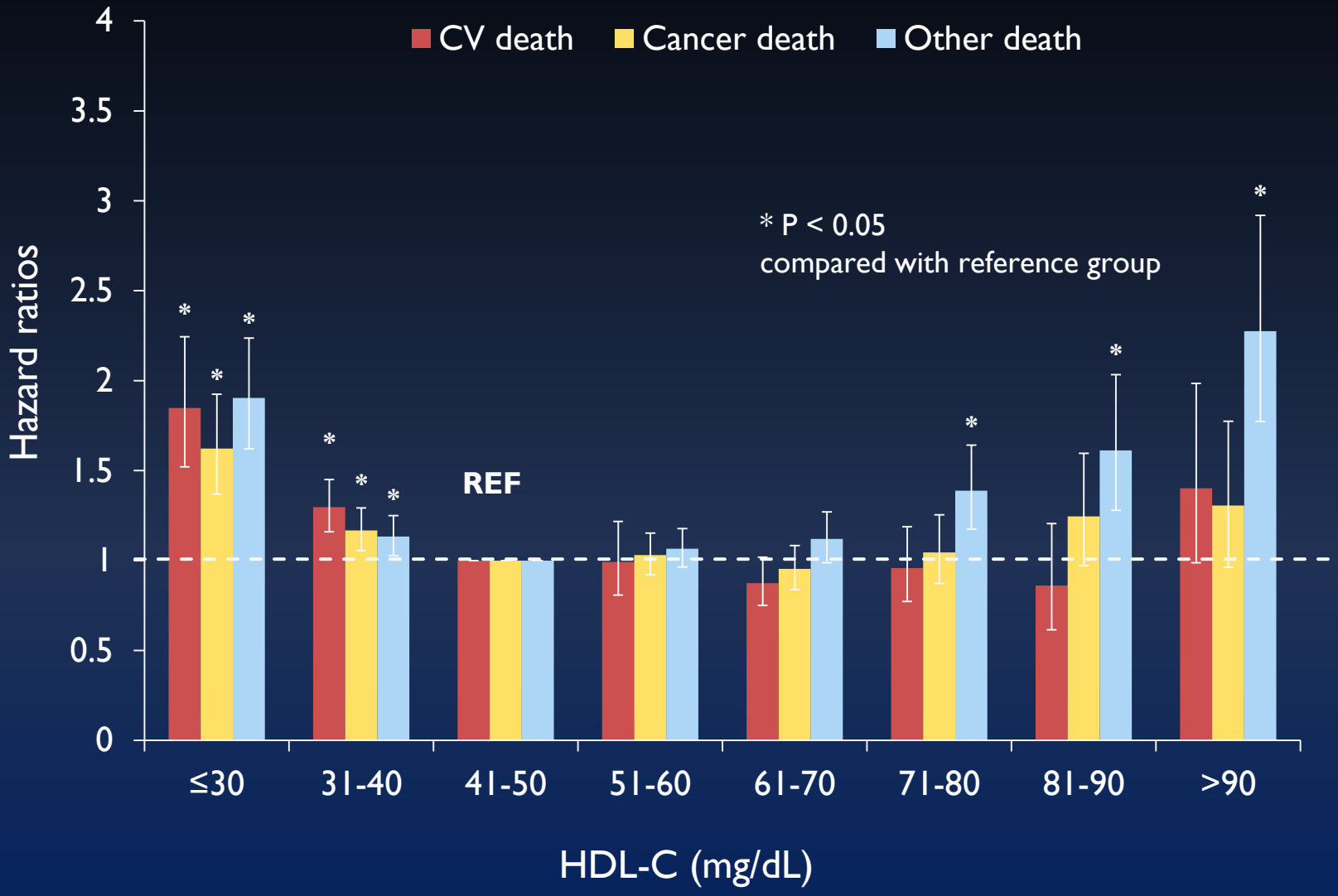


Age-standardized mortality in men



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



Additional analysis

- 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