Canadian Longitudinal Study on Aging: Advancing the Science of Population Health and Aging through Interdisciplinary Research

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DSECT Webinar, Sept. 12th, 2013
Population aging

- Due to declining fertility and increasing longevity (demographic transition)
- Unprecedented, accelerating, shifts will be permanent
- Profound implications for human life, including health
### Population Totals in Canada by Age Group and Year

<table>
<thead>
<tr>
<th>AGE</th>
<th>MALES</th>
<th>BOTH SEXES</th>
<th>FEMALES</th>
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1991 TOTALS: 13938100 | 28117600 | 14179500
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**1991 TOTALS**

- MALES: 13938100
- BOTH SEXES: 28117600
- FEMALES: 14179500
Rectangularization of the survival curve

FURTHER INCREASE IN LIFE EXPECTANCY

Squaring the survival curve

Compression of morbidity

- Morbidity compressed into a short period prior to death
- Represented an important shift in thinking
- Departure from the medical model of aging, which assumed that death always occurred as a result of a disease process, and that older age was a period of inevitable decline

Figure: Mortality According to Age in the Absence of Premature Death
Compression of morbidity

Fries’ paradigm based on the premise that:

- The length of human life is fixed
- Chronic disease can be postponed

- Predicted that the increase in life expectancy would plateau in the coming decades, particularly life expectancy from age 65 which excludes early life mortality
Evidence suggests otherwise

- Is average life expectancy approaching an upper limit to life expectancy?
  - The evidence that the average life span is 85 years is unconvincing
  - There is no evidence for further rectangularization of survival curves

- Will age at first infirmity increase?
  - There is no evidence for over-all declines in incidence of morbidity: on the contrary
  - Evidence for actual “(de)compression” of morbidity is ambiguous
Historical increases of life expectancy
Oeppen and Vaupel, Science 2002; C Finch adaptation

Phase 1
early urban

Phase 2
sanitation-nutrition

Phase 3?
regeneration
modern medicine
Social Policy Innovation

<table>
<thead>
<tr>
<th>Year</th>
<th>England</th>
<th>Norway</th>
<th>New Zealand</th>
<th>Iceland</th>
<th>Netherlands</th>
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<tr>
<td>2050</td>
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</tbody>
</table>

Life expectancy in years

90 80 70 60 50 40 30 1550 1600 1650 1700 1750 1800 1850 1900 1950 2000 2050
Demographic Futures

- Upward trend in life expectancy continue, cease, or reverse?
  + Effective interventions against age-related diseases
  + Improved environment for ageing
  + Life-cycle deceleration (delayed reproduction)

- Adverse effects of excess nutrition
- Adverse effects of alcohol and drug abuse
- Adverse effects of increasingly sedentary lifestyles
- Life-cycle acceleration (early maturation)
Why aging occurs

How aging is caused

Intrinsic

Extrinsic
# Genes Associated With Avoiding Late-Life Disease in Humans

<table>
<thead>
<tr>
<th>GENE</th>
<th>BIOCHEMICAL FUNCTION</th>
<th>COMMENTS</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOE</td>
<td>Lipoprotein metabolism</td>
<td>E2 variant is frequent in centenarians while E4 variant as a risk factor for Alzheimer’s disease is rare in centenarians.</td>
<td>Schachter et al. 1994</td>
</tr>
<tr>
<td>ACE</td>
<td>Angiotensin-converting enzyme</td>
<td>Plays a role in regulating blood pressure.</td>
<td>Schachter et al. 1994</td>
</tr>
<tr>
<td>PAI1</td>
<td>Plasminogen activator inhibitor 1</td>
<td>Plays a role in blood clotting, thus affecting risk of stroke and heart attack.</td>
<td>Mannucci et al. 1997</td>
</tr>
<tr>
<td>HLA-DR</td>
<td>Histocompatibility locus antigen</td>
<td>DR variant is frequent in centenarians; resists infection and inflammation?</td>
<td>Ivanova et al. 1998</td>
</tr>
<tr>
<td>WRN</td>
<td>Possesses both DNA helicase and exonuclease activity</td>
<td>Gene responsible for Werner’s Syndrome; mutation leads to a variety of aging-related pathologies, e.g., cataracts, cancer, osteoporosis, slow wound healing, etc.</td>
<td>Yu et al. 1996, Huang et al. 1998, Martin and Oshima 2000</td>
</tr>
<tr>
<td>B3AR</td>
<td>B-3 adrenergic receptor</td>
<td>Allelic form present affects time of onset of Type 2 diabetes.</td>
<td>Walston et al. 1995</td>
</tr>
<tr>
<td>MTHFR</td>
<td>5-, 10-methylenetetrahydrofolate reductase</td>
<td>Deficiency leads to increased levels of homocysteine and DNA hypomethylation; increases risk of cardiovascular disease and cancer.</td>
<td>Heijmans et al. 2000</td>
</tr>
<tr>
<td>KLOTHO</td>
<td>Membrane protein with β-glucosidase activity?</td>
<td>Homozygous variant form is underrepresented in elderly individuals.</td>
<td>Arking et al. 2002</td>
</tr>
</tbody>
</table>
# Genetic Heritability of Human Lifespan

Cournil & Kirkwood *Trends in Genetics* 2001

<table>
<thead>
<tr>
<th>Twin Studies</th>
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<tbody>
<tr>
<td>McGue et al (1993)</td>
<td>0.22</td>
</tr>
<tr>
<td>Herskind et al (1996)</td>
<td>0.25</td>
</tr>
<tr>
<td>Ljungquist et al (1998)</td>
<td>&lt;0.33</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Traditional Family Studies</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Philippe (1978)</td>
<td>0-0.24</td>
</tr>
<tr>
<td>Bocquet-Appel &amp; Jakobi (1990)</td>
<td>0.10-0.30</td>
</tr>
<tr>
<td>Mayer (1990)</td>
<td>0.10-0.33</td>
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<tr>
<td>Gavrilova et al (1998)</td>
<td>0.18-0.58</td>
</tr>
<tr>
<td>Cournil et al (2000)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Genes account for 25% of what determines disease and longevity
EPIGENETICS

ON/OFF SWITCH (GENE)

GUMMED UP ON/OFF SWITCH (GENE)

30 nm fiber 10 nm fiber

CANNOT

CAN

DNA AND CHROMOSOME LEVELS

HAc

Me

GUM

Me

GUM

HAc

Me

CANNOT

CAN
Non-Biological/Medical Determinants of Aging?

- Nutrition
- Lifestyle
- Environment
  - Physical
  - Social
  - Economic
  - Work Place
  - Psychological
- Chance
Intrinsic and Extrinsic Factors

Environmental influences
(e.g., rural, socio-economic, exercise, nutrition)

Genetics
(e.g., telomeres/oxidative stress, psychological & cognitive abilities, immune functions)

Chronic diseases
(e.g., diabetes, cancer, dementia, arthritis, cardio)

Aging
infections

Health Services Utilization

Time (Longitudinal Study)
The Canadian Longitudinal Study on Aging (CLSA)

A key strategic initiative of CIHR

The Canadian Longitudinal Study on Aging

More than 160 researchers - 26 institutions

Multidisciplinary - biology, genetics, medicine, psychology, sociology, demography, economics, epidemiology, nursing, nutrition, health services, biostatistics, population health
CLSA- The Concept

The Vision

A research platform - infrastructure to enable state-of-the-art interdisciplinary population based research and evidenced-based decision making.

The Aim

To study aging as a dynamic process and the inter-relationship among intrinsic and extrinsic factors from mid life to older age.
Innovation - Cell to Society

- Mid life to old age
- Quantitative traits
  - Physical
  - Social
  - Psychological
- Gene-environment interactions
- Disease, disability, psychosocial consequences
- Adaptation
Overall Aims of the CLSA

- The progression of **health** from middle-age to early old age to older old age
- The determinants of **well-being and quality of life**
- Risk Factors (including genetics) of **Chronic diseases**
- **Cognitive functioning** and **mental health**
- **Disability** and the compression of morbidity
- The examination of socioeconomic and health **inequalities** in an aging population
- **Social participation, social relationships and care giving** in an aging population
- **Retirement** and **post retirement** labor market activity
CLSA Architecture

Inter-Departmental study of 50,000 (at 11 sites)

Questionnaires, Database linkage

Follow-up over 20 years

Inception Cohort: 50,000

In-depth data collection on 30,000 (at 11 sites)

Clinical, Biological, Physical

Every 3 years age 45-85

Map of Canada showing various cities: Burnaby, Vancouver, Victoria, Calgary, Winnipeg, Sherbrooke, Montreal, Halifax, St. Johns, Ottawa, Hamilton, Montreal.
Sampling and Subject Selection

CLSA collaborated with Statistics Canada to develop Sampling Strategy

- **Target population**: People aged 45-85 living in private occupied dwellings in the ten provinces

- **Excluded**:
  - Residents of the three territories
  - Persons living on Indian reserves or Crown lands
  - Persons living in institutions
  - Full-time members of the Canadian Forces
  - Residents of some remote regions
Multi-stage sampling

- Sampling frame 2006 Census
- Selection
  - Clusters based on Census dissemination area blocks
  - Dwellings within cluster
  - Person within dwelling
- Response Rate
  - Household-level 80.8%
  - Person-level 92.1%
  - Overall 74.4%
CLSA – CCHS Healthy Aging

Participants were asked to share:
- Their contact information with the CLSA (for recruitment)
- Their survey responses with the CLSA (for analysis)

20,087 (76.3%) of Eligible Participants provided data to CLSA

N=30,865
N=26,248
N=4,617
N=11,742
N=8,345
N=527
N=5,634

Contact + Survey
Survey Only
Contact Only
Neither

45-85
>85

Canadian Longitudinal Study on Aging
Étude longitudinale canadienne sur le vieillissement
Aims of sampling

- Choose representative sample of eligible Canadians
  - 20K Tracking cohort; 30K Comprehensive cohort
  - Specified numbers in age-sex groups by province

- Options for methods of selection:
  - Using provincial health registries
  - Random digit dialing

- In Alberta and Quebec, we could not use registries
Example of requirement by province
Tracking cohort

<table>
<thead>
<tr>
<th>Alberta</th>
<th>45-54</th>
<th>55-64</th>
<th>65-74</th>
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<td>306</td>
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<tr>
<td># Providing Contact Info</td>
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<td>153</td>
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<td># Anticipated through CCHS</td>
<td>28</td>
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<td># Additional Participants</td>
<td>278</td>
<td>271</td>
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<td>224</td>
<td>151</td>
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<tr>
<td># Need to Sample*</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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* This will depend on the recruitment rate per number sampled
RDD approach

- Randomly sample numbers as far as possible in specified area codes and with next 3 digits in relevant area
- Identify eligible people at that number
- Randomly choose one person
- Recruit willing participants
Issues in using RDD

- Identifying numbers in specified area
- Having up-to-date list of numbers
- Ability to compute sample weights
- Presence of landlines and/or cellphones
- Eligibility within household – changes over time
- Method of initial contact
- Households without phones
- Numbers may be businesses, out of order, etc.
- People away from home (snowbirds, etc.)
Cell phones and landlines

- Statistics Canada survey December 2010
- Supplement to Labour Force Survey
- Households using cellphones exclusively:
  - Overall: 13%
  - Age 18-34: 50%
  - Over 35: 8%
  - Over 55: 4%
- Increasing over time
- Landlines reach nearly all our eligibles
‘Cold calling’ vs prior contact/letters

- Time and expense of mailing letters (only possible when we have name and address)
- May increase willingness to talk to interviewers (call display)
- Perhaps try both initially and then move to using one
Contacting subjects

- On average, anticipate making many calls to recruit a single person
  - Up to 7-10 calls to obtain response
  - Leave message?
  - Willingness to participate

- Working on assumption of 20% ‘recruitment rate’ for health registry data
  (15% in 75-85 age group)

- Exclude households without a phone
Some questions

- Should we try both cold calling and prior contact?
- Is it OK to exclude households without a phone?
- Should we leave a message after n calls fail to contact anyone at the number?
- Should we exclude cell phones?
Depth and Breadth of CLSA

PHYSICAL & COGNITIVE MEASUREMENTS
- Height, Weight
- Waist and hip measurements
- Bioimpedence
- Arterial pressure
- Mean heart rate
- Grip strength, timed up-and-go, chair raise, 4-m walk
- Standing balance
- Vision
- Hearing
- Spirometry
- Bone density
- Aortic calcification
- ECG
- Carotid intima-media thickness
- Cognitive Assessment

PSYCHOSOCIAL
- Social participation
- Social networks and support
- Care giving and Care receiving
- Mood, Psychological distress
- Coping, Adaptation
- Work to retirement transitions
- Job-Demand/Effort Reward
- Retirement Planning
- Social Inequalities
- Mobility-Lifespace
- Built Environments
- Wealth

LIFESTYLE & SOCIODEMOGRAPHIC
- Smoking
- Alcohol consumption
- Physical activity
- Nutrition
- Birth location
- Ethnicity/Race/Gender
- Marital status
- Education
- Income
Data Collection Overview

Potential Participants Sent Study Information

Participants Consent to Participate in CLSA

Participants Provide Questionnaire Data (n=50,000)

Physical/Psychological Data
- Neuropsychological Battery
- Performance Testing
- Anthropometric Measures
- Full body Bone Density
- Aortic Calcification
- ECG
- Carotid Intimal-Medial Thickness
- Pulmonary Function
- Vision and Hearing

Biological Data
- Blood
- Urine

Stored in Biobank (BBC) and Biomarker analysis

Stored in (NCC/SAC)

Questionnaire Data Processed

n=30,000

Telephone interview

n=20,000

Home Interview
Participants (50,000)

Enrolled

Questionnaire Data (50,000)

Physical Exam and Biological Specimen (30,000)

TIME

20 Years

Active Follow-up (F) Every 3 years
- Questionnaire
- Physical exam
- Biological samples

Maintaining Contact Interview (MC) mid-wave
- Update contact information
- Short Questionnaire

Passive Follow-up Every 3 years
- Health care utilization
- Disease registries
- Mortality databases

Data and Biological Sample Repositories

Researchers

Canadian Longitudinal Study on Aging
Étude longitudinale canadienne sur le vieillissement
Biological Samples

BIOCHEMICAL & HEMATOLOGICAL ANALYSIS (50 ml Blood; Urine)

General Hematology
- Basophils
- Eosinophils
- Neutrophils
- Lymphocytes
- Monocytes
- White blood count
- Red blood cells
- Hemoglobin
- Platelets

Lipid Profile
- HDL-cholesterol
- LDL-cholesterol
- Tryglycerides
- Glucose
- Fasting blood sugar

Genetic and Epigenetic Markers
Biospecimen Science

- The study of the molecular integrity of biospecimens
  - How pre-analytical handling affects analytic results
- Based on the desire to have high-quality well-annotated clinical samples to facilitate biomarker discovery and validation

Chaos in the Brickyard
Bernard Forscher Science 1963;142:339
Sources of Variation

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<tr>
<th>Pre-analytical</th>
<th>Analytical</th>
<th>Post-analytical</th>
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<tbody>
<tr>
<td>Patient state</td>
<td>Method type</td>
<td>Transmission of the test result</td>
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<tr>
<td>Biological variation</td>
<td>Calibration</td>
<td>Data analysis</td>
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<td>Patient preparation</td>
<td>Lot number</td>
<td>Reference intervals, decision limits, algorithms</td>
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<tr>
<td>Collection</td>
<td>Traceability</td>
<td>(multi-marker panels)</td>
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<tr>
<td>Processing</td>
<td>Interferences</td>
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<tr>
<td>Storage</td>
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</table>

**Biospecimen**

**Uncertainty of measurement**

**Interpretation**
Pre-analytical Variation (Bias)
Sample Quality is Imperative

- Lack of quality leads to false positives and false negatives, inaccuracy and non-reproducibility
  - Erodes public confidence
  - Wastes time and money
  - Impedes clinical development

High-quality data depends on high-quality analysis and high-quality specimens
Biospecimen Challenges

- Evidence-based best practices and standard operating procedures (SOP)
  - Reduction of process variation to yield unbiased samples
- Quality indicators/molecular markers and metrics for stored samples
- Certification of personnel and accreditation of biobanks
- Reporting criteria for biospecimens
  - Documentation/publication
Example Study Question

Physical Function
Mobility
Examples of precursors

*Individual (or intrinsic)*
- Chronic diseases (e.g., osteoarthritis)
- Neuropsychological conditions
- Cognition/Perceived health
- Medication use/Pain/Dizziness
- Poor vision
- Fear of falling/
- Obesity/Nutrition/weight loss/appetite
- Physical activity/fitness/strength
- Functional performance (measured & reported)
- Alcohol use
- Biomarkers (inflammation, hormonal, metabolism, genetics, epigenetics)
- Personality

*Contextual (or extrinsic or environmental)*
- Social participation
- Transportation resources
- Community/neighborhood characteristics
- Social network/support

Examples of consequences

*Diseases*
- Osteoporosis, sarcopenia

*Physical Health*
- Injuries/Frailty/Disability
- Poor nutrition status

*Psychological Health*
- Psychological distress
- Quality of life
- Loneliness
- Unmet needs

*Social Health*
- Social participation/engagement/capital
- Work Transitions
- Unmet needs
- Institutionalization
Mobility as a precursor:

Is mobility in mid- and later life associated with physical, psychological and social functioning? Specifically:

– How do changes in mobility impact upon indicators of psychological health including, depression, psychological distress, satisfaction with life, adjusting for other factors?
Mobility

Mobility as a mediator:

How does mobility in mid- and later life mediate relationships between determinants of health and health outcomes? Specifically:

– How does compromised mobility mediate the relationship between income and health?
Mobility

Mobility as an outcome:
How do physical, psychological, and social functioning in mid- and later life relate to changes in mobility? Specifically:

– What is the relationship between inflammatory biomarkers (e.g., IL-6, C reactive protein, albumin), hormonal biomarkers (e.g., IGF-1, T3, T4), metabolic (e.g., fasting glucose, cholesterol) or immunological markers (TNFα), oxidative stress (e.g. vitamin E and C), vitamin D, and (Epi) genetic markers (e.g., IGF-I and Apo-E) and changes in mobility and how is this relationship is modified by SES?

– What is the relationship between neighbourhood deprivation and incident mobility disability in aging population?
Where are we now?
CLSA Recruitment

Tracking Cohort
- Recruitment via CCHS complete
- Recruitment ongoing in all provinces through Ministry of Health (MoH) and/or Random Digit Dialing (RDD)
- Completion of all 20,000 baseline interviews by Spring 2013
- As of today:
  - 15,728 completed 60 minute baseline interview

Comprehensive Cohort
- Recruiting ongoing in all provinces through MoH and/or RDD
- Goal: complete first 8,000-10,000 baseline DCS visits by July 2013.
- As of today:
  - 5,029 in home interviews and 3,806 DCS visits completed (recruited)
Milestones for 2013

• Complete recruitment for Tracking Cohort – 20,000
• Recruit first 8,000-10,000 participants for Comprehensive Cohort
• Initiate Maintaining Contact for Tracking Cohort
• Data curation, derived variables and data cleaning
• Data access process, portal developed and tested
• Baseline tracking data released (early 2014)
• Planning and development for Wave 2
Upcoming areas of interest and development for the CLSA

- Core biomarker analysis
  - Imaging studies linking vascular imaging and the brain
  - Implementation of neurological conditions initiative
  - Selected possible enhancements to data collection
    - Environmental exposures
    - Life course, adaptation
    - Medication compliance
    - Contextual data
- Linkages and data harmonization
What would you like to see added to the CLSA?

Other Ideas for Research Questions?
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