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

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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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<tbody>
<tr>
<td>0-4</td>
<td>1000393</td>
<td>1553280</td>
<td>952887</td>
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<td>25-29</td>
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<td>30-34</td>
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<td>1171184</td>
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<td>1339986</td>
<td>666691</td>
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<td>1238387</td>
<td>620291</td>
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<td>60-64</td>
<td>578596</td>
<td>1190087</td>
<td>611491</td>
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<tr>
<td>65-69</td>
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<td>586592</td>
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<tr>
<td>70-74</td>
<td>364298</td>
<td>833991</td>
<td>469693</td>
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<tr>
<td>75-79</td>
<td>255599</td>
<td>622194</td>
<td>366595</td>
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<tr>
<td>80+</td>
<td>229898</td>
<td>670192</td>
<td>440294</td>
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</table>

**1991 Totals:**
- MALES: 13938100
- BOTH SEXES: 28117600
- FEMALES: 14179500
Rectangularization of 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
Distribution of life table deaths

- U.S. females
  - 1900
  - 1985
  - Theoretical

Life expectancy at birth (U.S. 1900)

Life expectancy at birth (U.S. 1988)

Range of theoretical estimates for average life-span

Verified longest lived individual as of 1990
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
Oopen and Vaupel, Science 2002; C Finch adaptation

Phase 1
early urban

Phase 2
sanitation-nutrition

Phase 3?
regeneration
modern medicine
Social Policy Innovation

Life-expectancy in years

1550 1600 1650 1700 1750 1800 1850 1900 1950 2000 2050

- England
- Norway
- New Zealand
- Iceland
- Netherlands
- Sweden
- Japan
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

Intrinsic

Extrinsic

How aging is caused
# 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 (\beta)-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

**Twin Studies**
- McGue et al (1993) 0.22
- Herskind et al (1996) 0.25
- Ljungquist et al (1998) <0.33

**Traditional Family Studies**
- Philippe (1978) 0-0.24
- Bocquet-Appel & Jakobi (1990) 0.10-0.30
- Mayer (1990) 0.10-0.33
- Gavrilova et al (1998) 0.18-0.58
- Cournil et al (2000) 0.27

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

ON/OFF SWITCH (GENE)

GUMMED UP ON/OFF SWITCH (GENE)

CANNOT

CAN

DNA AND CHROMOSOME LEVELS

30 nm fiber 10 nm fiber

CAN

CANNOT

HAc

Me

Me-

GUM

GUM

-HAc

Me-
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)

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

Aging

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

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

In-depth data collection on 50,000 (at 11 sites)
Questionnaires, Database linkage
Follow-up over 20 years
Every 3 years age 45-85
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
CLSA – CCHS Healthy Aging

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%
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
- >85 N=4,617
- 45-85
  - N=11,742 (Contact + Survey)
  - N=8,345 (Survey Only)
  - N=527 (Contact Only)
  - N=5,634 (Neither)
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 maybe BC, it appears we cannot 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>
<th>75-85</th>
<th>Total</th>
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<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>M</td>
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<tr>
<td># Required</td>
<td>306</td>
<td>306</td>
<td>306</td>
<td>306</td>
<td>204</td>
</tr>
<tr>
<td># Providing Contact Info</td>
<td>121</td>
<td>128</td>
<td>153</td>
<td>193</td>
<td>108</td>
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<tr>
<td># Anticipated through CCHS</td>
<td>28</td>
<td>35</td>
<td>56</td>
<td>82</td>
<td>53</td>
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<tr>
<td># Additional Participants</td>
<td>278</td>
<td>271</td>
<td>250</td>
<td>224</td>
<td>151</td>
</tr>
<tr>
<td># Need to Sample*</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

* 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.)
Obtaining lists of numbers

- Commercial organization, ASDE, in Quebec
- Can supply randomly chosen numbers
- Will state recency of population list of numbers
- If number is ‘listed’, can provide name and address attached to number (harder for cellphones)
- We are recruiting over 3 years, we will need ‘refreshed’ lists every so often
- Might over-sample in areas with many older people
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
Combining samples from cellphones and landlines

- Methods have been described
- Need to determine all phones in each household
- Keep logs of unfilled quotas (age-sex numbers)
- Interviewers construct rosters of eligibles within households and randomly choose one
Some issues with cell phones

- **Ethical:** incoming calls may cost user; privacy; activity when answering (driving, etc); children
- **Cost:** AAPOR states at least 2x, maybe 3-4x cost of landline survey
- **Getting addresses**
- **Quality of data (may be similar to landlines)**

Source: AAPOR
‘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

- How often should we refresh samples of numbers?
- 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

**HEALTH INFORMATION**
- Chronic disease symptoms (11 chronic conditions)
- Medication intake & Compliance
- Women’s health
- Self reported Health service use
- Oral health
- Preventative Health
- Administrative data Linkage Health Services & Drugs
- Other Administrative Data bases

**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

Canadian Longitudinal Study on Aging
Etude 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
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

Biological Data Stored in Biobank (BBC) and Biomarker analysis

n=30,000 Home Interview

n=20,000 Telephone interview

Questionnaire Data Processed

Stored in (NCC/SAC)
Participants (50,000) -> Enrolled

Questionnaire Data (50,000)

Physical Exam and Biological Specimen (30,000)

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
Example

Physical Function
Mobility
Mobility «activity & participation»

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?
Implementation Plans for Tracking Cohort of the CLSA (n=20,000)
Launch of the CLSA

- First selection of 20,000 started in late 2008 in collaboration with Statistics Canada CCHS Healthy Aging module (Tracking Cohort)
  - Approximately 12,500 have agreed to release their names to CLSA (5000 have been recruited)
- Remaining 15,000 for Tracking Cohort will be recruited in mid-2011
- Remaining 30,000 will be recruited in late 2011 (Comprehensive Cohort)
  - Provincial Client Registries or Random digit Dialing
Implementation Plans for Comprehensive Cohort of the CLSA (n=30,000)
Implementation Plan for the Comprehensive Cohort (n=30,000)

- Cohort of 30,000 persons to be recruited within 25 to 50 km radius of 11 data collection sites (DCS)
  - Victoria (3000), Vancouver (1500), Burnaby (1500), Calgary (3000), Winnipeg (3000), Hamilton (3000), Ottawa (3000), Montreal (3000), Sherbrooke (3000), Halifax (3000), St. John’s (3000)
Comprehensive Cohort Rolling Recruitment

- First batch of 1000 people to be recruited/site (mid-2011 to mid-2012)
  - Maintaining contact by phone (end of 2012-end 2013)

- Second batch of 1000 people to be recruited/site (mid-2012 to mid-2013)
  - Maintaining contact: (end of 2013-end of 2014)

- Third batch of 1000 people to be recruited/site (mid-2013 to mid 2014)
  - Maintaining contact: (end of 2014-end of 2015)
**Effective Design**
- Multidisciplinary Team
- Key initiative of CIHR
- Governance Structure
- Longitudinal Design
- Random selection
- Extensive data
- Extensive feasibility work
- Transparent data access policies
- Simple IP policy
- Harmonization with international cohorts
- State of the art facilities
  - Bio-repository
  - High Throughput biomarker labs
  - Statistical Analysis centre
  - Bioinformatics
  - Fully equipped data collection facilities

**Strong Scientific Program**
- Healthy Aging
  - Association studies based on candidate genes & diseases-related QTs
- Unique Approach:
  - Chronic conditions as Precursor, mediator Outcome
  - Binary outcomes and quantitative traits
- Quality of life
- Chronic disease management
- Risk factor identification
- Psychosocial aspects of Health
- Environment & Health
- Methodological development
  - Statistical modelling
  - Biological sample collection and storage

**Resource for the future**
- CFI-funded research facilities
- Supporting biomarker discovery research
- Supporting and developing complex diseases screening methodologies
- Personalized medicine
- Informing health & Social care policy
- Commercialization
- Building research capacity
- Platform for sub-studies
- Advancing Science of Aging
- Improving the health of Canadians