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
Rectangularization of the survival curve

FURTHER INCREASE IN LIFE EXPECTANCY

Squaring the survival curve

PERCENT SURVIVING

AGE

1900

1980

TRAUMA

IDEAL

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

  AND

- 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

Life-expectancy in years

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

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

Intrinsic \[\leftrightarrow\] 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>
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</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>
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<tr>
<td>ACE</td>
<td>Angiotensin-converting enzyme</td>
<td>Plays a role in regulating blood pressure.</td>
<td>Schachter et al. 1994</td>
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<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>
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<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</td>
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<td>Huang et al. 1998</td>
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<td>Martin and Oshima 2000</td>
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<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

**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)**

**30 nm fiber**

**10 nm fiber**

**CANNOT**

**CAN**

**DNA AND CHROMOSOME LEVELS**

- **Me**
- **GUM**
- **HAc**
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

Health Services Utilization

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

- More than 160 researchers – 26 institutions
- Multidisciplinary – biology, genetics, medicine, psychology, sociology, demography, economics, epidemiology, nursing, nutrition, health services, biostatistics, population health
Funders & Partners

▪ Strategic initiative of the Canadian Institutes of Health Research (CIHR)
▪ Funded by CIHR and the Canada Foundation for Innovation (CFI)
▪ Provinces and universities across Canada
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
Selected Research Goals

- The progression of health from middle age to early old age to older old age
- The determinants of well-being and quality of life
- Social participation, social relationships and caregiving in an aging population
- The examination of socioeconomic and health inequalities in an aging population
- Retirement and post-retirement labour market activity
- Cognitive functioning and mental health
- Disability and the compression of morbidity
Study Overview

50,000 women and men aged 45 - 85 at baseline

n=20,000
Randomly selected within provinces

n=30,000
Randomly selected within 25-50 km of 11 sites

Questionnaire
- By telephone (CATI)

Questionnaire
- In person, in home (CAPI)

Clinical/physical tests
Blood, urine (consent)
- At Data Collection Site

Interim contact, follow up every 3 years

Data Linkage (consent)
CLSA Architecture

Inter-Patient Collection of 50,000,000 (at 11 sites)
Questionnaire, Clinical, Biological, Physical
Follow-up over 20 years
Every 3 years age 45-85

Inception Cohort: 50,000

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

Map of Canada showing data collection sites:
Victoria, Burnaby, Vancouver, Calgary, Winnipeg, Sherbrooke, Montreal, Hamilton, Ottawa, St. Johns, Halifax.
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
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
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
Participants Consent to Participate in CLSA

Participants Provide Questionnaire Data (n=50,000)

DATA COLLECTION SITE VISIT
Physical/Psychological Data

Biological Data
- Blood
- Urine

Stored at Biorepository and Bioanalysis Centre (BBC)

Stored at (NCC/SAC)

Linkage to Admin Data

Questionnaire Data Processed

n=30,000 Telephone Interview

n=20,000 Home Interview

Potential Participants Sent Study Information

Participants

Canadian Longitudinal Study on Aging
Étude longitudinale canadienne sur le vieillissement
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
Mastodon - manages interactions with participants and securely stores identifying information

Sabretooth & Limesurvey – CATI software manages participant data collection, Interview scheduling and tracks the status of the interviews through to completion

Beartooth & Onyx – CAPI software used by the Data Collection Sites to coordinate the collection of questionnaire responses, physical measurements and biospecimens from participants

Opal – Central Data Repository – or databank – stores and manages all non-identifying data collected using Sabretooth, Beartooth and Onyx
Depth and Breadth of the CLSA

PSYCHOSOCIAL

- Social participation
- Social networks and support
- Caregiving and care receiving
- Mood, psychological distress
- Satisfaction with life
- Wealth
- Personality traits

- Work-to-retirement transitions
- Veteran identifier/ PTSD
- Retirement planning
- Social inequalities
- Mobility-lifespace
- Built environments
Depth and Breadth of the CLSA

HEALTH INFORMATION

- Chronic disease and symptoms
- Medication and supplement use
- Women’s health
- Self-reported health service use
- Oral health
- Administrative data linkage health services and drugs
- Other administrative databases
- General health
- Injuries
- Pain/discomfort
- Functional status
- ADL/IADL
Depth and Breadth of the CLSA

LIFESTYLE & SOCIODEMOGRAPHIC

- Smoking
- Alcohol consumption
- Physical activity
- Nutrition
- Birth location
- Ethnicity/race/gender
- Marital status
- Education
- Income
- Transportation
- Home ownership
At the Data Collection Site

- Reception
  - Sign in
  - Bar code scan
  - Contraindications Q

- Measurement Room 1
  - Hip Waist ratio
  - Height/Weight (BMI)
  - Heart rate & BP
  - ECG
  - c-IMT/Plaque sweep
  - Spirometry

- Measurement Room 2
  - DEXA (BMD, body composition, aortic calcification)

- Measurement Room 3
  - Event PMT
  - Audiometer
  - Stroop & COWAT (F,A,S) Choice Reaction
  - Social Network Q

- Measurement Room 4
  - Standing balance
  - Chair rise
  - Visual acuity
  - Fundus photograph
  - Ocular pressure
  - Grip strength

- Measurement Room 5
  - Timed PMT
  - Disease Symptoms Q

- Biospecimen Room
  - 50 ml blood draw
  - Sample processing

- Hallway
  - 4m walk
  - Timed Up and Go

- Check out
  - Review of results
  - Snack
  - Honorarium

TOTAL TIME
2.5 – 3 HRS
Biospecimen Room
Collection, processing, analysis

- 5 – 6 participants per day
- 50 mL blood
- Urine sample
- Hematology tests
- Collection to storage time
  2 hour

AcT DIFF, Beckman Coulter
Biospecimen processing: 42 aliquots per participant
Storage & Shipping

Matrix Tubes
- 500-μL V bottom screw top tubes
- Laser etched 2D unique barcode
- 96 well open-bottomed boxes for fast scanning
- Stored at DCS -80°C for a maximum of 5 days

Microwell Plates
- 3 section GenPlates (IntegenX)
- 96 wells per participant (10 μL whole blood per well)
- Dried overnight, sealed with adhesive transparent cover

Shipping
- Precharged vapour shippers (-160°C) with data logger
- Weekly to BBC via overnight courier
Biorepository and Bioanalysis Centre (BBC)

- 31 nitrogen freezers (-180°C)
  - space for 5 million aliquots
- Personal Archive
  - dry storage, humidity controlled, at room temperature
- Laboratory Information System (LabWare)
  - Sample tracking system
  - Quality control
- Consumable warehouse
Biomarker analysis
Disease Ascertainment Algorithms

- Diseases will not diagnosed by clinicians
- DAAs developed by CLSA Clinical Working Group
- Validated by pilot studies¹,²

- Osteoarthritis-knee, hip, hand
- Parkinsonism
- CAO
- Diabetes
- Hypo- and Hyperthyroidism
- Ischemic heart disease
- HBP
- Stroke/Cerebrovascular event
- Osteoporosis
- Depression
- Dementia

Proposed Data Linkages

- Regular linkage with mortality databases between waves of data collection
  - Decedent Questionnaire implemented for first follow-up
- Air pollution data (in collaboration with Health Canada)
- Administrative data linkage health services & drugs & other administrative databases for participant who provide consent
CLSA Recruitment: Where are we now?

**Telephone-Administered Questionnaires**
- Goal: Completion of all 20,000 baseline interviews Spring 2014
- As of last week:
  - 20,376 completed 60-minute baseline interview
  - 1,082 completed maintaining contact interview

**In-home Interviews and DCS Visits**
- Goal: complete first 8,000-10,000 baseline DCS visits by mid 2013
- As of last week:
  - 15,298 In home interviews completed
  - 12,777 DCS visits completed
What is required to create a centralized platform like CLSA?

- Good governance
- Coordinated ongoing ethics approval process
- Transparent Data and Sample Access Policies
- Transparent Data Ownership and IP Policies
- Integrated and secure IT infrastructure
CLSA Governance Structure

- CIHR Advisory Committee on Ethical, Legal and Social Issues
- International Scientific Advisory Board
- CLSA Advisory Council
- Scientific Management Team
- Data and Sample Access Committee
- Intellectual Property and Commercialization Committee
- Operations Committee
- Training and Research Capacity Committee
- Knowledge Translation and Communications Committee
- CIHR Oversight

Canadian Longitudinal Study on Aging
Étude longitudinale canadienne sur le vieillissement
Coordinated REB Process

- First known coordinated approach for a national observational study in Canada
- 11 sites, 11 REBs, one standardized set of study documentation for informed consent
- Online documentation process developed by the Public Health Agency of Canada (PHAC)
- Submit to McMaster (lead) REB
  - Provisional approval, comments posted on PHAC portal for other sites to review
  - Sites post local reviews; one set of comments sent to CLSA team for response
- Annual amendments, coordinated ethics renewals
Data and Sample Access

- Data and samples available to the research community
- Fundamental tenets:
  - The rights, privacy and consent of *participants* must be protected and respected at all times
  - The confidentiality and security of *data and biological samples* must be safeguarded at all times
  - CLSA data and biological samples are resources that will be used optimally to support research to benefit all Canadians.
What is the process to access data?

- 20,000 CATI Interviews: anticipate data to be available mid-2014
- Application process via CLSA website portal
- Review: Administrative, Data and Sample Access Committee recommendation
- Approval, data/sample sharing agreements
- Raw data and/or samples to investigator
- Return of derived variables to CLSA dataset
CLSA funded by the Government of Canada through the CIHR and CFI and by Provincial Governments

Transforming Everyday Life into Extraordinary Ideas

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www.clsa-elcv.ca
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 Telephone Interviews – 20,000
• Recruit first 10,000 participants for Comprehensive Assessment (DCS)
• Initiate Maintaining Contact Interview
• Data curation, derived variables and data cleaning
• Data access process, portal developed and tested
• Baseline tracking data released (Spring 2014)
• Planning and development for Wave 2
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