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

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OTC Summer Institute, June, 2011
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
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
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

Deaths

Age

0 10 20 30 40 50 60 70 80 90 100 110 120 130 140
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
Oepen 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>
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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>
</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

### 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)

CAN 30 nm fiber

CANNOT 10 nm fiber

CANNOT -Me

CAN -HAc

DNA AND CHROMOSOME LEVELS

Me-

GUM

Me-

GUM

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)

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

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

**Aging**

**Health Services Utilization**

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

A key strategic initiative of CIHR

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
Interdisciplinary Research Agenda
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)

Questionnaire, Clinical, Biological, Physical

Follow-up over 20 years

Every 3 years age 45-85

Inception Cohort: 50,000

Data collection on all 50,000

Clinical, Biological, Physical

Halifax

St. Johns

Burnaby

Ottawa

Victoria

Vancouver

Calgary

Winnipeg

Sherbrooke

Montreal

Sherbrooke

Hamilton

Montreal

Halifax

St. Johns
# 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
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
Participants (50,000) → Enrolled

Questionnaire Data (50,000)

Physical Exam and Biological Specimen (30,000)

Data and Biological Sample Repositories

Researchers

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 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

n=30,000

n=20,000

Home Interview

Telephone interview

Stored in Biobank (BBC) and Biomarker analysis

Stored in (NCC/SAC)

Questionnaire Data Processed
Equipment and Infrastructure Supporting Research on Aging

**Computer-Assisted Telephone Interview Centres**
Collect health and psychosocial data (located in Halifax and Sherbrooke).

**Data Collection Centres**
Collection of nutrition, physical, clinical data, & biological specimens.

**Genetics and Epigenetics Centre**
Genotyping, epigenetic analysis, and bioinformatics, (located in Vancouver)

**Biological Processing Centre**
Bio-banking, biomarker discovery & analysis (located in Hamilton).

**National Coordinating Centre**
Oversight, project management, data management, communication for overall initiative (located in Hamilton)

**Statistical Analysis Centre**
Assimilation, distribution and analysis of all CLSA data (located in Montreal)
Example

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/neighbourhood 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 (currently being recruited)

- Remaining Tracking Cohort will be recruited in late 2011

- Remaining 30,000 will be recruited in late 2011 (Comprehensive Cohort)
  - Provincial Client Registries
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 (late-2011 to late-2012)
  - Maintaining contact by phone (early 2013 - early 2014)

- Second batch of 1000 people to be recruited/site (late-2012 to late-2013)
  - Maintaining contact: (early 2014 - early 2015)

- Third batch of 1000 people to be recruited/site (late-2013 to late 2014)
  - Maintaining contact: (early 2015 - early 2016)
Future and Current Legacy of the CLSA Research Platform

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
Canadian Investment

$50M Canadian investment in national platform

- $23.5M CIHR for 5 Years
- $10M CFI for 5 Years
- $10M Provinces for 5 Years
- $6.5 M Universities and other partners**
- Invaluable in-kind contribution from Statistics Canada on design and recruitment
Possible Discussion Points

- Value of the CLSA platform
- Data access and IP policies
- Opportunities for collaboration for the core data collection CLSA
- Opportunities for analyses of the data and biological samples
- Opportunities for using CLSA facilities for non CLSA research
- Opportunities for sub-studies