Transforming Everyday Life into Extraordinary Ideas
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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</thead>
<tbody>
<tr>
<td>80+</td>
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<td>670192</td>
<td>440294</td>
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<tr>
<td>75-79</td>
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<td>622194</td>
<td>366595</td>
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<td>70-74</td>
<td>364298</td>
<td>833991</td>
<td>469693</td>
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<tr>
<td>65-69</td>
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<td>1084588</td>
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<td>60-64</td>
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<td>620291</td>
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<td>50-54</td>
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<tr>
<td>0-4</td>
<td>1000393</td>
<td>1953280</td>
<td>952887</td>
</tr>
</tbody>
</table>

**1991 Totals:** 13938100 | 28117600 | 14179500
Rectangularization of the survival curve

FURTHER INCREASE IN LIFE EXPECTANCY

Squaring the survival curve

PERCENT SURVIVING

AGE

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
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
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

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 ↔ 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 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)

DNA AND CHROMOSOME LEVELS
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)

E. Inflammation

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

Aging

Health & Social 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
Canadian Longitudinal Study on Aging (CLSA)

A research platform – infrastructure to enable state-of-the-art, interdisciplinary population-based research and evidenced-based decision-making that will lead to better health and quality of life for Canadians.
Our 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
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
Depth and Breadth of CLSA

PHYSICAL & COGNITIVE MEASUREMENTS
- Height & weight
- Waist and hip measurements
- Blood Pressure
- Grip strength, timed up-and-go, chair raise, 4-m walk
- Standing balance
- Vision (retinal imaging, Tonometer & visual acuity)
- Hearing (audiometer)
- Spirometry
- Body composition (DEXA)
- Bone density (DEXA)
- Aortic calcification (DEXA)
- ECG
- Carotid Plaque sweep (ultrasound)
- Carotid intima-media thickness (ultrasound)
- Cognitive assessment (30 min. battery)

HEALTH INFORMATION
- Chronic disease symptoms (disease algorithm)
- Medication and supplements intake
- Women’s health
- Self-reported health service use
- Oral health
- Preventative health
- Administrative data linkage health services & drugs & other administrative databases

PSYCHOSOCIAL
- Social participation
- Social networks and support
- Caregiving and care receiving
- Mood, psychological distress
- PTSD
- Coping, adaptation
- Injuries and consumer products
- Work-to-retirement transitions
- Retirement planning
- Social inequalities
- Mobility-lifespace
- Built environments & Contextual Factors
- Income, Wealth and Assets

LIFESTYLE & SOCIODEMOGRAPHIC
- Smoking
- Alcohol consumption
- Physical activity (PASE)
- Nutrition (nutritional risk and food frequency)
- Birth location
- Ethnicity/race/gender
- Marital status
- Education
Bio specimens
42 aliquots per participant
CLSA Infrastructure

- National Coordinating Centre (McMaster)
- Biorepository and Bioanalysis Centre (McMaster)
- IT Infrastructure (McMaster)
- Statistical Analysis Centre (McGill)
- Genetics and Epigenetics Centre (UBC)
- 4 Computer-Assisted Telephone Interview Sites
  - Victoria, Winnipeg, Sherbrooke and Halifax
- 11 Data Collection Sites
  - Victoria, Vancouver, Surrey, Calgary, Winnipeg, Hamilton/Toronto, Ottawa, Montreal, Sherbrooke, Halifax and St. John’s
Biorepository and Bioanalysis Centre (BBC)

Biorepository

- 31 nitrogen tanks (5 million aliquots)
- Autofilled from a bulk nitrogen tank
- Cryocarts
- Personal Archive, dry storage at room temperature (humidity controlled)
- LIMS (LabWare)
- CryoMORE, (Air Liquide) safety monitoring system
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
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:
  - Statistics Canada
  - Using provincial health registries
  - Random digit dialing
- In Alberta and maybe BC, it appears we cannot use registries
Tracking Cohort of the CLSA
(n=20,000)
Baseline Recruitment and Data Collection

- First selection of 20,000 started in late 2011
  - Pre-recruits via Stats. Can, RPDB and RDD~33,000
    - Completed 60 minute questionnaire by telephone on over 13,000 individuals
    - Plan to complete tracking by the end of January 2013
- Mid 2013 we will begin our maintaining contact interviews (30 minute telephone interview)
  - Minimize loss to follow-up
  - Collect additional data
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-2012 to mid-2013)
  - Pre-recruits via RPDB and RDD~11,000
    - We have completed home interviews on 3500 individuals and DCS visit on over 2500 individuals
      - Maintaining contact by phone (end of 2013-end 2014)

- Second batch of 1000 people to be recruited/site (mid-2013 to mid-2014)
  - Maintaining contact: (end of 2014-end of 2015)

- Third batch of 1000 people to be recruited/site (mid-2014 to mid-2015)
  - Maintaining contact: (end of 2015-end of 2016)
Data and Sample Access

• Data and Sample Access is Open
  • All researchers have access to data
    • No special access to the “creators” of the platform
    • Individual level data versus aggregate data
    • Genetic versus Health (Depression) versus Social data

• Ethical and Legal Considerations
  • How the data are used and what purpose?
  • Public sector versus Private sector access to data
Use of the CLSA Platform: Examples
CLSA Program of Research on Bone Health
Objectives

• Theme 1:
  • What are the rare genetic variants associated with osteoporotic fracture?
  • How do such variants influence the risk of fracture?
  • Do such variants improve our ability to identify individuals at risk of fracture?
    • Require large sample sizes
    • Harmonization with other studies across the world
Objectives Contd..

• Theme 2:
  • How can osteoporosis and sarcopenia be defined for Canadian men and women using imaging, functional and clinical risk data?
  
  • Can measures combining volumetric bone density, muscle area, and muscle adiposity improve our ability to identify individuals at risk of fracture?
  
  • What are the longitudinal associations between loss of muscle mass, loss of muscle strength and loss of physical function by fracture types and gender?
    • Using techniques such as Peripheral Quantitative CT and MRI
Canadian Longitudinal Study on Aging (CLSA) Mobility Initiative—An Emerging Team in Mobility in Aging

CIHR Funded (investigator Initiated)
CLSA-MI Objectives

- Design a comprehensive assessment of mobility to be implemented as part of the CLSA cohort;

- Engage an inter-disciplinary team of researchers and decision-makers to focus and implement research on mobility in aging;

- Serve as a platform for researchers to advance knowledge in the field of mobility and aging;

- Provide training opportunities in an interdisciplinary research focussed on mobility and aging;

- Implement knowledge translation and dissemination strategies
CLSA-MI Theoretical Framework

**Mobility**

«activity & participation» *

[Diagram showing the relationship between mobility and its precursors and consequences]

**Examples of precursors**

*Individual (or intrinsic)*
- Chronic diseases (e.g., osteoarthritis)
- Neuropsychological conditions
- Cognition/Perceived health
- Medication use/Pain/Dizziness
- Poor vision/Incontinence
- Fear of falling/of being attacked
- Obesity/thinness/Nutrition/weight loss/appetite
- Physical activity/fitness/Strength
- Functional performance (measured & reported)
- Alcohol use
- Biomarkers (inflammatory, hormonal, metabolism, gene, …)
- Personality

*Contextual (or extrinsic or environmental)*
- Social location factors
- 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
- Unmet needs
- Institutionalization

* Mobility is to be measured by the Life-Space Assessment questionnaire (Baker et al., 2003; Allman et al., 2004)
CLSA-MI – An Embedded Study

Measures in CLSA Core
- Grip Strength
- 4 Meter Walk
- Functional Status
- ADL and IADL

Measures added by CLSA-MI
- Chair Stand
- Unipodal Standing
- TUG
- Life Space Assessment
- Transportation
- Built Environment
Environment and Biological Processes of Chronic Inflammation: Link between Vascular Aging and Brain Health
Carotidal atherosclerosis

Endothelial cells insult

(vascular) Aging

Comorbidity

Peripheral inflammation

Chemokines dysregulation

AGEs

ROS and N₂ reactive species

T-cells / macrophages recruitment

MMPs

Cognitive decline

Toxicity and Apoptosis

NT dysfunction

Immune dysfunction

Vascular dysfunction

Stroke

Hypercholesterolemia

Hypertension

Diabetes

Dyslipidemia

Genetics and lifestyle (ApoE, obesity, smoking, social and environmental stressors, etc.)

Exercise

Diet

Social and intellectual enrichment

Drugs

Aging

Comorbidity

Peripheral inflammation

Cognitive decline

AGING

Diabetes

Hormones

Infection

Hypercholesterolemia

Hypertension

Dyslipidemia

Genetics and lifestyle (ApoE, obesity, smoking, social and environmental stressors, etc.)

Exercise

Diet

Social and intellectual enrichment

Drugs

Aging

Comorbidity
Data harmonization Platform

Building a Global Network of Harmonized Cohorts
Prospective Harmonization

Harmonization achieved **before**
the initiation of data collection

- Stringent or input harmonization
  - Same questions, same protocols, same measures: One common set of procedures

- Flexible or ex-ante output harmonization
  - Common set of target variables, but with a certain level of flexibility in the specific questions, protocols, measures, etc. **However, inferential equivalency must be ensured!**
Retrospective Harmonization

Harmonization making use of existing data

- Flexible or ex-post harmonization
  - Various...
  - Designs of studies
  - Questions, procedures, measures, etc.
  - Sources of information, timelines

Questionnaires
Physical and cognitive measures
Social and environmental indicators
Biochemical measures
Registries (census, hospitalizations)
To generate knowledge we need:

- Quality
- Quantity
- Usage
Global Landscape

**Infrastructure**

- Studies (data and bio-samples)

**Tools**

- Methods, software and expertise supporting harmonization and synthesis of information in different research areas

**Research**

- New scientific knowledge

Logos of various research projects and initiatives are shown on the map, including CARTogene, BBMRI, BioSHARE.eu, Lifelines, KORA, HUNT Biosciences, nuguene, maelstrom, and PhenX.
Need to generate compatible data!
Identify variables and evaluate harmonization potential

Variable selected based on its:
(1) Scientific relevance and
(2) Harmonization potential

Multiple variables

Generic variable allowing to combine the largest number of studies

Statistical models

Pairing algorithms
<table>
<thead>
<tr>
<th>Role</th>
<th>Names and Affiliations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead PI</td>
<td>Parminder Raina <em>(McMaster)</em></td>
</tr>
<tr>
<td>CO-PI</td>
<td>Christina Wolfson <em>(McGill)</em> and Susan Kirkland <em>(Dalhousie)</em></td>
</tr>
<tr>
<td>Key Senior Co-Investigators</td>
<td>Gerry Mugford, Patrick Parfrey <em>(Memorial)</em>, Helene Payette <em>(Sherbrooke)</em>, Ron Postuma <em>(McGill)</em>, Vanessa Taller, Larry Chambers <em>(Ottawa)</em>, Harry Shannon, Cynthia Balion, Christopher Patterson, Lauren Griffith and Mark Oremus <em>(McMaster)</em>, Mary Thompson and Chang Bo <em>(Waterloo)</em>, Deb Sheets, Lynne young, Holly Tuokko, <em>(Victoria)</em>, Verena Menec <em>(Manitoba)</em>, David Hogan and Marc Poulin <em>(Calgary)</em>, Max Cynader, Michael Hayden and Michael Kobor <em>(UBC)</em> and Andrew Wister, Scott Lear <em>(SFU)</em></td>
</tr>
<tr>
<td>Scientific Working Group</td>
<td>See our website – <a href="http://www.clsa-elcv.ca">www.clsa-elcv.ca</a></td>
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</table>
praina@mcmaster.ca

CLSA funded by the Government of Canada through CIHR and CFI, and provincial governments and universities

www.clsa-elcv.ca