The webinar, "Age of menopause and its relation to frailty and biological age in the CLSA comprehensive cohort" will begin shortly.

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CLSA Webinar Series

Age of menopause and its relation to frailty and biological age in the CLSA comprehensive cohort

Dr. Chris Verschoor, McMaster University

12 to 1 PM ET | JUNE 21, 2018

Frailty is a complex pathophysiological phenomenon that will impact a significant proportion of adults over the age of 65 and contributes to the risk of several adverse health outcomes. Although women have a disproportionately higher risk of frailty, the sex-specific factors related to this syndrome are not well-described. Using the CLSA comprehensive cohort, this research examines the relationship of age at menopause and hysterectomy status with prevalent frailty in older women. The frailty index was inversely related to age at menopause, decreasing 1.2% of the mean with every year of menopause onset, and was significantly higher for women categorized in the premature or early menopause and hysterectomy groups. The odds for being classified as frail using Fried’s criteria was higher for the premature menopause and hysterectomy groups. Interestingly, using a battery of physiological and functional measures to estimate biological age, we also show that age at menopause is associated with accelerated aging. In conclusion, our study supports a role for age at menopause and hysterectomy in the risk of frailty in older women, and confirms a previously reported association with accelerated aging.

Register online at bit.ly/clsawebinars

Webinars will be broadcast using WebEx. Further instructions will be sent by email.

www.clsa-elcv.ca
Age of menopause and its relation to frailty and biological age in the CLSA comprehensive cohort

Chris Verschoor, MSc, PhD
Assistant Professor
Dept. of Health Research Methods, Evidence and Impact
McMaster Institute of Research on Aging (MIRA)
McMaster University
We are getting older
The cost of aging... is no surprise

Healthcare spending by age

%GDP spent on health care and retirement

Chronic conditions

What do we do about it?
A focus on healthy aging

Healthy aging
Maintaining good health as we age

- Physical health
- Mental health
- Social health
- Quality of life
- Independence

... as we age

Need to embrace strategies that prevent or mitigate the root cause of age-related decline (unhealthy aging)

“Looks like you’re going to live to a ripe old age.”
A focus on healthy aging

Aging → Independence → Mortality

Frailty

Healthy Aging

- Social activity
- Diet
- Genes
- Exercise
- Productive pursuits
“Frailty is a clinical state in which there is an increase in an individual's vulnerability for developing increased dependency and/or mortality when exposed to a stressor”

– Morley et al., 2013: JAMDA
How do we measure frailty?

**Fried’s phenotype model**
(Fried et al., 2001: J Ger Med Sci)

- **Exhaustion**
- **Weakness**
- **Weight loss**
- **Slowness**
- **Low physical activity**

Robust (0)
Pre-frail (1, 2)
Frail (3+)

**Rockwood’s frailty index**
(Searle et al., 2008: BMC Geriatrics)

- Satisfaction with life
- Biomarkers
- Perceptions of health
- Diseases
- Social support
- Depression
- Physical activity

Frailty index
Why measure frailty?
A major determinant of frailty: Sex!

“Meta-analysis of the data confirmed that, in every age group, females had higher Frailty Index scores than males. All studies found that females tolerated this frailty better, as demonstrated by a lower mortality rate at any given level of frailty or age. Overall, this systematic review established that sex differences in the FI demonstrate the well-known male-female health-survival paradox.”

The mechanism(s) of enhanced frailty in women?
Loss of female sex hormones and its pathological consequences

MP<45 vs. MP≥45
Loss of female sex hormones and its pathological consequences

Vaccine response

Lifespan

Tumour burden

Nguyen et al., 2011: Vaccine

Goldfarb and Pugh, 1990: Cancer Res.

Nothing on frailty though
Research question and hypothesis

**Primary research question**
What is the relationship between natural or surgically-induced menopause and frailty?

**Hypothesis**
Early age of menopause or having had a hysterectomy will be associated with higher levels of frailty later in life for community-dwelling older women.
Methods

Study Design

- Cross-sectional analysis of the Canadian Longitudinal Study on Aging Comprehensive Baseline Dataset version 3.0
  - 30,097 community-dwelling adults aged 45-85 (15,320 women)
Methods
Exclusion criteria and Menopause classification

- **Total** (n=30,097)
- **Men** (n=14,777)
- **Women** (n=15,320)

**Breast, ovarian or other genital cancer diagnosis**
- (n=1,247)

**Menopause classification**
- *missing, refused, or don’t know* (n=95)

**Age at menopause**
- *missing, refused, don’t know, outlier or less than age* (n=419)

**Pre-menopause or peri-menopause**
- *5 years or less from age at menopause*
  - (Total: n=3,998)
  - [Pre: n=2,416; Peri: n=1,582]

- **Premature**
  - 30-39 yrs
    - (Total: n=298)
    - [incl. Fl: n=298]
    - [incl. Fried: n=231]

- **Early**
  - 40-45 yrs
    - (Total: n=1,213)
    - [incl. Fl: n=1,195]
    - [incl. Fried: n=1,002]

- **Normal**
  - 46-54 yrs
    - (Total: n=4,747)
    - [incl. Fl: n=4,703]
    - [incl. Fried: n=4,021]

- **Late**
  - 55-62 yrs
    - (Total: n=1,121)
    - [incl. Fl: n=1,106]
    - [incl. Fried: n=957]

- **Hysterectomy**
  - (Total: n=2,182)
  - [incl. Fl: n=2,148]
  - [incl. Fried: n=1,769]
• Fried’s frailty phenotype (Healthy, Pre-frail, Frail)

• Frailty Index
  • 93 component index spanning chronic diseases, functional status, activities of daily living, depression, satisfaction with life, nutritional risk, physical activity, and perceived health.

![Frailty Index Graph](image)

0.101 ± 0.069 (min/max = 0/0.53)
• Statistical analysis
  • Menopause related variable classification
    • Continuous: Age at menopause (30-62)
    • Categorical: Premature (30-39), early (40-45), normal (46-54), late (55-62), hysterectomy
  • Association analysis
    • Binomial logistic regression (Fried: Frail vs. Healthy/Pre-frail)
    • Linear regression (Frailty index)

• Covariates
  • Age
  • Marital status (5 levels)
  • Ethnicity (7 levels)
  • Co-residence (yes/no)
  • Smoking (3 levels)
  • Alcohol consumption (8 levels)
  • Annual income (5 levels)
  • Education (4 levels)
  • Social support (MOS social support survey, 0-5)
  • HRT use ever (yes/no)
Results

Frailty by menopause classification

Frailty index

Fried's model
### Results

#### Frailty by menopause classification

<table>
<thead>
<tr>
<th>Menopause classification</th>
<th>Frailty Index [β (95% CI)]</th>
<th>Fried - Healthy/Pre-frail vs. Frail [OR (95% CI)]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
<td>Adjusted</td>
</tr>
<tr>
<td>Normal (46-54 yrs)</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Premature (30-40 yrs)</td>
<td>0.038 (0.029 to 0.046)</td>
<td>***</td>
</tr>
<tr>
<td>Early (41-45 yrs)</td>
<td>0.012 (0.008 to 0.017)</td>
<td>***</td>
</tr>
<tr>
<td>Late (55+ yrs)</td>
<td>0.003 (-0.002 to 0.008)</td>
<td></td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>0.029 (0.025 to 0.032)</td>
<td>***</td>
</tr>
</tbody>
</table>

- Associations with the frailty index and Fried’s frailty estimated by linear and binomial logistic regression, respectively. Adjusted models included age, marital status, ethnicity, co-residence, smoking, alcohol consumption, annual income, education, social support and HRT use ever.
- Regression coefficient (β) and Odds ratio (OR), and respective 95% confidence intervals (CI) presented.
Results
Frailty index and age at menopause

Frailty decreases ~7.5% of the mean per 5-years difference in age at menopause.
## Results

### Frailty index and HRT use

<table>
<thead>
<tr>
<th></th>
<th>Frailty Index [β (95% CI)]</th>
<th>Fried - Healthy/Pre-frail vs. Frail [OR (95% CI)]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
<td>Adjusted</td>
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<tr>
<td><strong>HRT use</strong></td>
<td></td>
<td></td>
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<tr>
<td>Yes (Ref=No)</td>
<td>0.011 (0.008 to 0.014)</td>
<td>0.005 (0.002 to 0.009)</td>
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<td>***</td>
<td>**</td>
</tr>
<tr>
<td><strong>Length of HRT use (years)</strong></td>
<td>0.0012 (0.0009 to 0.0014)</td>
<td>0.0002 (-0.0002 to 0.0005)</td>
</tr>
<tr>
<td></td>
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<td>***</td>
</tr>
<tr>
<td><strong>Age at HRT onset (years)</strong></td>
<td>-0.0013 (-0.0016 to -0.00099)</td>
<td>-0.0004 (-0.0008 to 0.00005)</td>
</tr>
<tr>
<td></td>
<td>***</td>
<td></td>
</tr>
<tr>
<td><strong>Type of HRT used</strong></td>
<td>Combined (Est+Prog)</td>
<td>Ref</td>
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<tr>
<td></td>
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<tr>
<td>Estrogen alone</td>
<td>0.016 (0.013 to 0.021)</td>
<td>0.003 (-0.003 to 0.009)</td>
</tr>
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<td>***</td>
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<tr>
<td>Progesterone alone</td>
<td>-0.001 (-0.011 to 0.01)</td>
<td>-0.002 (-0.015 to 0.01)</td>
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<td></td>
<td></td>
<td>0.78 (0.39 to 1.58)</td>
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<td></td>
<td>0.6 (0.2 to 1.81)</td>
</tr>
<tr>
<td>Estrogen Gel</td>
<td>-0.01 (-0.018 to -0.001)</td>
<td>-0.007 (-0.017 to 0.003)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.67 (0.38 to 1.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 (0.44 to 2.27)</td>
</tr>
<tr>
<td>IUD with Progesterone</td>
<td>-0.015 (-0.043 to 0.012)</td>
<td>-0.006 (-0.04 to 0.028)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>na</td>
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<td>na</td>
</tr>
</tbody>
</table>
• Frailty was significantly higher in women that reported having had a hysterectomy, or reached menopause earlier than 46.

• Frailty is ~7.5% lower with every five years of age at natural menopause

• Few associations with HRT-related variables were observed, but there are latent complexities inherent to these variables that may be confounding the analyses.
Healthy aging or accelerated aging?

Ferrucci et al., 2002: J End Invest
Accelerated aging = Biological age – Chronological age

An estimate of someone’s age that is based on biological factors (ie. biomarkers) that change with age

17-year survival

Yoo et al., 2017: BMC Geriatrics
Biological age: how it is measured

Neutrophil count

Lung function

Cognitive score

55 years old, normal  BA = 55  Diff = 0
85 years old, very healthy BA = 67  Diff = -18
65 years old, frail BA = 86  Diff = +21  Age acceleration
Accelerated aging ≈ Frailty

Early menopause/ Hysterectomy

Accelerated Aging

Frailty

Menopause accelerates biological aging

Morgan E. Levine, Ake T. Lu, Brian H. Chen, Dena G. Hernandez, Andrew B. Singleton, Luigi Ferrucci, Stefania Bandinelli, Elias Salfati, JoAnn E. Manson, Austin Quach, Cynthia D. J. Kusters, Diana Kuh, Andrew Wong, Andrew E. Teschendorff, Martin Widschwendter, Beate R. Ritz, Devin Absher, Themistocles L. Assimes, and Steve Horvath.
Methods

- Cross-sectional analysis of the Canadian Longitudinal Study on Aging Comprehensive Baseline Dataset version 3.0
- Identical exclusion and classification criteria as previous

- Biological age was estimated using the equation developed by Klemera and Doubal (Mech Ageing Dev. 2006 Mar;127(3):240-8), training on a random sample of 80% of the dataset
- Accelerated aging defined as $\Delta BA$, the difference between biological age and chronological age
- Biomarkers (27 in total)
  - Hematology - complete blood counts (WBC diff., RBCs, platelets, etc.)
  - Physiological - blood pressure, pulse, spirometry, lean mass
  - Performance – physical function tests (gait speed, TUG, grip strength, etc.)
  - Cognition – cognitive tests (REYI/II, MAT, COWAT, Stroop, etc.)
Biological age in the CLSA

BA vs. CA

ΔBA
Biological age and frailty

Frailty Index

Fried’s Frailty
Biological age and age at menopause

Fully adjusted model
Coefficient: -0.1269
95% CI: -0.194 - -0.0598
p=0.0002

Every year of age at menopause results in ~1.5 months reduction in biological age.
Early or premature menopause or having had a hysterectomy increases biological age by at least 1 year.
Similar to frailty, age at menopause or menopause classification is associated with increased biological age (accelerated aging).

Premature menopause (<40 years) has the most substantial effect followed by early menopause (40-45 years) or having had a hysterectomy.
Thanks!

**Collaborators**
- Hala Tamim, York University
- Dan Belsky, Duke University
- CLSA
  - David Kanters
  - Jinhui Ma
  - Lauren Griffith
  - Parminder Raina
  - Stacey Voll (U Victoria)

**Funding provided by...**

![McMaster University Institute for Research on Aging](image)

![What Is Your Real Biological Age?](image)
Thank you for attending the CLSA Webinar Series. Webinars will resume in September 2018.

For updates, please visit the CLSA website.

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