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

clsa élcv
Canadian Longitudinal Study on Aging
Étude longitudinale canadienne sur le vieillissement

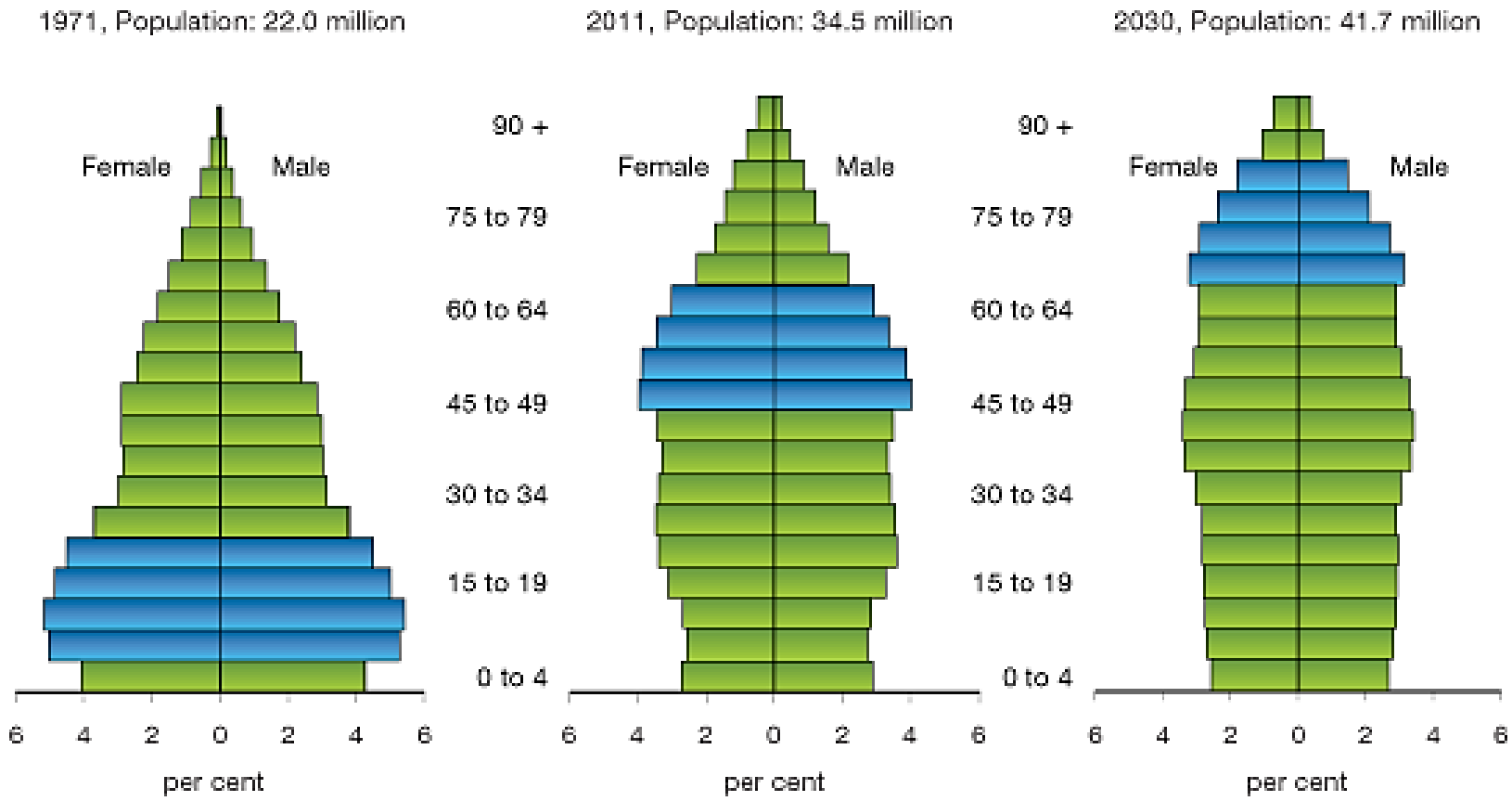
Webinars will be broadcast using WebEx.
Further instructions will be sent by email.

www.clsa-elcv.ca

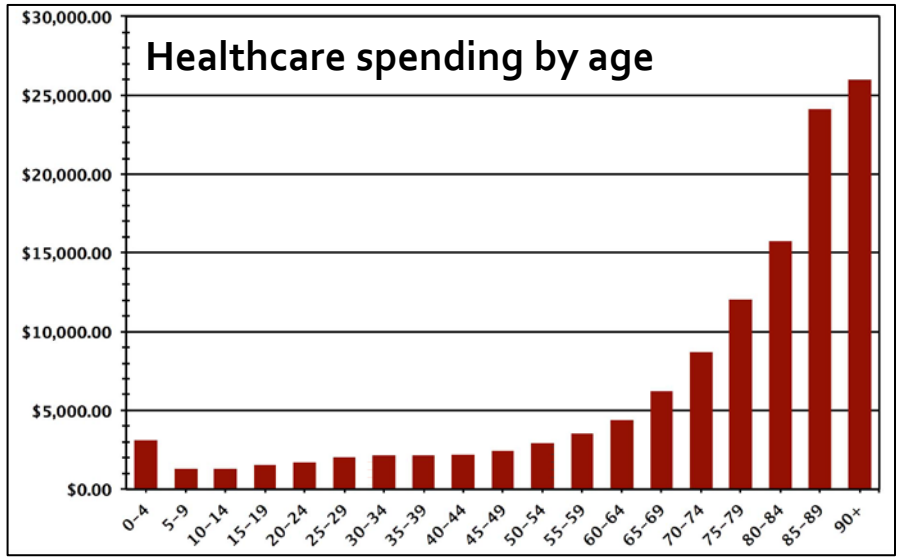
Age of menopause and its relation to frailty and biological age in the CLSA comprehensive cohort

Chris Verschoor, MSc, PhD
Assistant Professor
Dept. of Health Research Methods, Evidence and Impact
McMaster Institute of Research on Aging (MIRA)
McMaster University

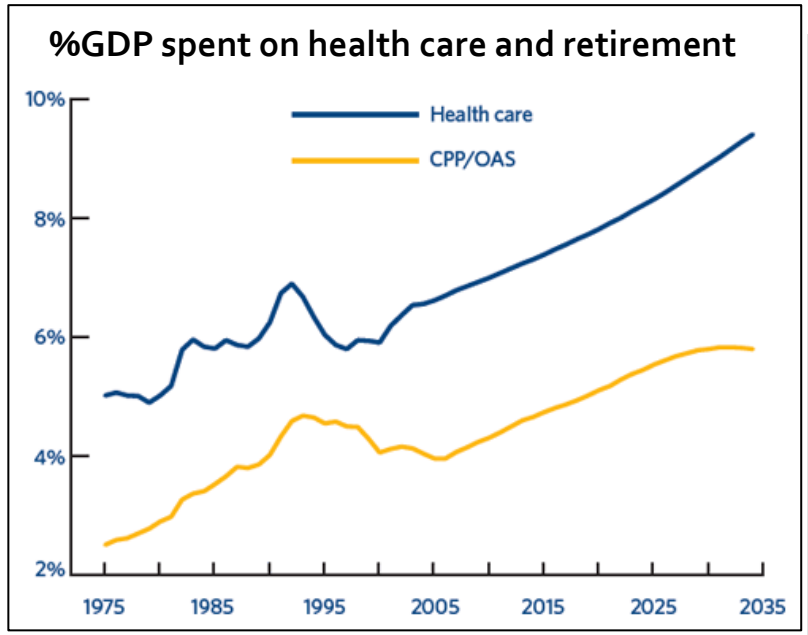
We are getting older



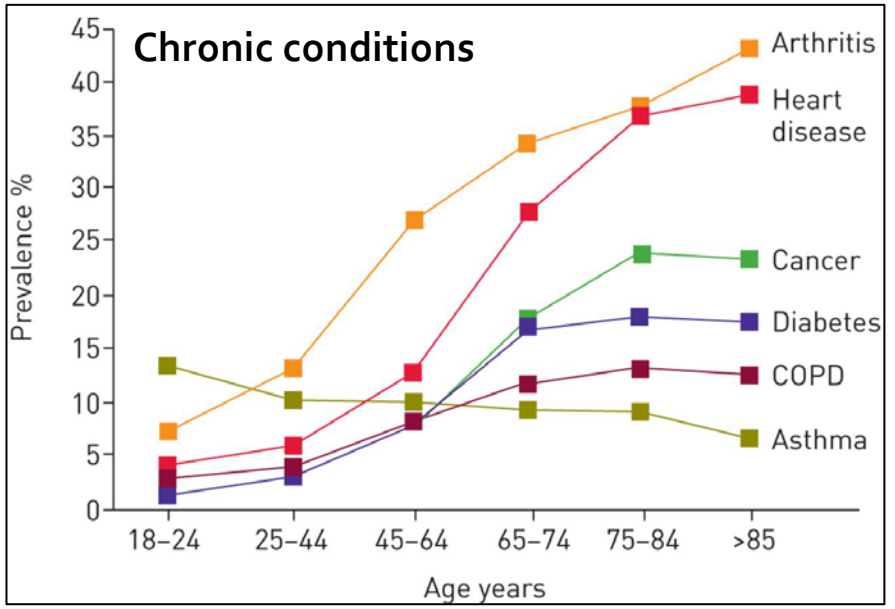
The cost of aging…
..is no surprise



Health Canada



Statistics Canada



European Respiratory Journal 2014 44: 1332-1352

A focus on **healthy aging**

Healthy aging

maintaining good health as we age

Physical health

Mental health

Social health

Quality of life

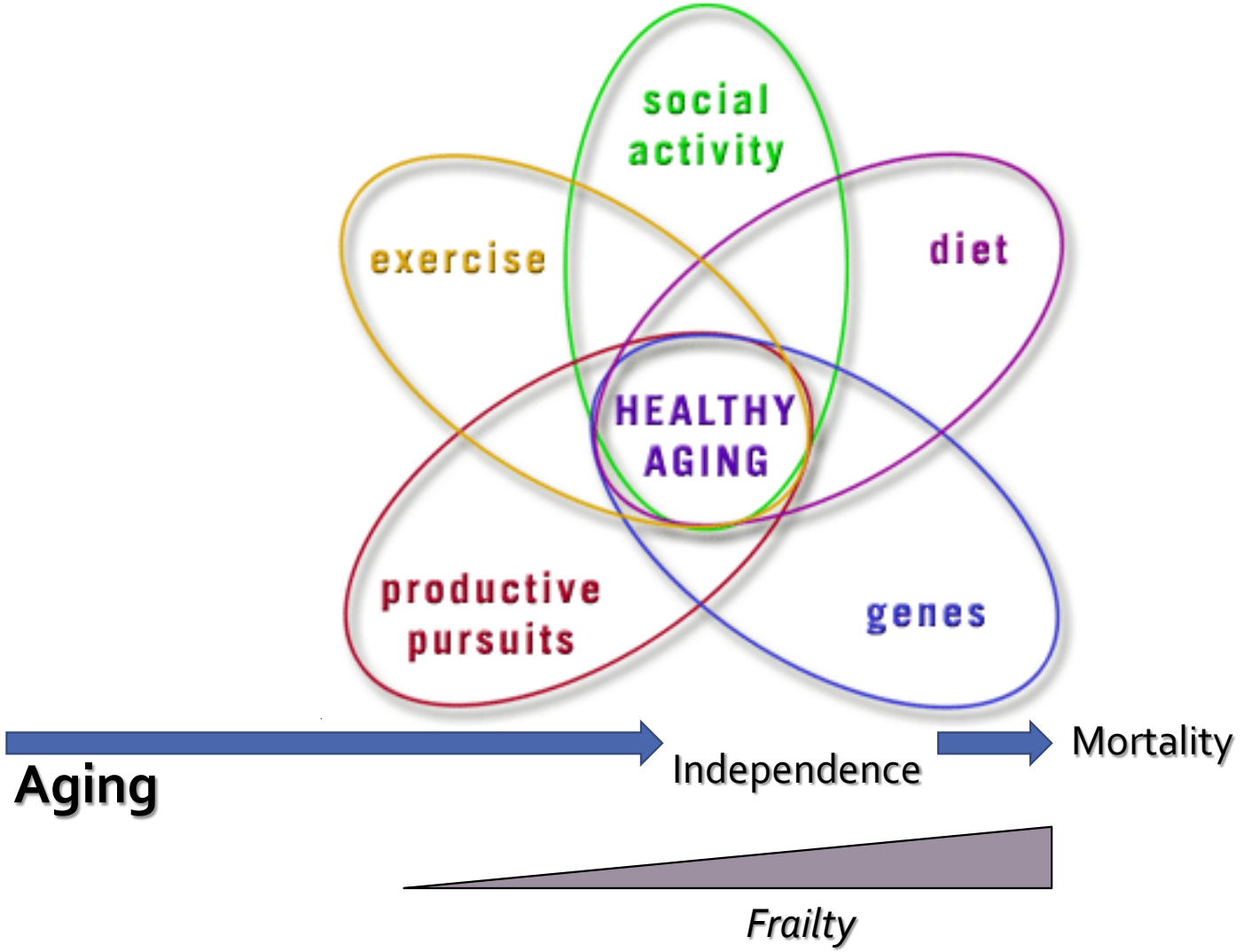
Independence

… as we age

"Looks like you're going to live to a ripe old age."

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

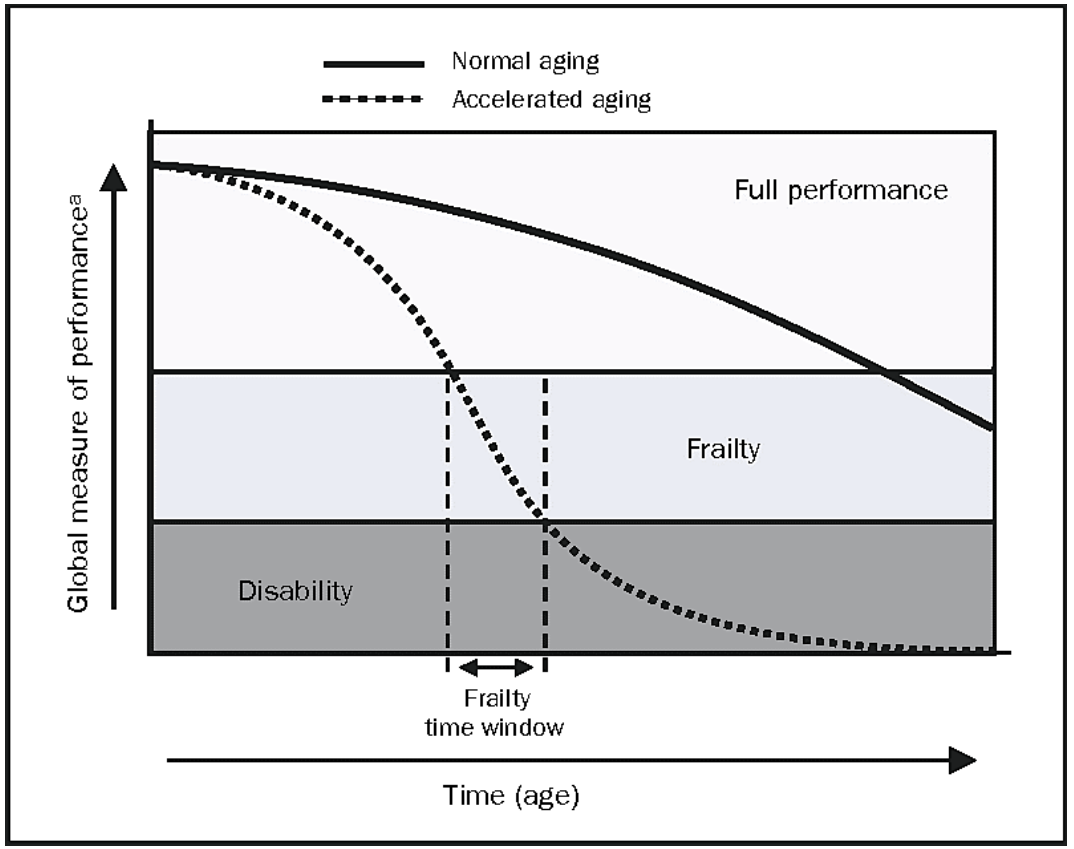
A focus on **healthy aging**



Frailty in older adults

"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



Ferrucci et al., 2002: J End Invest

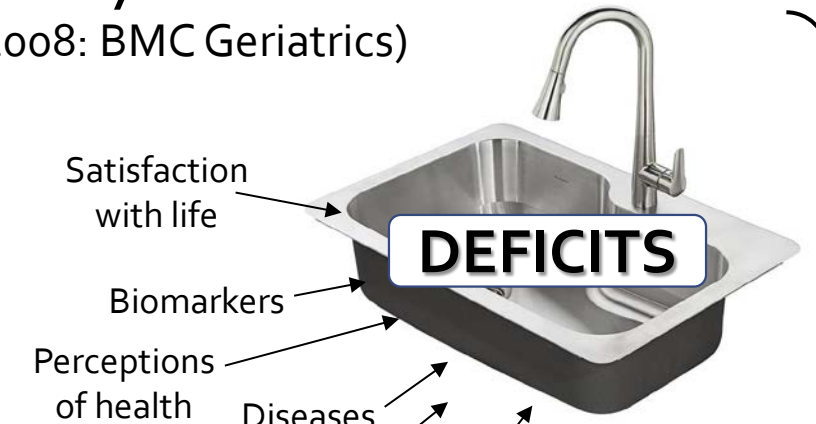
How do we measure frailty?

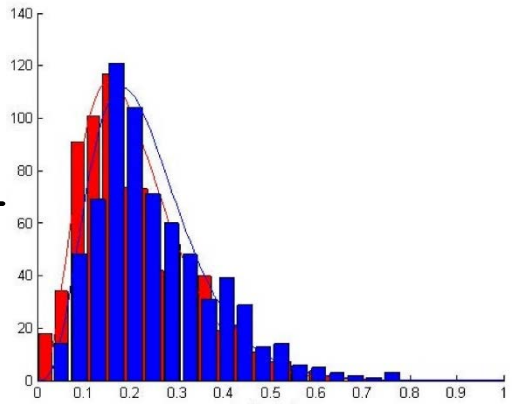
Fried's phenotype model
(Fried et al., 2001: J Ger Med Sci)

Exhaustion
Weakness
Weight loss
Slowness
Low physical activity

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

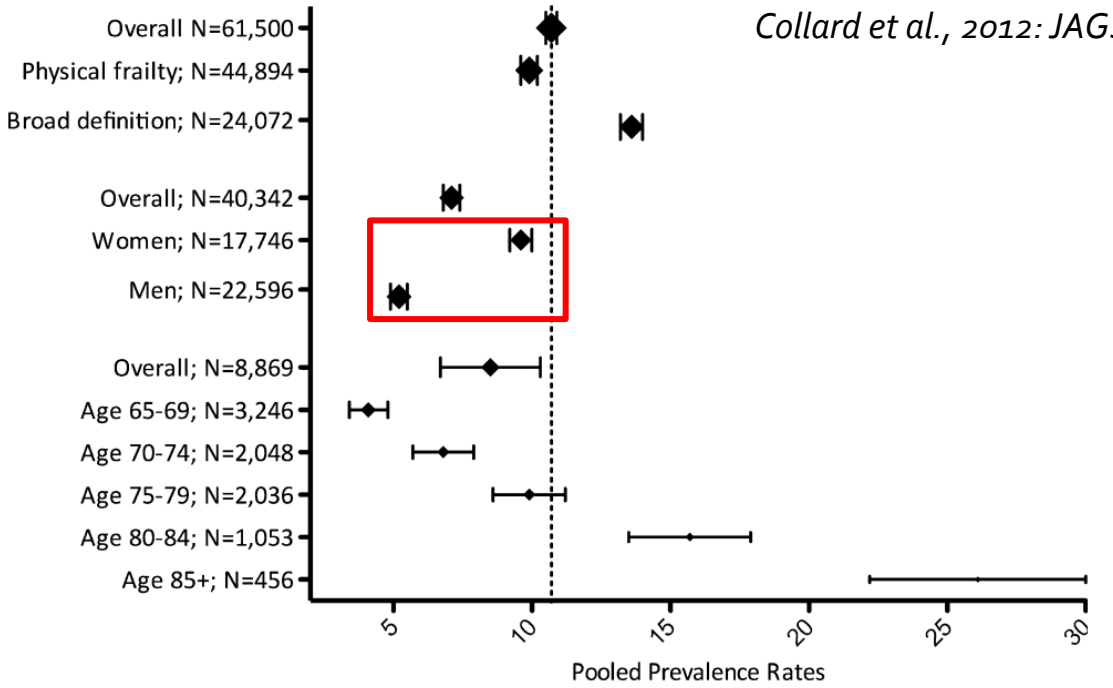
Rockwood's frailty index
(Searle et al., 2008: BMC Geriatrics)





Why measure frailty?

A major determinant of frailty: Sex!



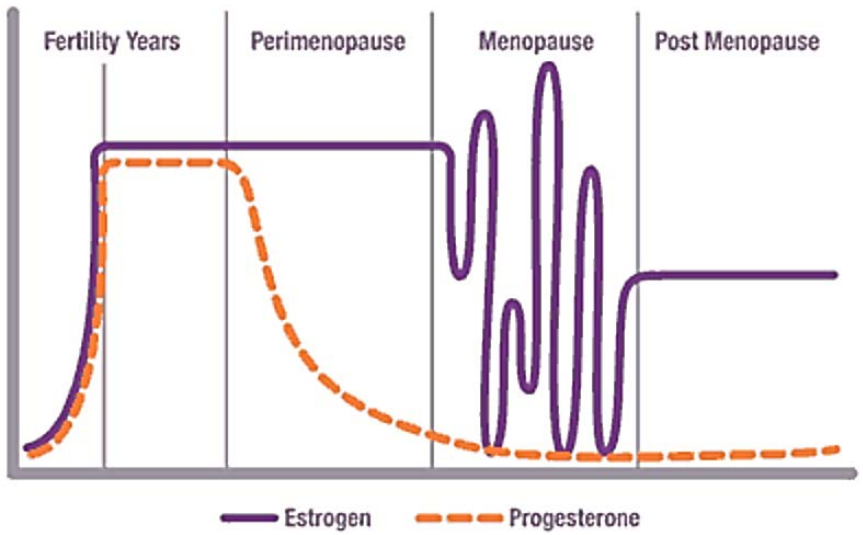
Collard et al., 2012: JAGS

"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**."

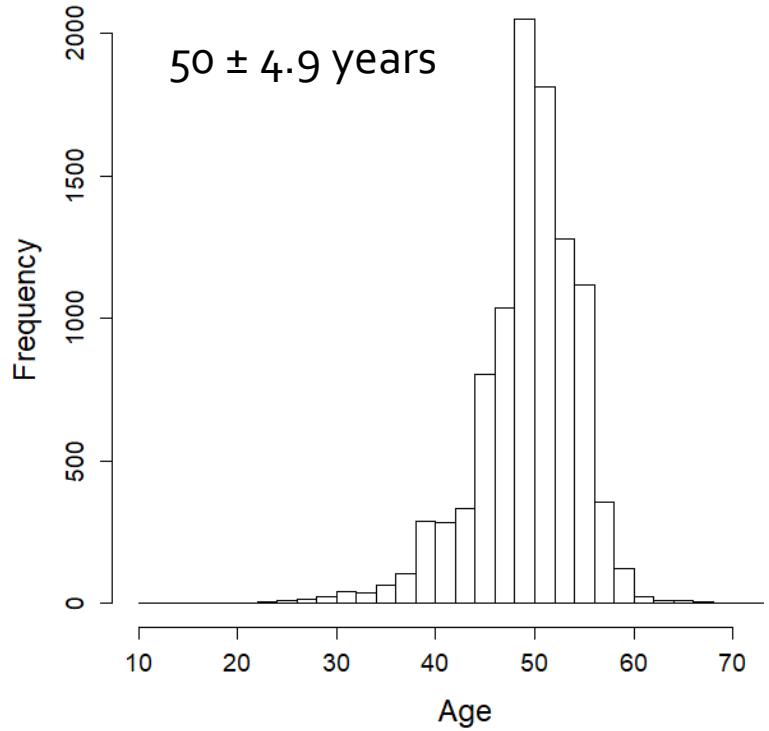
Gordon et al., 2017: Exp. Geron.

The mechanism(s) of enhanced frailty in women?

Hormone changes over the lifespan



Age at menopause in Canadian women



Loss of female sex hormones and its pathological consequences

JAMA Cardiology | Original Investigation

JAMA Cardiol. 2016;1(7):767-776.

Association of Age at Onset of Menopause and Time Since Onset of Menopause With Cardiovascular Outcomes, Intermediate Vascular Traits, and All-Cause Mortality

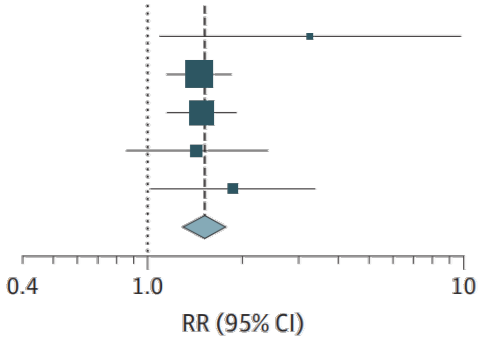
A Systematic Review and Meta-analysis

Taulant Muka, MD, PhD; Clare Oliver-Williams, PhD; Setor Kunutsor, MD, PhD; Joop S. E. Laven, MD, PhD; Bart C. J. M. Fauser, MD, PhD; Rajiv Chowdhury, MD, PhD; Maryam Kavousi, MD, PhD; Oscar H. Franco, MD, PhD

MP<45 vs. MP≥45

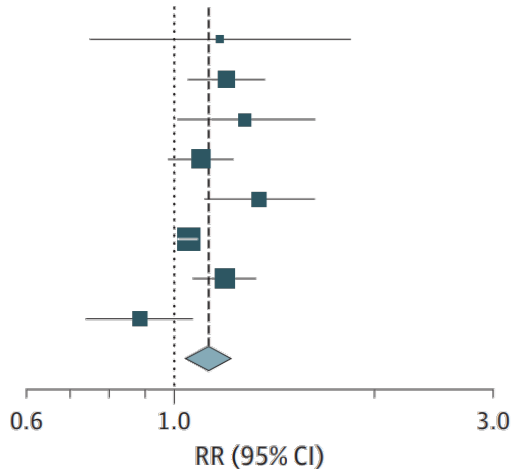
Coronary heart disease risk

Source	Reference Comparison Age, y	Participants, No.	RR (95% CI)
Cooper et al,[16] 1999	≥51	867	3.24 (1.08-9.79)[a]
Hu et al,[17] 1999	50-54	35616	1.45 (1.14-1.83)[b]
Løkkegard et al,[18] 2006	>45	10533	1.47 (1.14-1.90)[b]
Pfeifer et al,[15] 2014	>45	600	1.42 (0.85-2.39)[b]
Wellons et al,[19] 2012	≥46	2509	1.85 (1.01-3.37)[b]
Overall			1.50 (1.28-1.76)

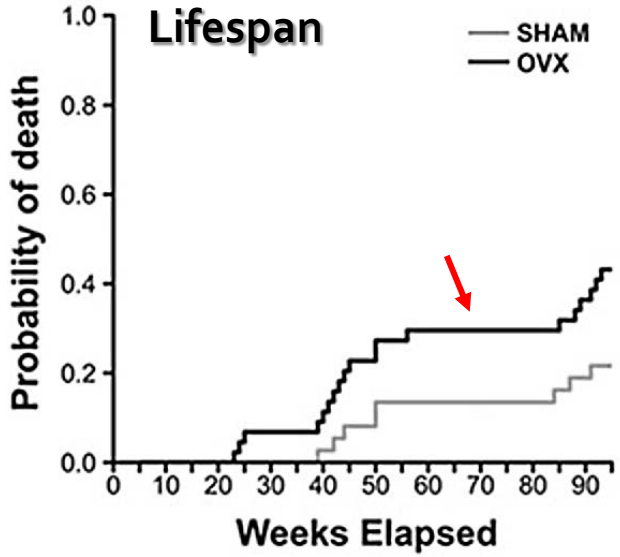


All-cause mortality risk

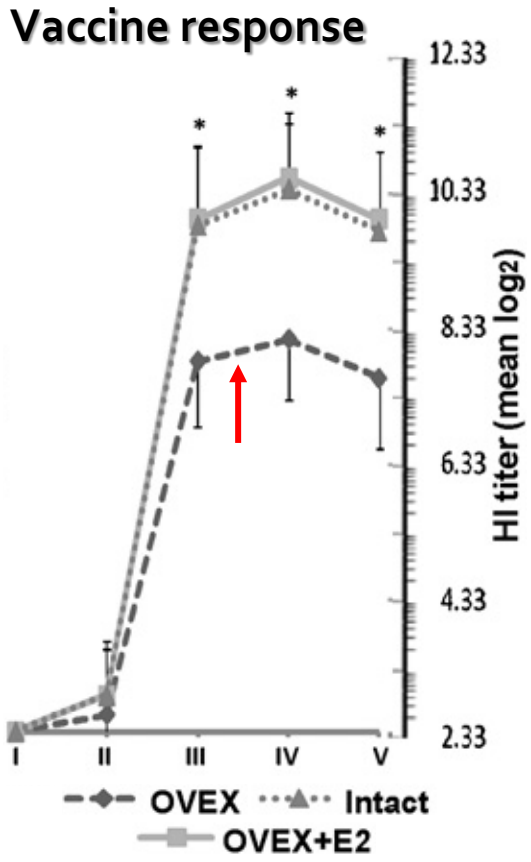
Source	Reference Comparison Age, y	Participants, No.	RR (95% CI)
Amagai et al,[23] 2006	45-49	4683	1.16 (0.74-1.83)
Hong et al,[24] 2007	45-49	2658	1.19 (1.04-1.36)
Cooper et al,[16] 1998	≥50	3191	1.27 (1.00-1.62)[a]
Jacobsen et al,[7] 1999	49-51	6182	1.09 (0.97-1.22)
Li et al,[25] 2013	50-54	11212	1.33 (1.10-1.62)
Mondul et al,[26] 2005	50-54	68154	1.04 (1.00-1.08)
Ossewarde et al,[27] 2005	50-54	12134	1.18 (1.06-1.32)
Tom et al,[28] 2012	50-54	1684	0.88 (0.73-1.06)
Overall			1.12 (1.03-1.21)



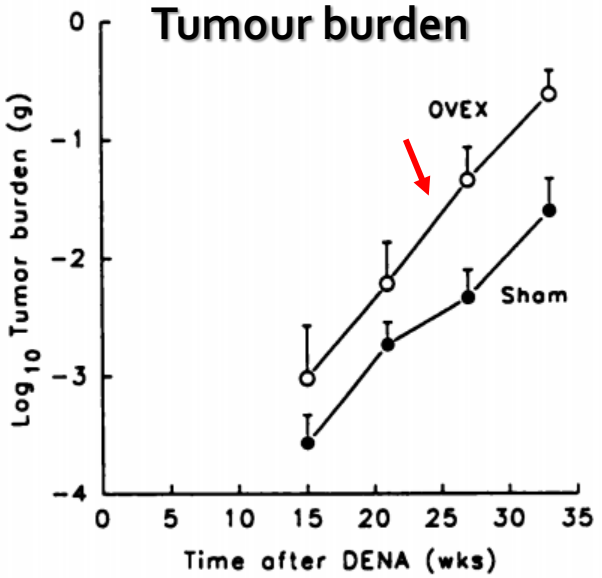
Loss of female sex hormones and its pathological consequences



Benedusi et al., 2015: Oncotarget



Nguyen et al., 2011: Vaccine



Goldfarb and Pugh, 1990: Cancer Res.

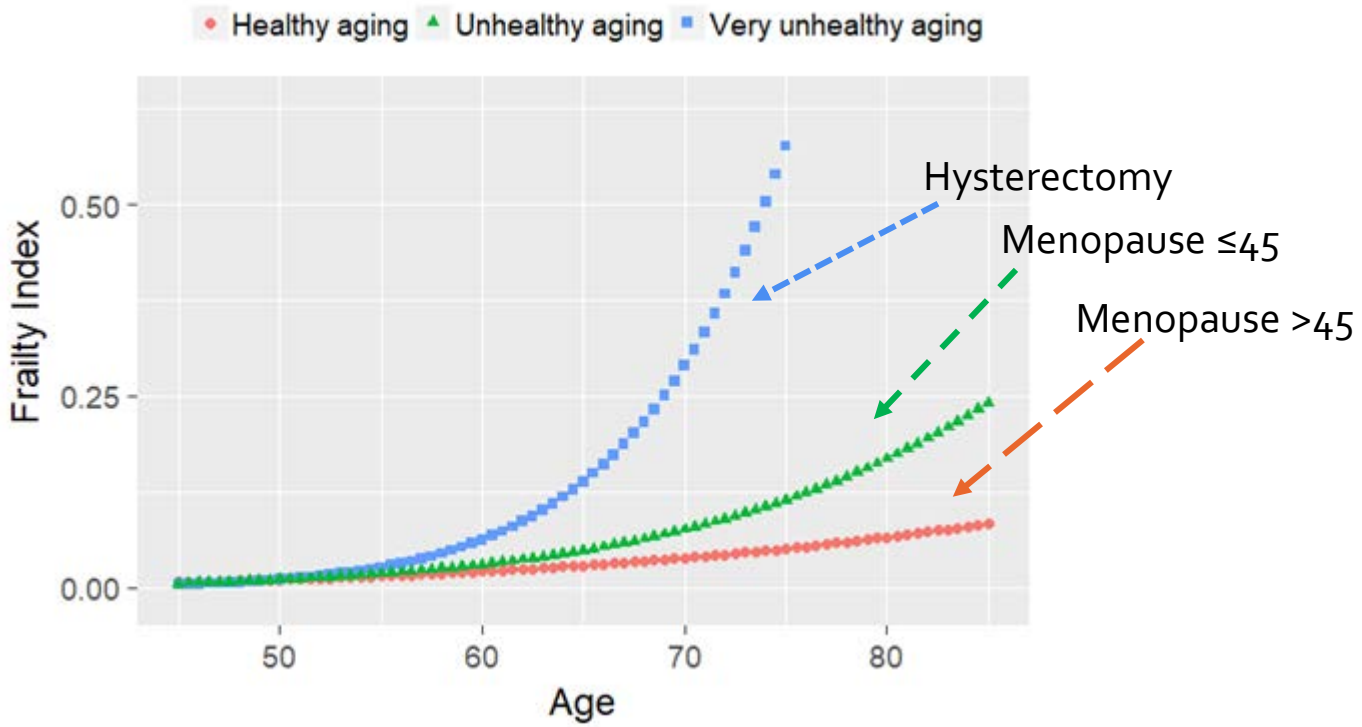
Research question and hypothesis

Primary research question

What is the relationship between natural or surgically-induced menopause and frailty?

Hypothesis

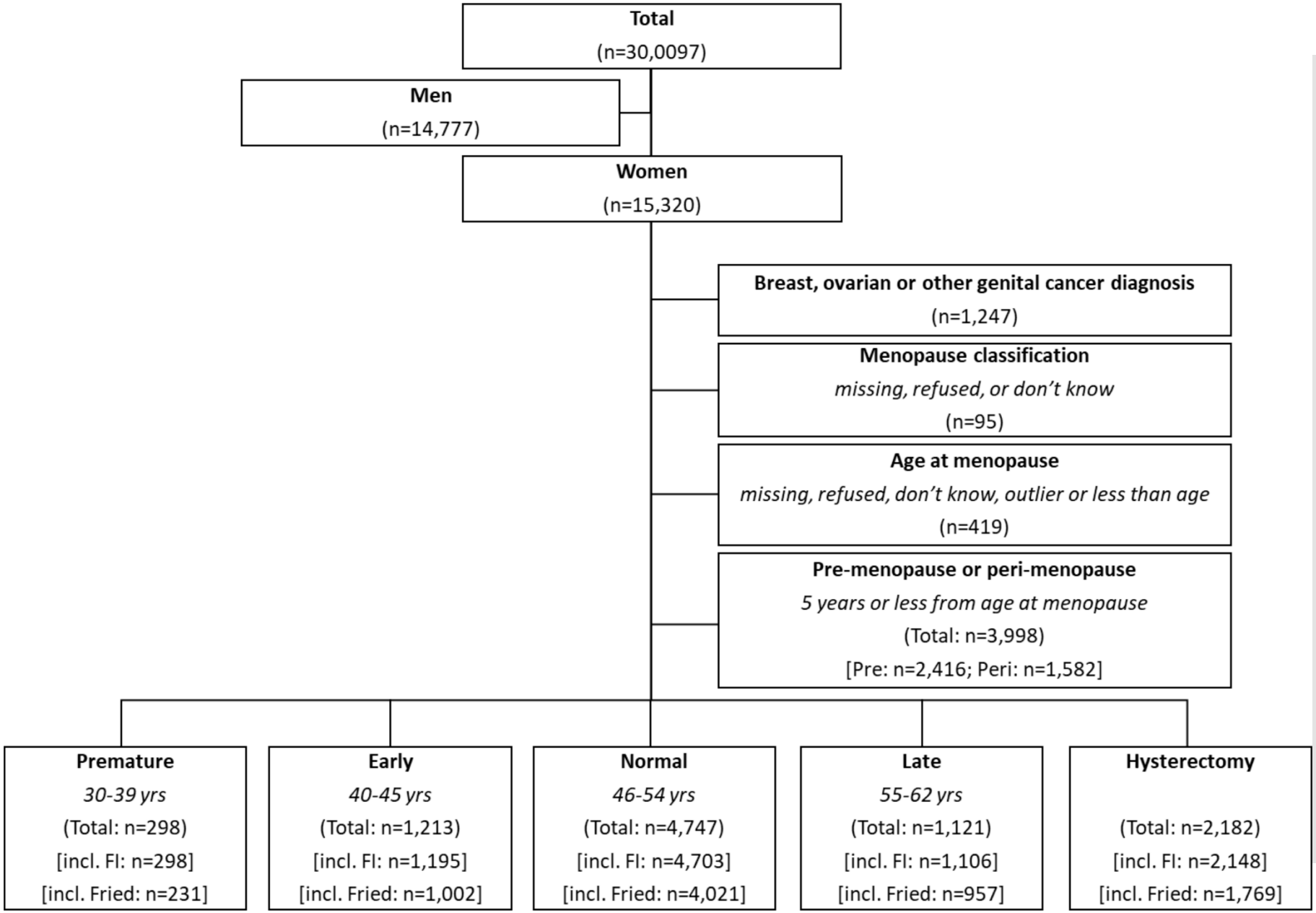
Early age of menopause or having had a hysterectomy will be associated with higher levels of frailty later in life for community-dwelling older women.



Methods
Study Design

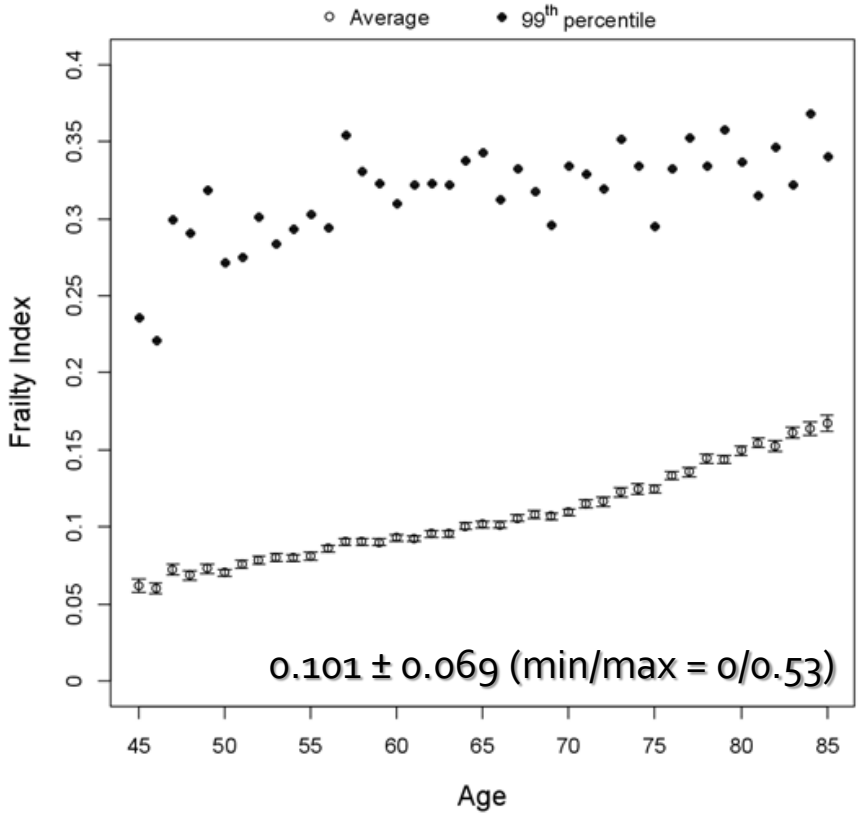
- Cross-sectional analysis of the Canadian Longitudinal Study on Aging Comprehensive Baseline Dataset version 3.0
    - 30,097 community-dwelling adults aged 45-85 (15,320 women)

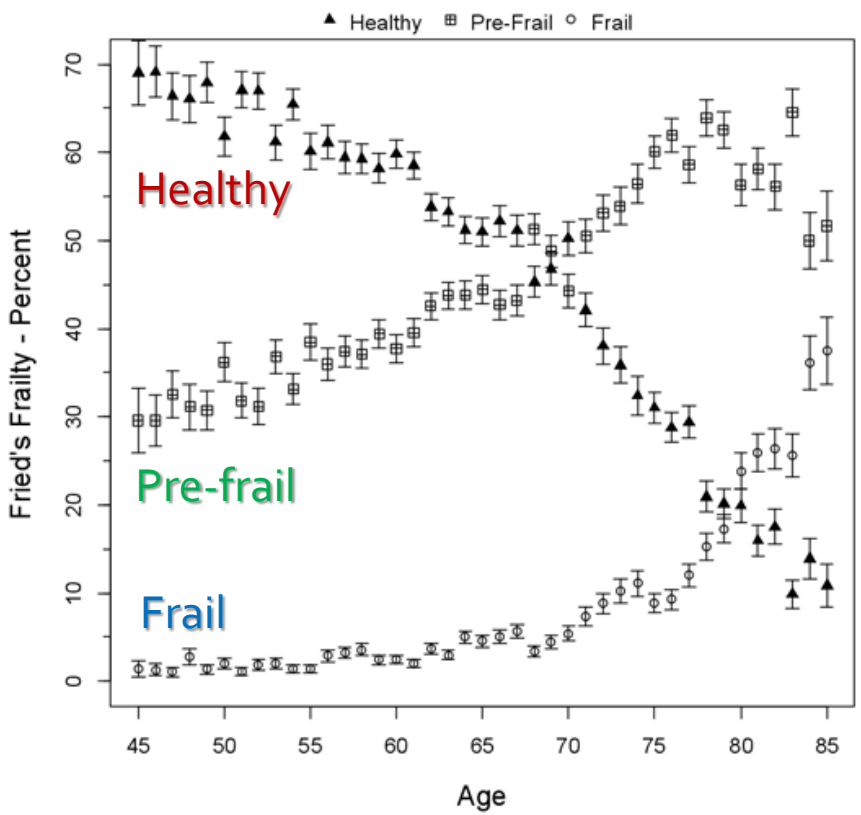
Methods
Exclusion criteria and Menopause classification



Methods
Frailty measures

- 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.





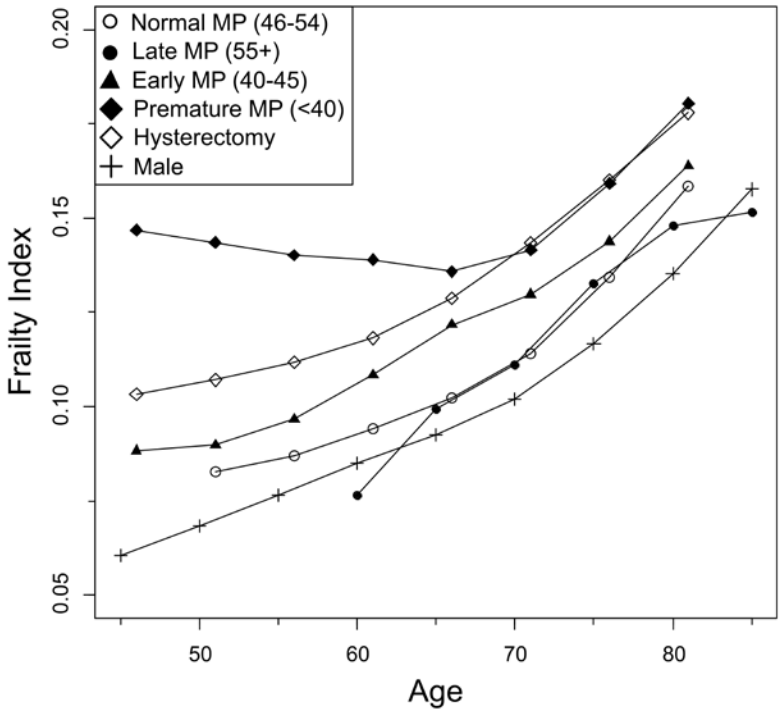
Methods
Statistical analysis and Covariates

- 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)

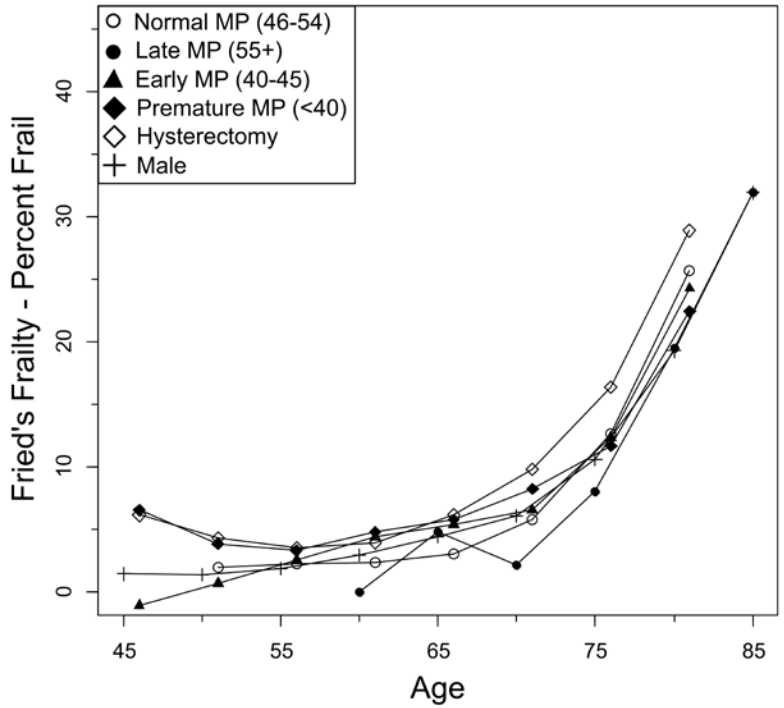
- Covariates
  - Age
  - Marital status (5 levels)
  - Ethnicity (7 levels)
  - Co-residence (yes/no)
  - Smoking (3 levels)
  - Alcohol consumption (8 levels)
  - Annual income (5 levels)
  - Education (4 levels)
  - Social support (MOS social support survey, 0-5)
  - HRT use ever (yes/no)

Results
Frailty by menopause classification

Frailty index



Fried's model

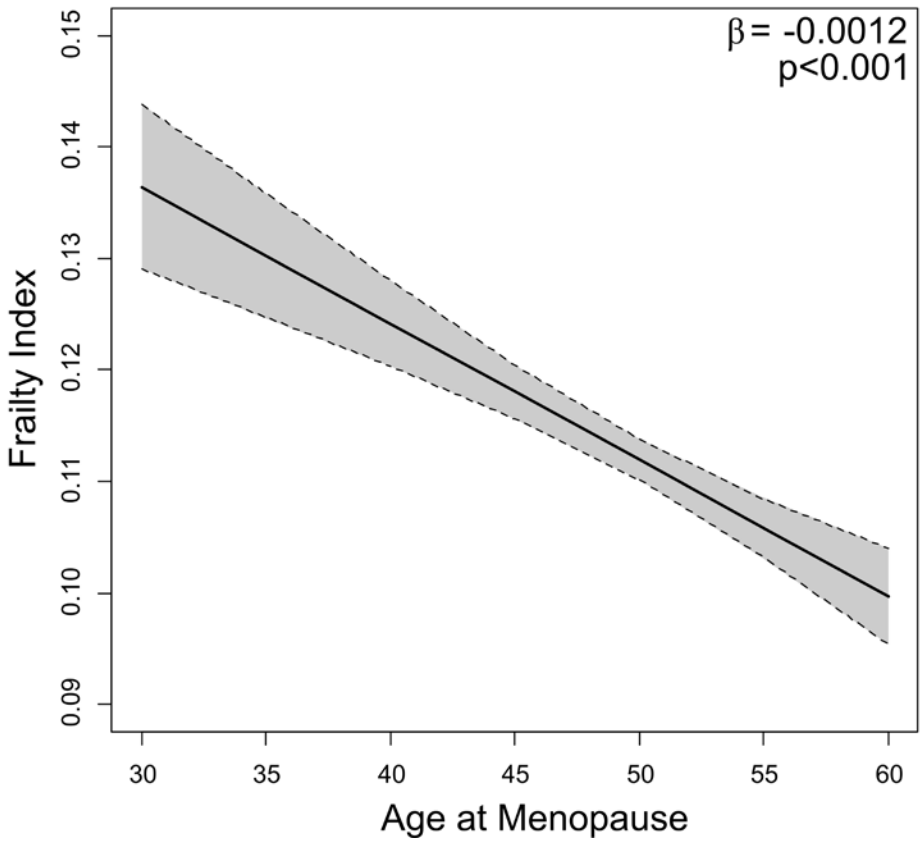


Results
Frailty by menopause classification

		Frailty Index [β (95% CI)]				Fried - Healthy/Pre-frail vs. Frail [OR (95% CI)]			
		Unadjusted		***Adjusted***		***Unadjusted***		***Adjusted***	
Menopause classification	Normal (46-54 yrs)	*Ref*		*Ref*		*Ref*		*Ref*	
	Premature (30-40 yrs)	0.038 (0.029 to 0.046)	***	**0.024 (0.015 to 0.034)**	***	1.17 (0.7 to 1.95)		1.45 (0.75 to 2.81)	
	Early (41-45 yrs)	0.012 (0.008 to 0.017)	***	**0.008 (0.002 to 0.013)**	**	1.22 (0.94 to 1.6)		1.04 (0.71 to 1.53)	
	Late (55+ yrs)	0.003 (-0.002 to 0.008)		-0.004 (-0.01 to 0.001)		1.04 (0.78 to 1.38)		0.78 (0.51 to 1.19)	
	Hysterectomy	0.029 (0.025 to 0.032)	***	**0.021 (0.017 to 0.025)**	***	1.76 (1.44 to 2.14)	***	**1.48 (1.11 to 1.99)**	**

- 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



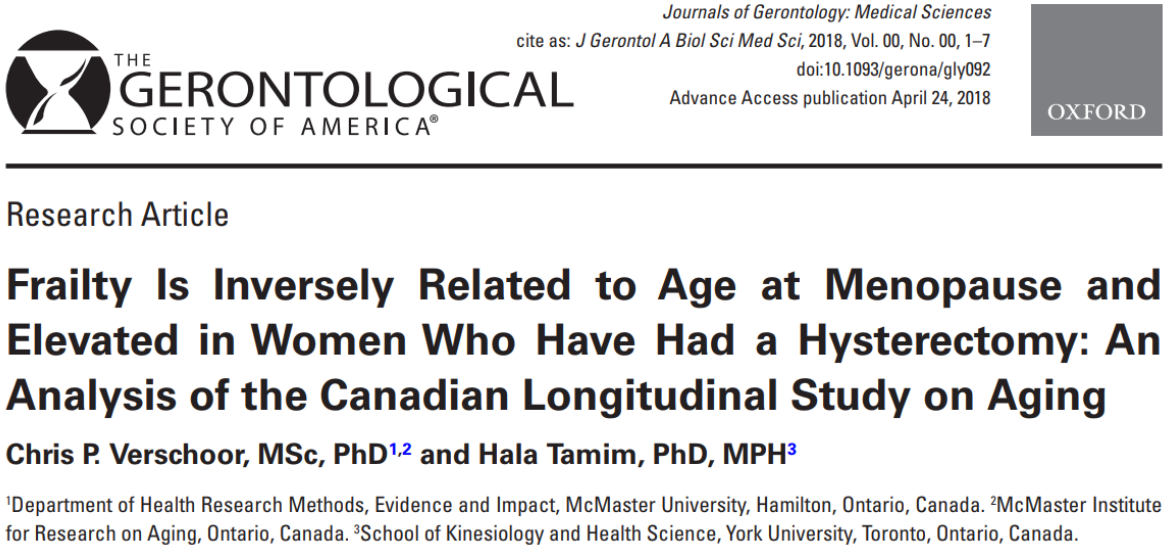
Frailty decreases ~7.5% of the mean per 5-years difference in age at menopause

Results
Frailty index and HRT use

		Frailty Index [β (95% CI)]				Fried - Healthy/Pre-frail vs. Frail [OR (95% CI)]			
		Unadjusted		Adjusted		Unadjusted		Adjusted	
HRT use	Yes (Ref=No)	0.011 (0.008 to 0.014)	***	**0.005 (0.002 to 0.009)**	**	1.17 (0.99 to 1.38)		1.17 (0.91 to 1.5)	
Length of HRT use (years)		0.0012 (0.0009 to 0.0014)	***	0.0002 (-0.0002 to 0.0005)		1.03 (1.02 to 1.04)	***	0.99 (0.97 to 1.01)	
Age at HRT onset (years)		-0.0013 (-0.0016 to -0.00099)	***	-0.0004 (-0.0008 to 0.00005)		0.98 (0.97 to 1)	*	1.01 (0.98 to 1.04)	
Type of HRT used	Combined (Est+Prog)	Ref		Ref		Ref		Ref	
	Estrogen alone	0.016 (0.011 to 0.021)	***	0.003 (-0.003 to 0.009)		1.29 (0.98 to 1.71)		1.04 (0.68 to 1.58)	
	Progesterone alone	-0.001 (-0.011 to 0.01)		-0.002 (-0.015 to 0.01)		0.78 (0.39 to 1.58)		0.6 (0.2 to 1.81)	
	Estrogen Gel	-0.01 (-0.018 to -0.001)	*	-0.007 (-0.017 to 0.003)		0.67 (0.38 to 1.2)		1 (0.44 to 2.27)	
	IUD with Progesterone	-0.015 (-0.043 to 0.012)		-0.006 (-0.04 to 0.028)		na		na	

Summary

- 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.



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OXFORD

Research Article

Frailty Is Inversely Related to Age at Menopause and Elevated in Women Who Have Had a Hysterectomy: An Analysis of the Canadian Longitudinal Study on Aging

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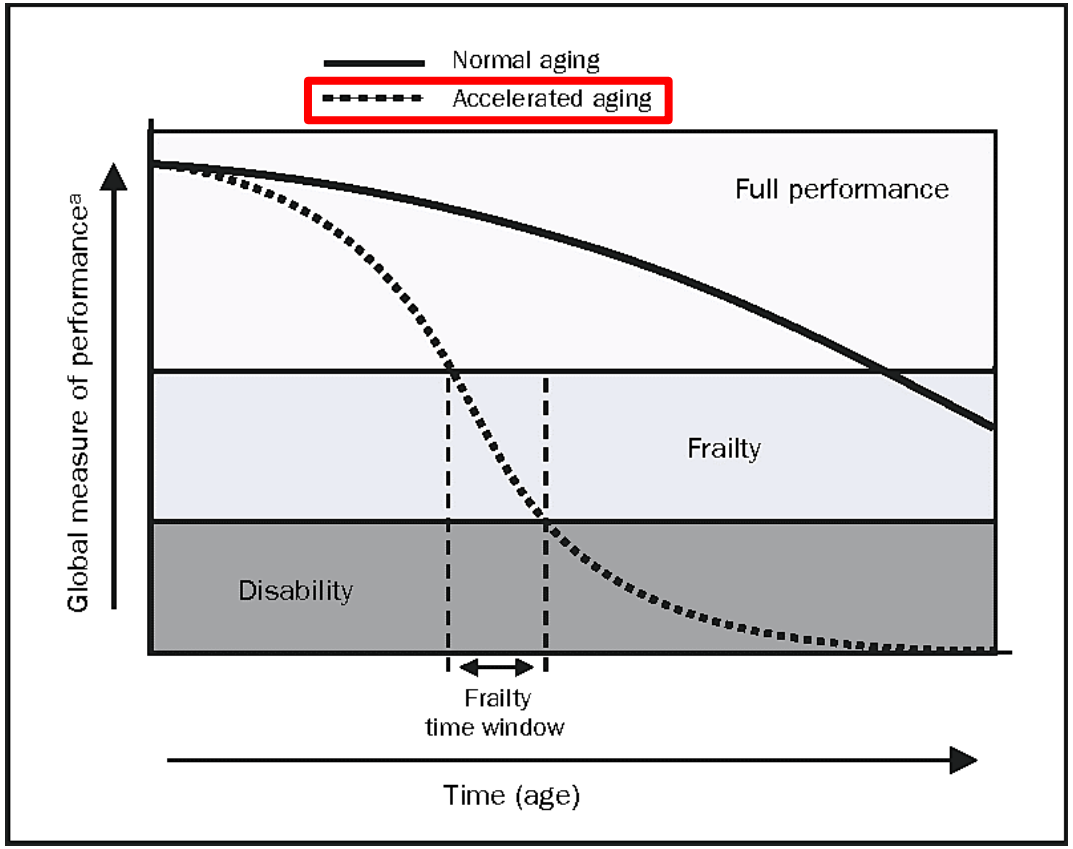
[1]Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada. [2]McMaster Institute for Research on Aging, Ontario, Canada. [3]School of Kinesiology and Health Science, York University, Toronto, Ontario, Canada.

Healthy aging or accelerated aging?

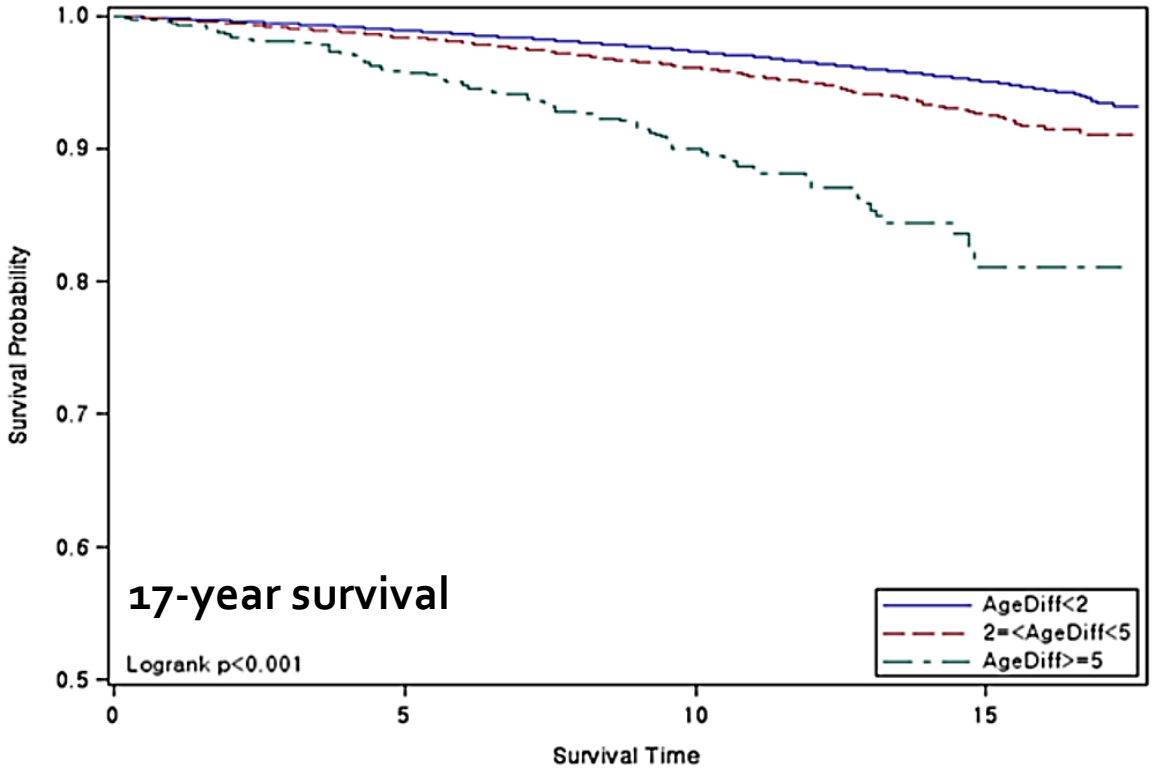


Ferrucci et al., 2002: J End Invest

Biological age

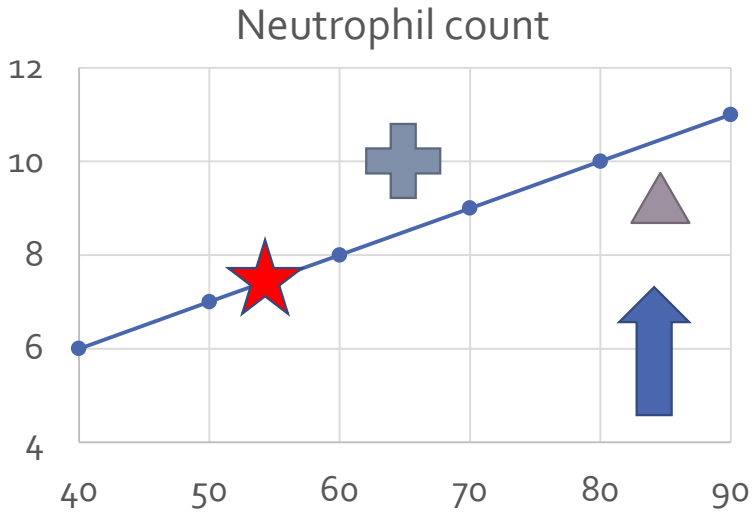
Accelerated aging = **Biological age** – Chronological age

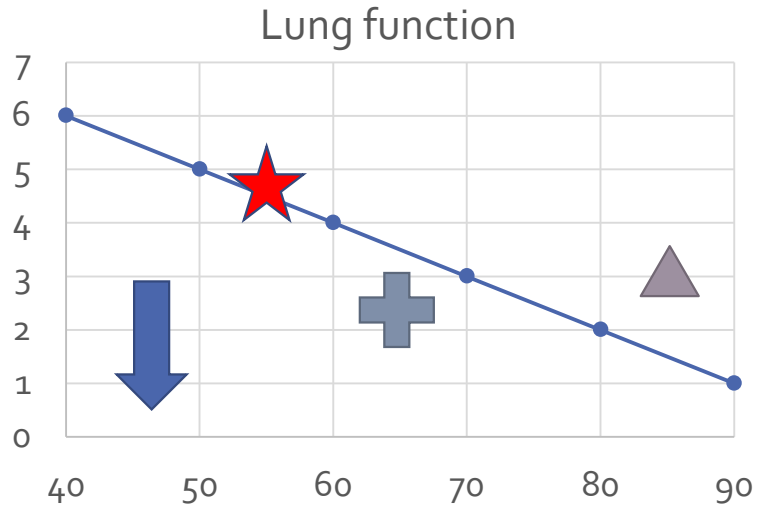
An estimate of someone's age that is based on biological factors (ie. biomarkers) that change with age

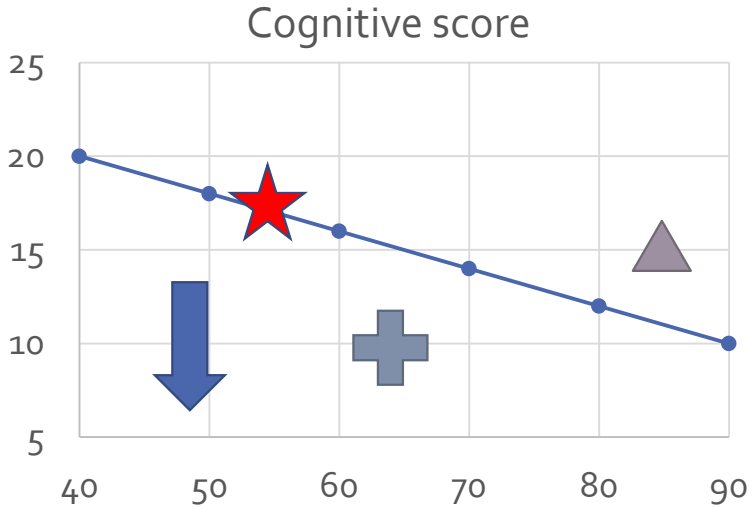


Yoo et al., 2017: BMC Geriatrics

Biological age: how it is measured







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**

Biological aging and age at menopause

Accelerated aging ≈ Frailty

Early menopause/ Hysterectomy → Accelerated Aging

Early menopause/ Hysterectomy → Accelerated Aging → Frailty

PNAS | August 16, 2016 | vol. 113 | no. 33 | 9327–9332

Menopause accelerates biological aging

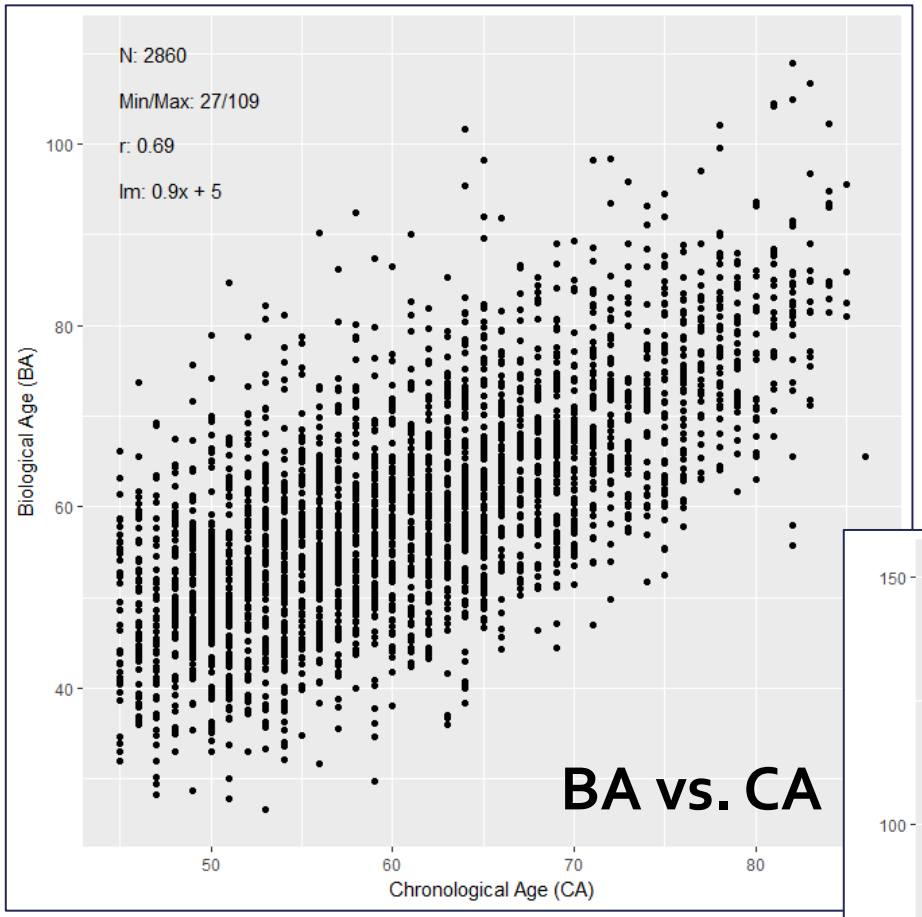
Morgan E. Levine[a,b], Ake T. Lu[a], Brian H. Chen[c], Dena G. Hernandez[d], Andrew B. Singleton[d], Luigi Ferrucci[c], Stefania Bandinelli[e], Elias Salfati[f], JoAnn E. Manson[g], Austin Quach[a], Cynthia D. J. Kusters[h], Diana Kuh[i], Andrew Wong[i], Andrew E. Teschendorff[j,k,l,m], Martin Widschwendter[j], Beate R. Ritz[h], Devin Absher[n], Themistocles L. Assimes[f], and Steve Horvath[a,o,1]

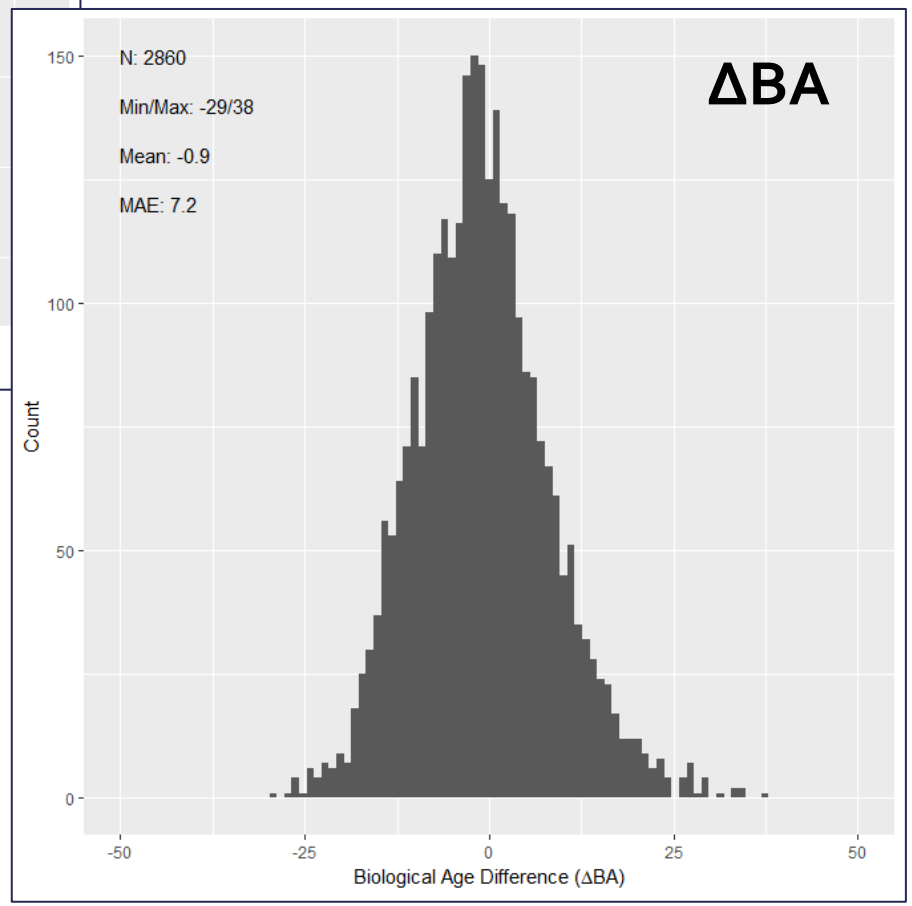
Methods

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

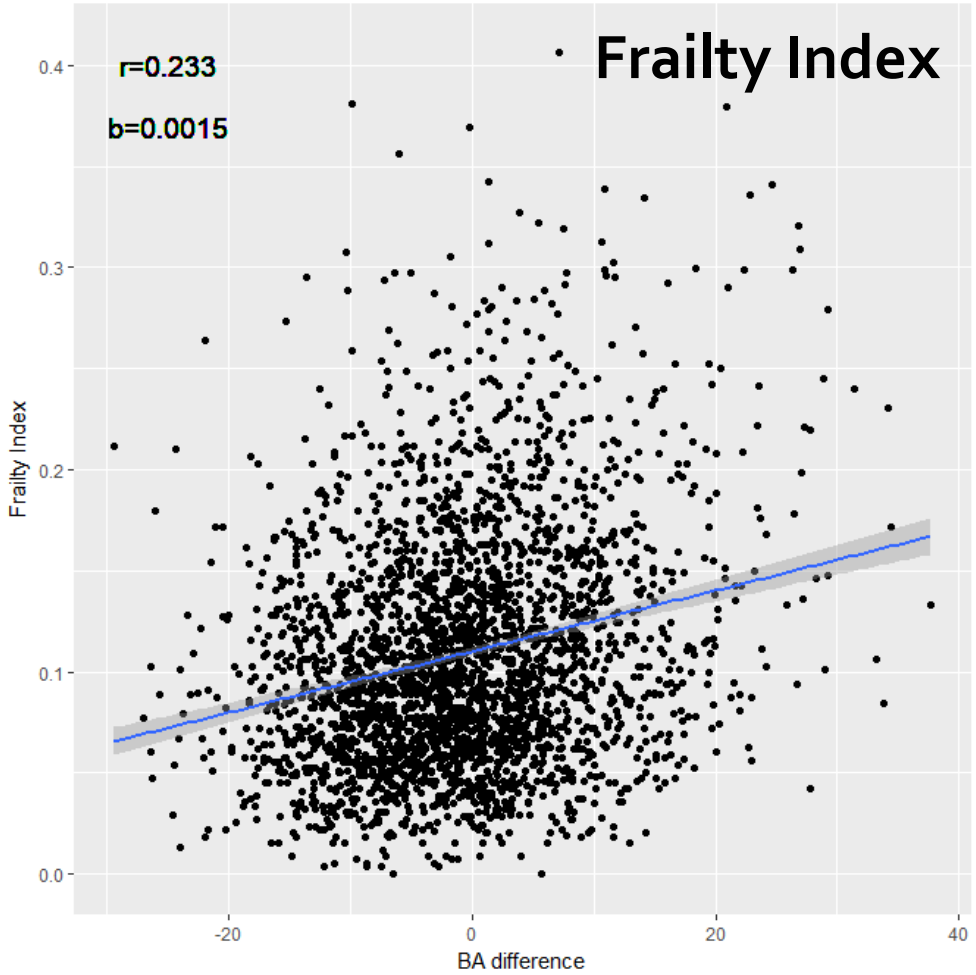
- Biological age was estimated using the equation developed by Klemera and Doubal (Mech Ageing Dev. 2006 Mar;127(3):240-8), training on a random sample of 80% of the dataset
- Accelerated aging defined as ΔBA, the difference between biological age and chronological age
- Biomarkers (27 in total)
  - 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.)

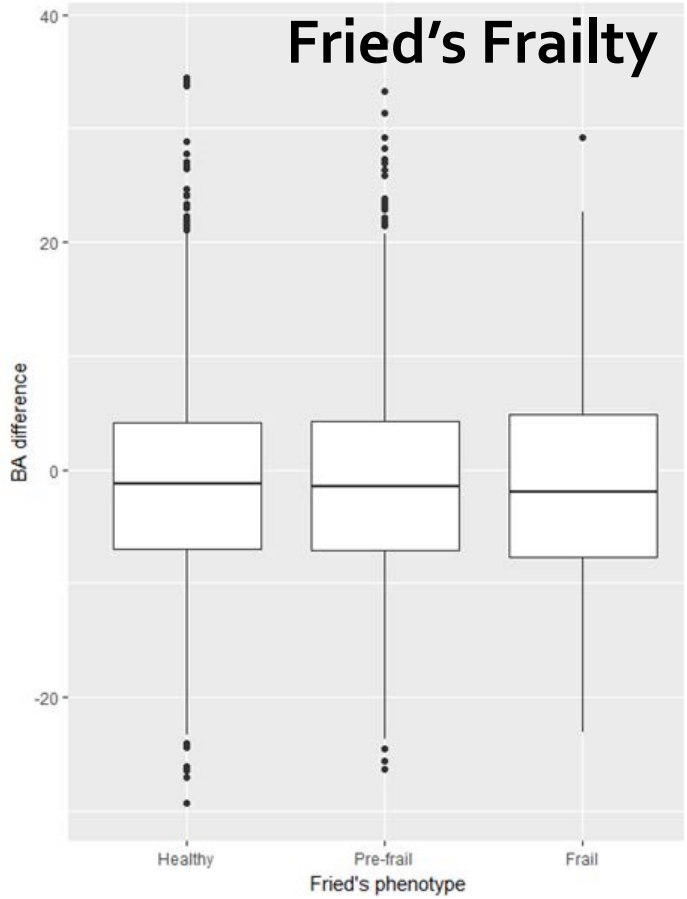
Biological age in the CLSA



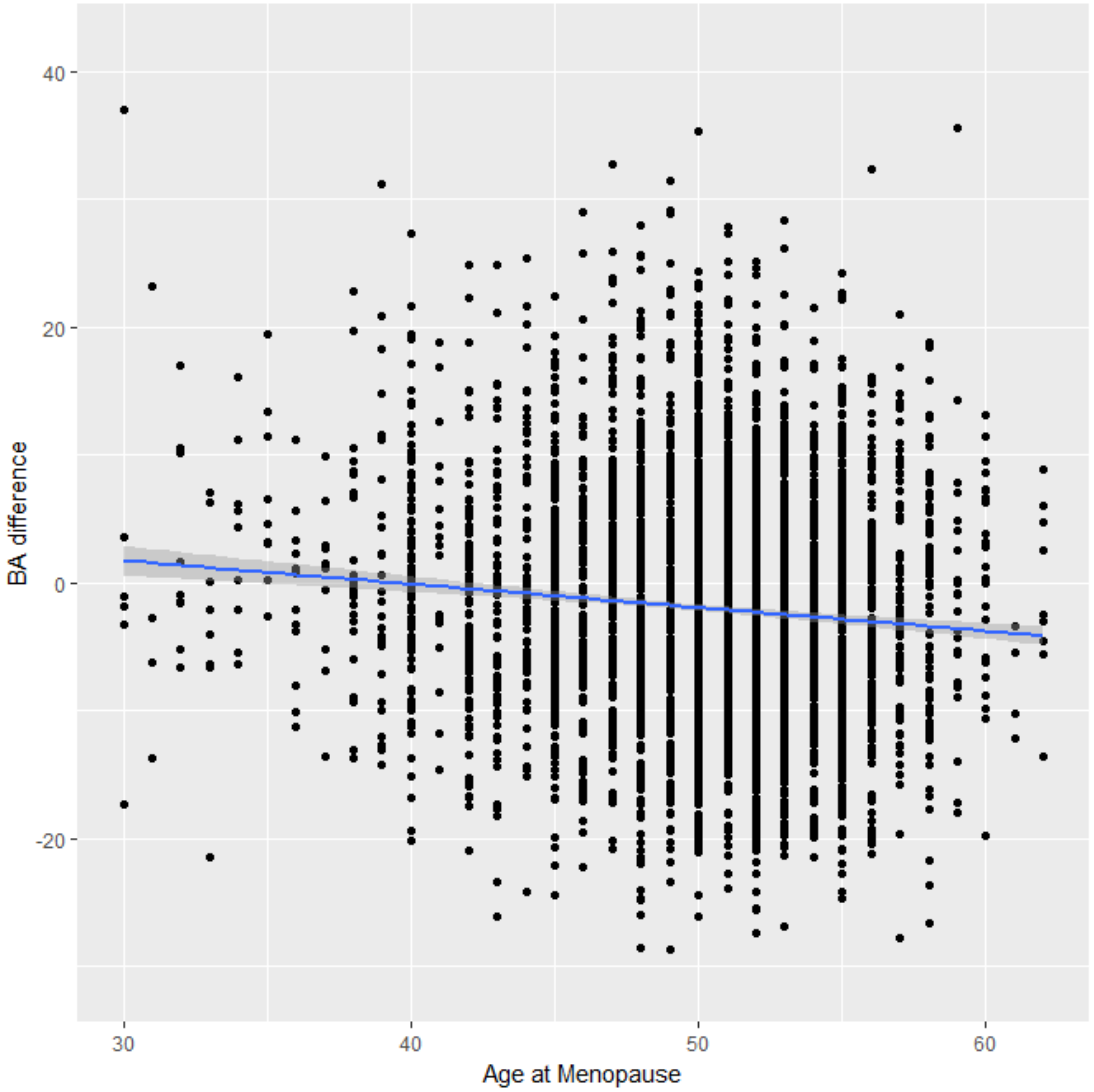


Biological age and frailty





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

Biological age and menopause classification

Menopause classification	Coefficient	95% CI	p
Normal (46-54 yrs)	*Ref*	*Ref*	
Premature (30-40 yrs)	2.79	1.09 - 4.50	**
Early (41-45 yrs)	1.38	0.46 - 2.30	**
Late (55+ yrs)	0.20	-0.70 - 1.11	
Hysterectomy	1.53	0.82 - 2.24	***

Early or premature menopause or having had a hysterectomy increases biological age by at least 1 year

Summary

- 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

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CLSA

- David Kanters
- Jinhui Ma
- Lauren Griffith
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- Stacey Voll (U Victoria)

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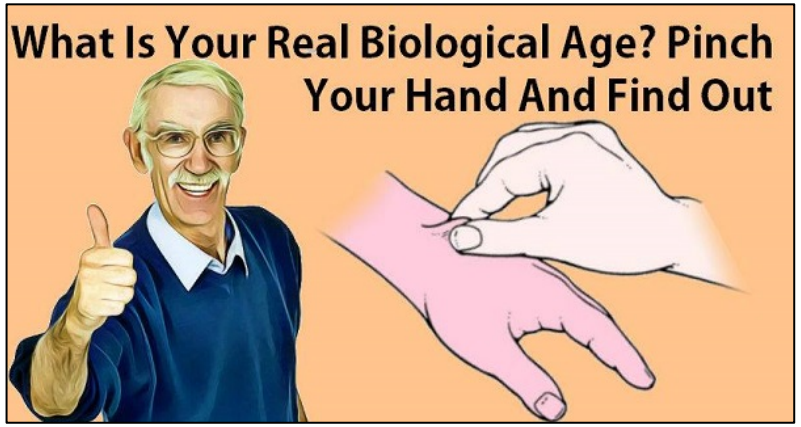

UPCOMING CLSA WEBINARS

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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