香港中文大學
The Chinese University of Hong Kong

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

35th Anniversary
三十五週年

Mr. OS and Ms. OS study

Professor Timothy Kwok
Director
Jockey Club Centre for Osteoporosis Care and Control
Deputy Director
JC Institute of Ageing

Content

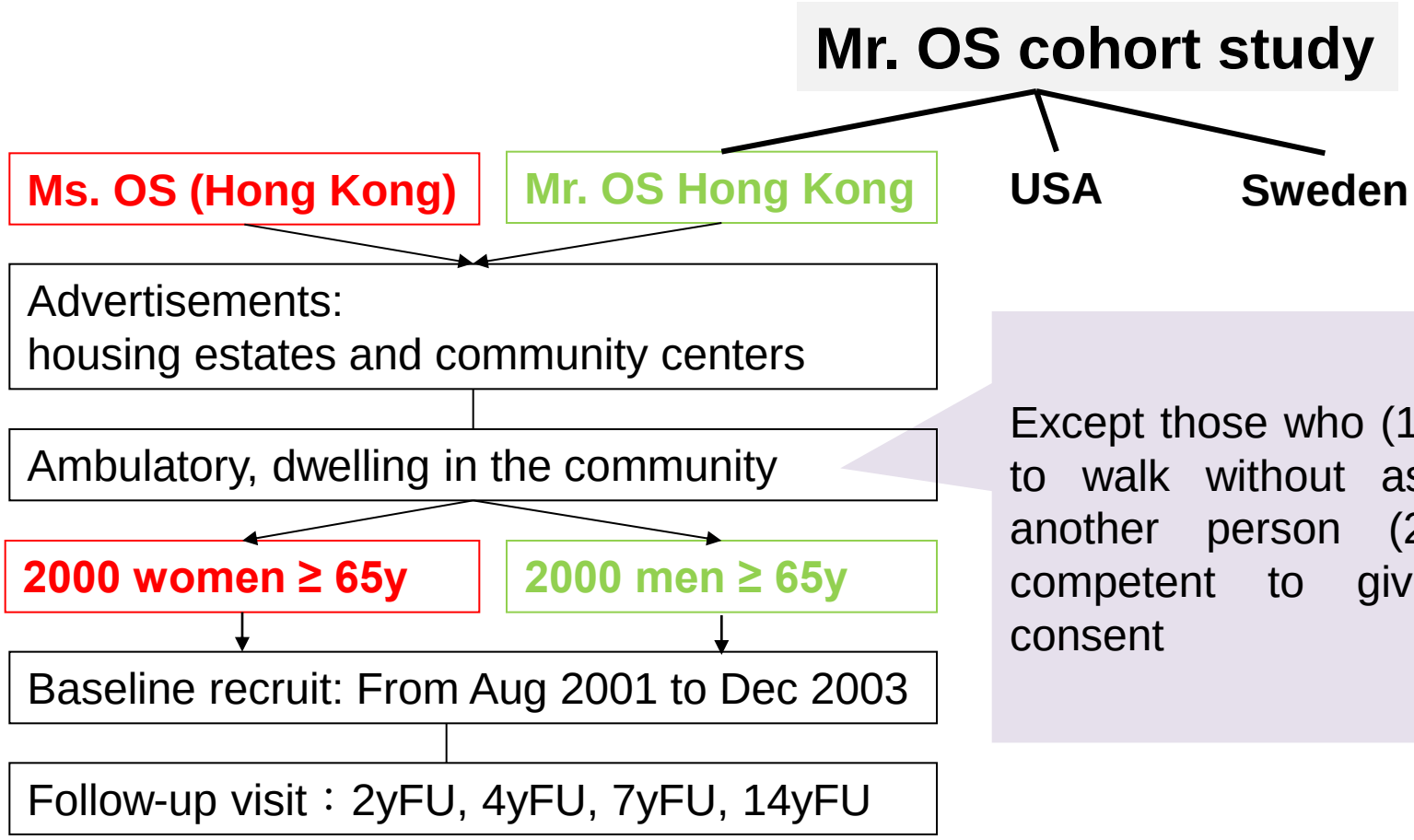
- Study design
- Examples of analysis
- How you can participate
- Discussion

Mr & Ms Os (Hong Kong)

Study Design

- The first ever cohort study on osteoporosis in Asian older men and women
- Mr Os (Hong Kong) is the Chinese arm of an international study of osteoporosis in men (USA (n=5994) and Sweden (n = 3014)).
- Ms Os (Hong Kong) is the study for women, alongside with Mr Os (Hong Kong).
- 2000 men and 2000 women (average age 72 years) in 2001 -2003
- Stratified by age groups: 65-69; 70-74; 75+

Study Design & Recruitment



Except those who (1) are unable to walk without assistance of another person (2) are not competent to give informed consent

Questionnaires

- Lifestyle, medical history and medication use
- Fracture history
- Self rated socioeconomic status (SES, community ladder)
- Physical activity (PASE)
- Cognitive function (MMSE, CSID)
- SF12
- IADL
- Geriatric depression scale
- Prostate health/ women health
- Back and joint health
- Food frequency (dietary quality index, DQI)

Measurement – I

- Height and Weight
- BP, pulse
- Ankle / arm BP index
- Visual function: acuity, contrast sensitivity and stereopsis
- Neuromuscular : grip strength, single and repeated chair stand, 6 meter usual pace and 20cm narrow walk

Measurement – II

- BMD at hip & lumbar spine and body composition by DXA
- Ultrasound on heel
- MRI in subgroups (baseline M=177 F=218, perfusion, marrow fat, disc and vertebral height, endplate and true volume, 14YFU N~500 spine)
- pQCT at distal radius and tibia (Baseline M=466 F=443, 2YFU M=1728 F=37, 4YFU M=358; BMD)
- QCT (Male spine=329, Male hip=332 at 2YFU)
- X-ray (spine at baseline and spine and hip at 4YFU)

Bio-sample (serum, DNA)

- ACE genotype
- Serum ACE activity
- Male sex hormones
- Telomere (M=976, F=1030)
- Serum vitamin D
- IGF
- CRP
- PTH (M=991)
- Amino acid
- Homocysteine, vitamin B12 and folate

Follow-up

- Two yearly follow-up (site visit) for 4 years
- Fall incidence by every 4 months (telephone FU) for four years
- Hospital discharge diagnosis for six years
- Fracture rate for ten years
- Survival for 14 years

Follow up – site visit

Visit	Time	Male	Female	Total
Baseline	Aug 01 - Dec 03	2000	2000	4000
2Y FU	Aug 03 - Dec 05	1745	1682	3427
4Y FU	Aug 05 - Nov 07	1566	1587	3153
7Y FU	Jan 08 - Jan 10	989	889	1878
14Y FU	Nov 15 - Aug 17	509	552	1061 +400

Special features at year 7

- Overall 53% of the surviving cohort participated
- The unfit were not invited
- Cardiorespiratory fitness
- No DXA

New variables at year 14

- Questionnaire
  - Loneliness
  - Neighbourhood cohesion
  - SARC-F
  - FRAIL
- Cognitive tests – MOCA, verbal fluency (voice recorded)
- Actigraph – physical activity over 7 days (N=600)
- Fasting glucose, lipids, creatinine (n=1030)
- Lung function test (N=302)
- MRI spine (N=420)
- Indoor air pollutant monitoring for three days (N=121)

New variables at year 14

- Consent for access to electronic medical records for ten years
- History of address verified to estimate historical air pollution exposure
- 512 pair of spouses at baseline; 82 pair followed up at year 14; 26 spouses joined study
- Fall incidence 3 monthly

Characteristics – Baseline (I)

	Mean (SD)/ Freq (%)		p-value
	Male	Female	
Baseline	N=2000	N=2000	
Age	72.39 (5.01)	72.58 (5.36)	0.2541
Weight (kg)	62.44 (9.38)	54.52 (8.50)	<.0001
Height (cm)	163.10 (5.72)	150.90 (5.31)	<.0001
BMI (kg/m^2)	23.45 (3.13)	23.92 (3.45)	<.0001
PASE score	97.28 (50.30)	85.36 (33.16)	<.0001
SF12 – physical	50.53 (7.59)	46.60 (8.76)	<.0001
SF12 – mental	55.83 (6.77)	55.05 (7.76)	0.0007
Time to complete 5 stands (s)	12.65 (3.90)	13.42 (5.04)	<.0001
Appendicular lean muscle/ height^2 (kg/m^2)	7.20 (0.82)	6.06 (0.73)	<.0001
Grip strength (kg)	33.90 (6.73)	22.31 (4.41)	<.0001
Walking speed (m/s)	1.07 (0.23)	0.96 (0.21)	<.0001
Sarcopenia	187 (9.35%)	106 (5.3%)	<.0001

Characteristics – Baseline (II)

	Mean (SD)/ Freq (%)		p-value
	Male	Female	
Baseline	N=2000	N=2000	
Smoking	238 (11.9%)	37 (1.85%)	<.0001
Alcohol use (>12 drinks in p12m)	471 (23.55%)	51 (2.55%)	<.0001
Diabetes	293 (14.65%)	286 (14.3%)	0.7531
Hypertension	836 (41.8%)	871 (43.55%)	0.2632
Cardiovascular disease	366 (18.3%)	330 (16.5%)	0.1332
COPD	232 (11.6%)	101 (5.05%)	<.0001
Depressed	169 (8.45%)	203 (10.16%)	0.0642
Cognitive impaired[a]	81 (4.05%)	266 (13.3%)	<.0001
Osteoporosis	273 (13.65%)	983 (49.15%)	<.0001

[a] Mini-Mental State Examination score ≤18 in illiterate, ≤20 in 1–2 years of schooling and ≤22 in more than 2 years of schooling

Characteristics – 14Y FU (I)

	Mean (SD)/ Freq (%)		p-value
	Male	Female	
14Y FU	N=509	N=552	
Age	83.34 (3.69)	83.33 (4.03)	0.9851
Weight (kg)	61.33 (9.10)	52.92 (8.70)	<.0001
Height (cm)	161.97 (6.00)	149.53 (5.93)	<.0001
BMI (kg/m^2)	23.34 (2.96)	23.66 (3.64)	0.1237
PASE score	76.60 (43.42)	68.35 (38.38)	0.0013
SF12 – physical	48.53 (8.75)	42.30 (10.22)	<.0001
SF12 – mental	52.86 (8.09)	51.18 (9.31)	0.0018
Time to complete 5 stands (s)	11.49 (4.74)	12.95 (5.46)	<.0001
ALM/ height^2 (kg/m^2)	6.52 (0.74)	5.56 (0.71)	<.0001
Grip strength (kg)	23.49 (6.04)	13.85 (4.24)	<.0001
Walking speed (m/s)	0.86 (0.22)	0.74 (0.22)	<.0001
Sarcopenia	239 (54.94%)	198 (37.22%)	<.0001

Characteristics – 14Y FU (II)

	Mean (SD)/ Freq (%)		p-value
	Male	Female	
14Y FU	N=509	N=552	
Smoking	18 (3.54%)	7 (1.27%)	0.015
Alcohol use	79 (15.52%)	18 (3.26%)	<.0001
Diabetes	102 (20.04%)	115 (20.83%)	0.7487
Hypertension	331 (65.29%)	400 (72.6%)	0.0102
Cardiovascular disease	67 (13.16%)	71 (12.86%)	0.8843
COPD	46 (9.09%)	37 (6.74%)	0.1564
Depressed	60 (11.81%)	91 (16.61%)	0.0262
MoCA			<.0001
Normal	461 (91.29%)	424 (76.95%)	
MCI	26 (5.15%)	67 (12.16%)	
AD	18 (3.56%)	60 (10.89%)	
Osteoporosis	51 (10.06%)	280 (51.38%)	<.0001

Publication - I

	Theme	Coordinator	No of papers
1	Fracture/osteoporosis	Kwok T	23
2	Cognitive function	Kwok T	4
3	Fall	Kwok T	5
4	Frailty	Woo J	12
5	Sarcopenia	Woo J	12
6	Spousal relationship	Fung H	1
7	Psychology	Fung H	3
8	Indoor air	Ho KF	0
9	Environment	Lau K/Woo J	3
10	Sleep	Wing YF	3
11	Vertebral #	Wang YX	7
12	Bone imaging	Griffith J	16

Total no. of publications: 156 (updated to July 2018)*

*Full publication list please refer to Appendix_2_Publication_list_july_2018

Publication - II

	Theme	Coordinator	No of papers
13	Accelerometry/Physical activity	Kwok T	2
14	Biomarker of ageing	Tang N	13
15	Dietary intakes	Woo J	11
16	Lung function	Ko F	0
17	Men's health	Wong S	8
18	Depression	Wong S	9
19	Vitamin D	Lee J	4
20	Sex hormone	Kwok T	7
21	Sulphur containing amino acids	Kwok T	0
22	Body fat/ Body composition	AuYeung TW	9
23	Social factors	Woo J	2
24	Others		2

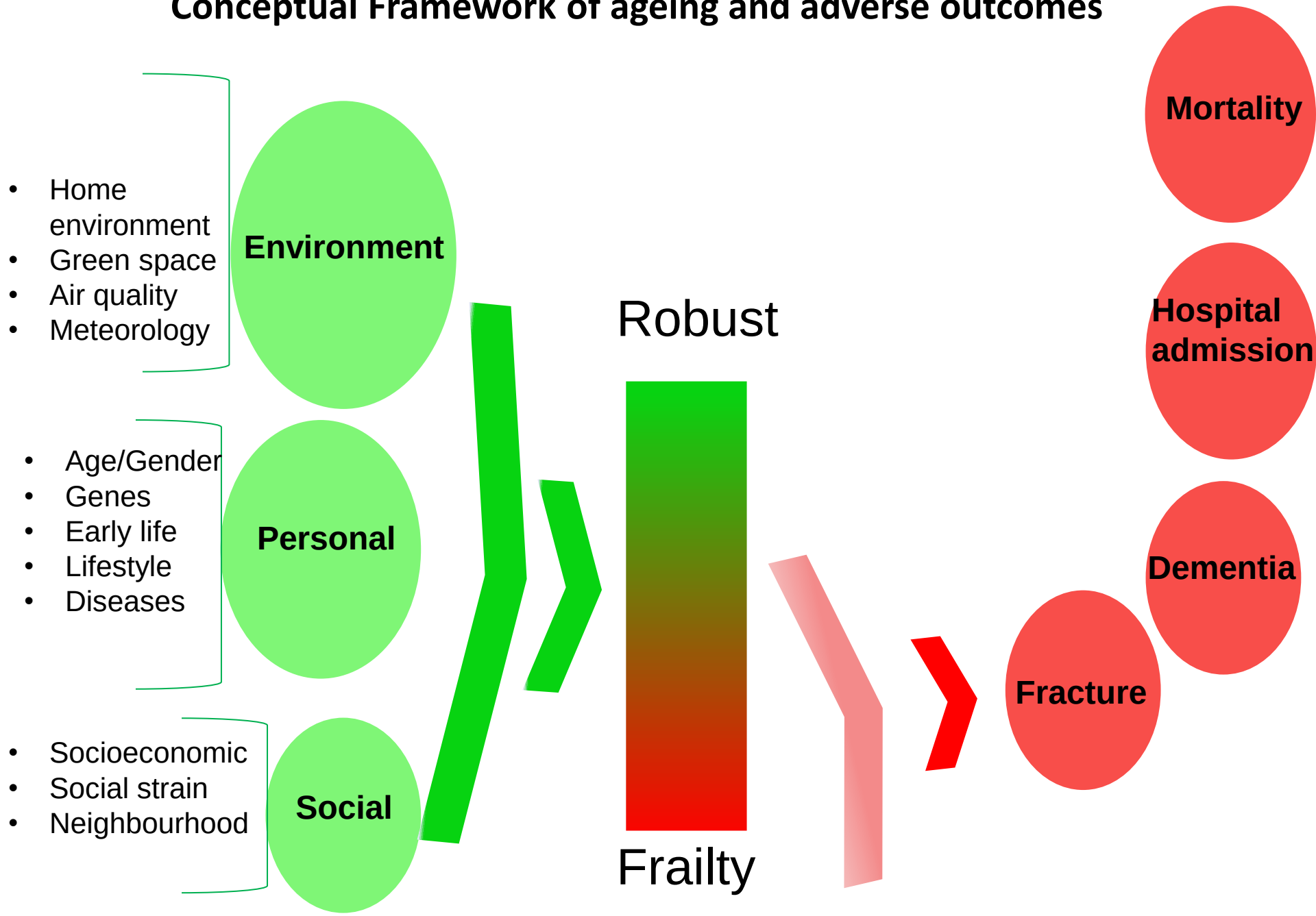
Total no. of publications: 156 (updated to July 2018)*

*Full publication list please refer to Appendix_2_Publication_list_july_2018

Funding

- National Institutes of Health R01 grant AR049439–01A1
- Research Grants Council Earmarked Grant CUHK4101/02 M
- JC Centre for osteoporosis care and control
- HMRF 2x for serum analysis
- Therese Chow dementia prevention research centre

Conceptual Framework of ageing and adverse outcomes



Using data from the MrOs study, we examined…

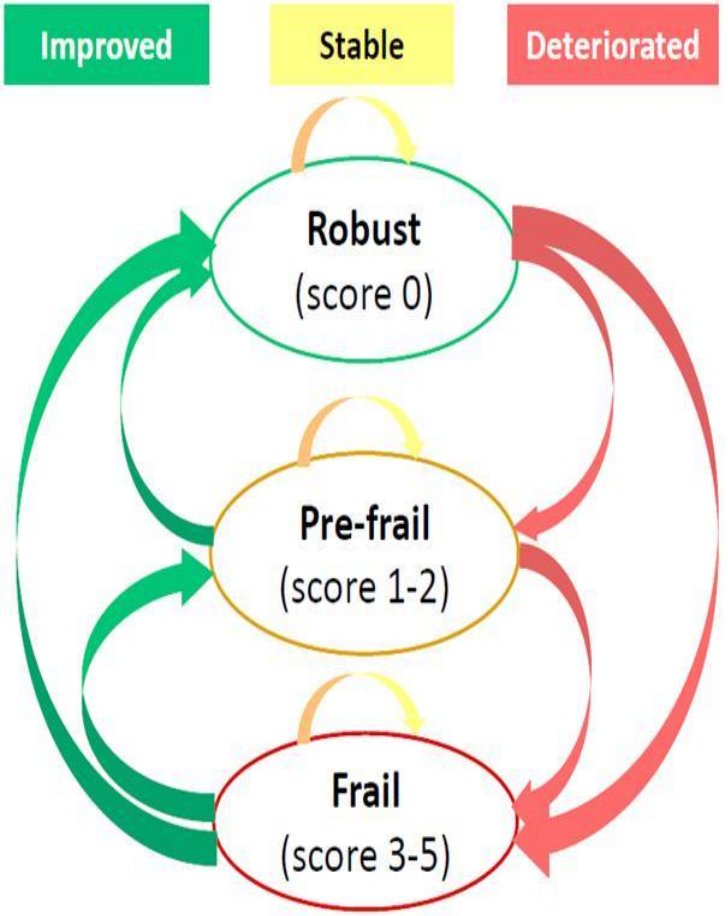
Transitions, consequences, and factors associated with frailty

We found that…

Transitions in frailty states

- Frailty is reversible
- At baseline, 850 (48.7%) men and 884 (52.6%) women were pre-frail. Among these, 23.4% men and 26.6% women improved after 2 years; 11.1% of men and 6.6% of women worsened

  (Lee J JAMDA 2014;15:281-86)



We found that…

Consequences of frailty

- Frailty was associated with an increase in functional limitation after 4 years (OR 1.33, 95% CI 1.01-1.76)

  (Woo J Age 2014;36:923-31)

- Cognitive frailty (pre-frailty + cognitive impairment) was associated with increased risks of functional limitation after 4 years (OR 1.78, 95% CI 1.26-2.51) and mortality over 12 years (OR 1.46, 95%CI 1.02-2.07)

  (Yu R Frontiers in Medicine 2018;5:Article 5)

We also found that…

Factors associated with frailty

- Hospitalizations, older age, previous stroke, lower cognitive function, diabetes, and osteoarthritis were associated with worsening or less improvement in frailty

  (Lee J JAMDA 2014;15:281-86)

- Older age, being a woman, and low levels of physical activity were common risk factors for frailty across three Chinese populations: Hong Kong, Taiwan urban, Taiwan rural.
- Living alone was associated with frailty in Hong Kong men, but not in Hong Kong women or Taiwanese people

  (Yu R IJERPH 2017;14:1096)

Recently, we found that…

Factors associated with frailty

- Older people living in neighborhoods with a higher percentage of green space were associated with improvement in frailty status, independent of a wide range of individual characteristics (OR 1.29 95% CI 1.04-1.60)

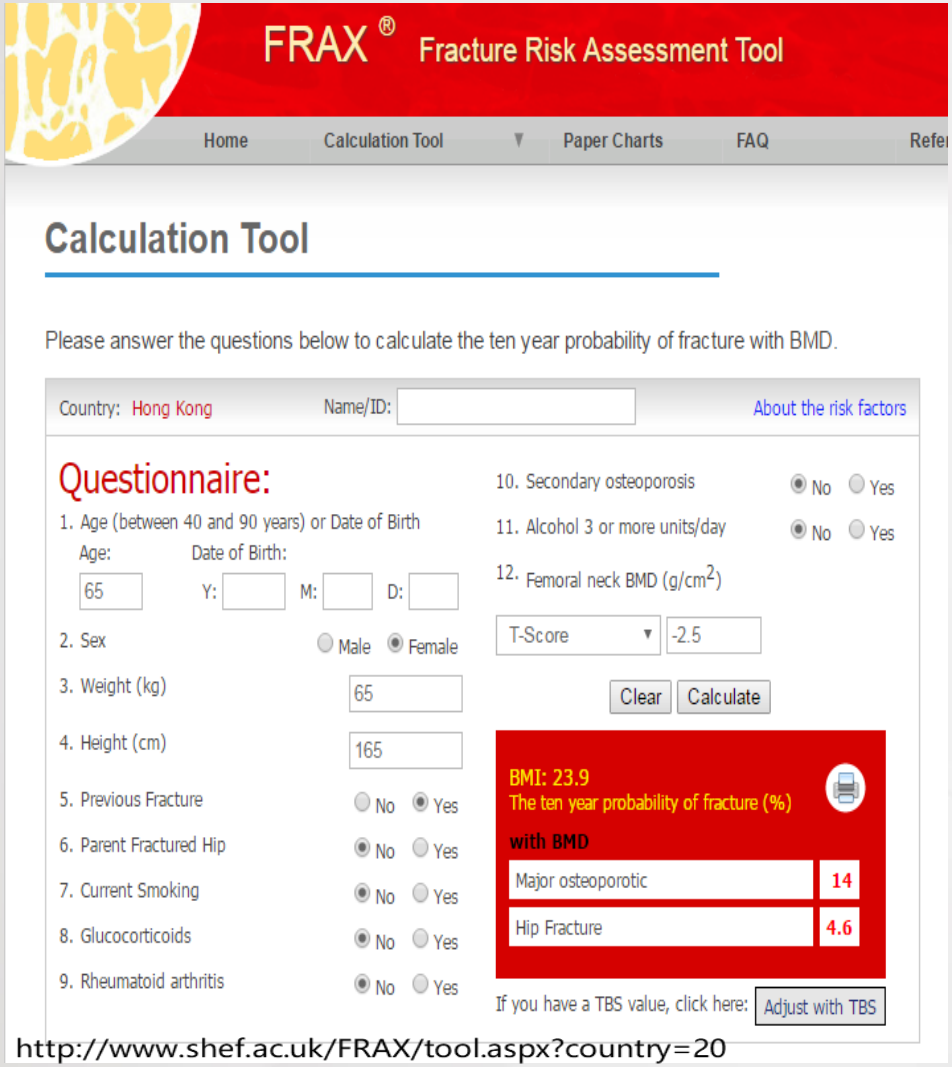
  (Yu R JAMDA 2018;19(6):528-34)

Hip fx in HK

Hip fracture patients in 2012 (n= 2914)		
Female		67.9%
Community dwelling		73.7%
Age (yr)	60-69	6.3%
	70-79	25.2%
	80-89	50.0%
	≥ 90	18.5%
Osteoporosis diagnosis		4.2%

[1] Leung KS, Yuen WF, Ngai WK, Lam CY, Lau TW, Lee KB, Siu KM, Tang N, Wong SH, Cheung WH (2017) How well are we managing fragility hip fractures? A narrative report on the review with the attempt to setup a Fragility Fracture Registry in Hong Kong. Hong Kong Med J

FRAX



http://www.shef.ac.uk/FRAX/tool.aspx?country=20

A large-scale trial in UK [2]

(community women aged 70-85 years)

Prescreening using FRAX questionnaire

↓

Subsequent DXA test for selected people

↓

Subsequent treatment for selected people

↓

A 30% reduction in 5-y hip fracture risk

[1] Kanis JA, Oden A, McCloskey EV, Johansson H, Wahl DA, Cooper C (2012) A systematic review of hip fracture incidence and probability of fracture worldwide. Osteoporos Int 23:2239-2256

[2] Shepstone L, Lenaghan E, Cooper C, et al. (2018) Screening in the community to reduce fractures in older women (SCOOP): a randomised controlled trial. Lancet 391:741-747

SARC-F

Sarcopenia ~ loss of muscle mass
~ decline in muscle function

Editorial

SARC-F: A Simple Questionnaire to Rapidly Diagnose Sarcopenia

Theodore K. Malmstrom PhD [a,b], John E. Morley MB, BCh [b,*]

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[b] *Division of Geriatric Medicine, Saint Louis University School of Medicine, St. Louis, MO*

Its increasing propensity to *hip fracture*

- **Possible association with osteoporosis**
- **Possible association with incident fall risk**

a number of other factors play into the role of diagnosing the propensity to have a fracture.[28,29] This is particularly true in older persons with diabetes mellitus who often have good bone mineral density but weak bones, and this is coupled with an increase in sarcopenia.[30–33] This has led to the concept that the questions associated with the Fracture Risk Assessment Tool (FRAX) (www.shef.

Table 1
SARC-F Screen for Sarcopenia

Component	Question	Scoring
Strength	How much difficulty do you have in lifting and carrying 10 pounds?	None = 0 Some = 1 A lot or unable = 2
Assistance in walking	How much difficulty do you have walking across a room?	None = 0 Some = 1 A lot, use aids, or unable = 2
Rise from a chair	How much difficulty do you have transferring from a chair or bed?	None = 0 Some = 1 A lot or unable without help = 2
Climb stairs	How much difficulty do you have climbing a flight of 10 stairs?	None = 0 Some = 1 A lot or unable = 2
Falls	How many times have you fallen in the past year?	None = 0 1–3 falls = 1 4 or more falls = 2

Analysis & Results

➢ Threshold deriving and predictive ability test

Table The associations of baseline FRAX and SARCF score with hip fracture risk in men and women.

	Hip fracture						
	Mean ± SD / n (%)		HR (95%CI)	HR (95%CI) [c]	Sensitivity	Specificity	AUC (95%CI)
Men	**No (n=1937)**	**Yes (n= 63)**					
FRAX score	3.40 ± 2.51	4.92 ± 2.61	1.14 (1.09, 1.20)	-	-	-	0.70 (0.64, 0.76)
SARCF score	0.37 ± 0.83	0.60 ± 0.98	1.33 (1.08, 1.63)	1.24 (1.02, 1.52)	-	-	0.57 (0.51, 0.63)*
FRAX category_high [a]	469 (23.9)	37 (58.7)	5.42 (3.28, 8.96)	5.22 (3.15, 8.64)	58.7	76.1	0.67 (0.61, 0.74)
SARCF category_high [b]	479 (24.7)	24 (38.1)	2.03 (1.22, 3.38)	1.82 (1.09, 3.03)	38.1	75.3	0.57 (0.51, 0.63)*
FRAX category_high or SARCF category_high	799 (41.3)	48 (76.2)	5.15 (2.88, 9.20)	-	76.2	58.8	0.67 (0.62, 0.73)
Women	**No (n=1931)**	**Yes (n=69)**					
FRAX score	6.32 ± 5.04	10.63 ± 6.53	1.08 (1.06, 1.10)	-	-	-	0.72 (0.66, 0.79)
SARCF score	0.91 ± 1.34	1.25 ± 1.71	1.17 (1.01, 1.35)	1.15 (0.99, 1.33)	-	-	0.55 (0.49, 0.62)*
FRAX category_high [a]	579 (30.0)	48 (69.6)	5.39 (3.23, 9.00)	5.24 (3.13, 8.79)	69.6	70.0	0.70 (0.64, 0.75)
SARCF category_high [b]	440 (22.8)	22 (31.9)	1.60 (0.97, 2.66)	1.25 (0.75, 2.09)	31.9	77.2	0.55 (0.49, 0.60)*
FRAX category_high or SARCF category_high	843 (43.6)	54 (78.3)	4.73 (2.67, 8.38)	-	78.3	56.4	0.67 (0.62, 0.72)

[a] Threshold of FRAX score determined using CART in OS cohort for hip fx: high risk- ≥ 4.5 for men and ≥ 7.5 for women;

[b] Threshold of SARCF score determined using CART in OS cohort for hip fx: high risk- ≥ 1.0 for men and ≥ 2.0 for women;

[c] adjusted for FRAX score and SARC-F score or FRAX category_high and SARC-F category_high;

* significant difference when compared with FRAX score or its category.

Analysis & Results

➢ Performance and population effect in men

Table The predictive performance and population efect of different screen and intervention strategy for hip fracture prevention in men

Screen strategy		Hip Fx (total n=63 in men) Sensitivity (%)								
Men										
Strategy 1 (ST1)		28.6								
Strategy 2 (ST2)		41.[illegible]								
Strategy 3 (ST3)		[illegible].9								
Strategy 4 (ST4)	2	49.2	83.1	0.66 (0.60, 0.72)	31 (49.2)	65 (34.8)	3.22	1.94	10.01	39.8
Strategy 5 (ST5)		49.2	80.8	0.65 (0.59, 0.71)	31 (49.2)	72 (38.5)	3.22	2.02	8.38	37.3
Strategy 6 (ST6)	1	68.3	74.3	0.71 (0.65, 0.77)	43 (68.3)	75 (40.1)	3.22	1.36	8.80	57.8

Men	N of hip fx	(-1)			
Strategy 1 (ST1)		5.04			
Strategy 2 (ST2)		7.28	275	69	39
Strategy 3 (ST3)		6.16	325	138	36
Strategy 4 (ST4)	2	8.68	230	98	41
Strategy 5 (ST5)		8.68	0	230	46
Strategy 6 (ST6)	1	12.04	0	166	45

NN: number needed; (-1): to prevent one incident hip fracture

Suboptimal ST: prescreening with FRAX and SARC-F, then performing DXA for those with a FRAX score ≥ 4.5%, or a SARC-F score ≥ 1.0, with treatment when the FRAX (included aBMD and TBS) score ≥ 4.0%.

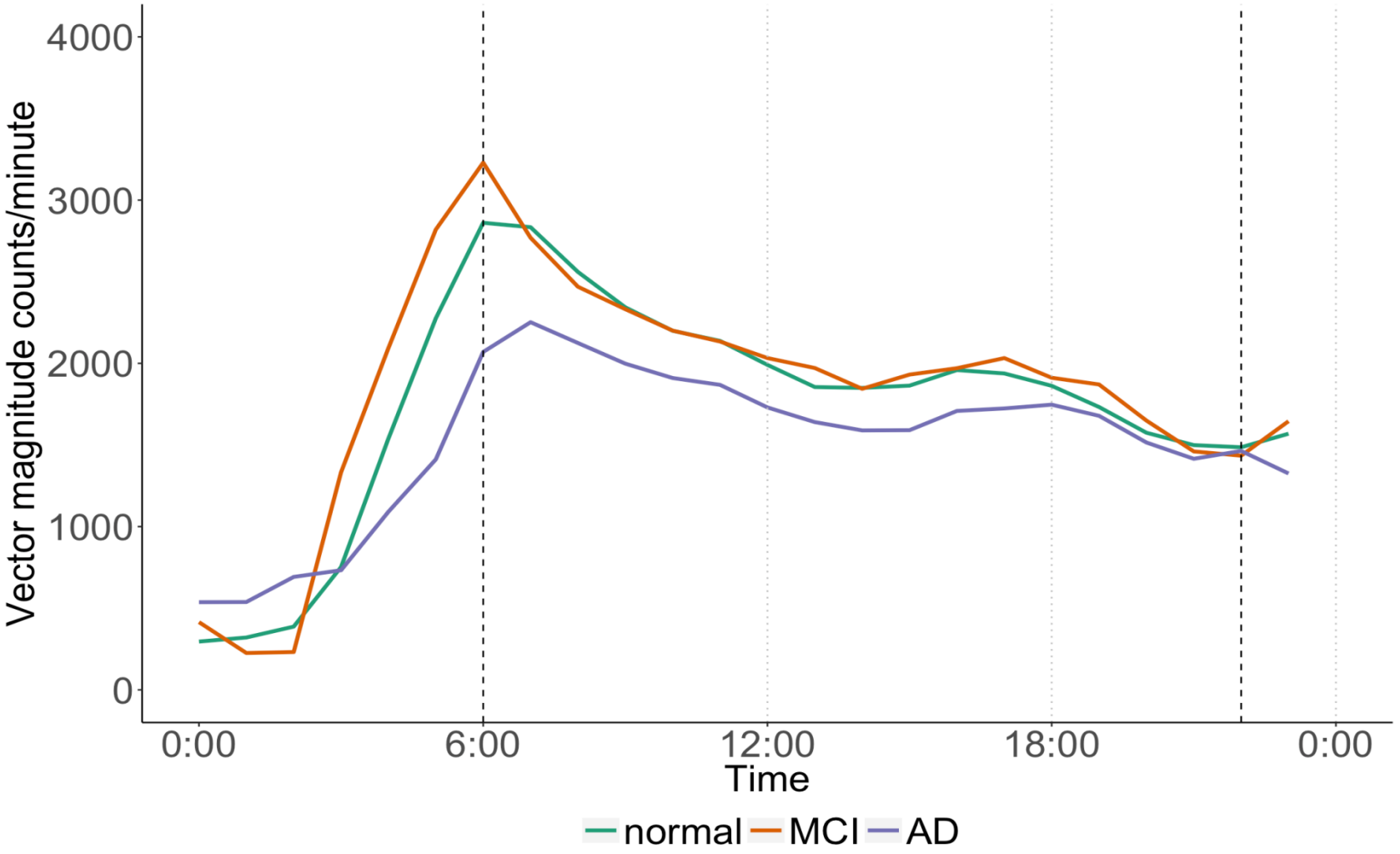
Best ST: performing using DXA on the hip and spine for all people, with treatment when the FRAX (included aBMD and TBS) score equal to or above 4.0%.

Physical activity measured by Accelerometer

		Robust	Pre-frail	Frail
Physical activity	Average daily counts/min	2125.8 ± 38.5	1907.3 ±	1749.1 ±
Sedentary behavior	% of wake time in Sedentary behavior	54.9 ± 0.8	59.2 ± 0.6*	62.8 ± 1.1*
	No. of sedentary bouts (> 1 min)	92.5 ± 1.1	90.1 ± 0.9	89.6 ± 1.6
	No. of sedentary bouts (≧ 30 min)	2.9 ± 0.1	3.5 ± 0.1*	4.1 ± 0.2*
	No. of sedentary breaks	58.8 ± 1.0	55.3 ±0.8	54.6 ± 1.4*

* $p < 0.05$ when comparing with robust individuals

Activity: Robust > Pre-frail > Frail
Sedentary behavior: Frail > Pre-frail > Robust



Example: compare PA between cognitively normal, MCI and AD

Areas to be explored

- Year 14
- Frozen serum, DNA
- Aortic calcification on spine X ray at baseline and year 4
- Hip X ray at year 4
- PQCT tibia and radius
- QCT spine
- Hospital admissions
- CMS records
- Spousal inter-dependence, bereavement
- Sexual health of older men (year 2)
- Sleep questionnaires
- Back and joint pain questionnaire
- Perceived social ladder
- Resilience
- Big data analysis method

Way Forward

- Year 16 follow-up (pending HMRF)
- Old-old cohort
- Open access to data
- More Os investigators

How you can use participate

- Data analysis
- Access to MrOs US data set
- Grant application – frozen serum, DNA, further follow-up, new cohort
- Combine with other data sets

How to access data

- JOCOC website (http://www.jococ.org/en/mros-msos.php)
  - Explanatory power point
  - List of variables at various time points
  - List of themes and coordinators
  - List of publications
- Submit your analysis plan to data manager - Jason Leung (jason-leung@cuhk.edu.hk)
- Feedback from relevant coordinator
- Liaise with data manager for relevant data
- Outcome of data analysis will be followed up

Analysis plan submission form

- **Fill in the form and attach a 1-2 page description of your analysis plan**

MrOS Analysis Plan Submission Form

Date:

Investigator's Name:

Clinical Center:

Sponsor (if not a MrOS investigator):
Relationship to Sponsor:

Telephone: e-mail:

Other investigators who will be working on this analysis:

Analysis Plan Title:

Data sets to be used:

Primary variables to be used in the analysis:

Does this analysis plan involve a consortium or meta-analysis project? ☐ YES ☐ NO

If YES,

1. Does this plan propose to use GWAS data? ? ☐ YES ☐ NO
2. Who is the investigator leading the analysis?

*Please refer to Appendix_3_AnalysisPlanForm

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Discussion