Interactions Between OA & Other Common Conditions

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  - Tetyana Kendzerska MD PhD, post doctoral fellow

Objectives

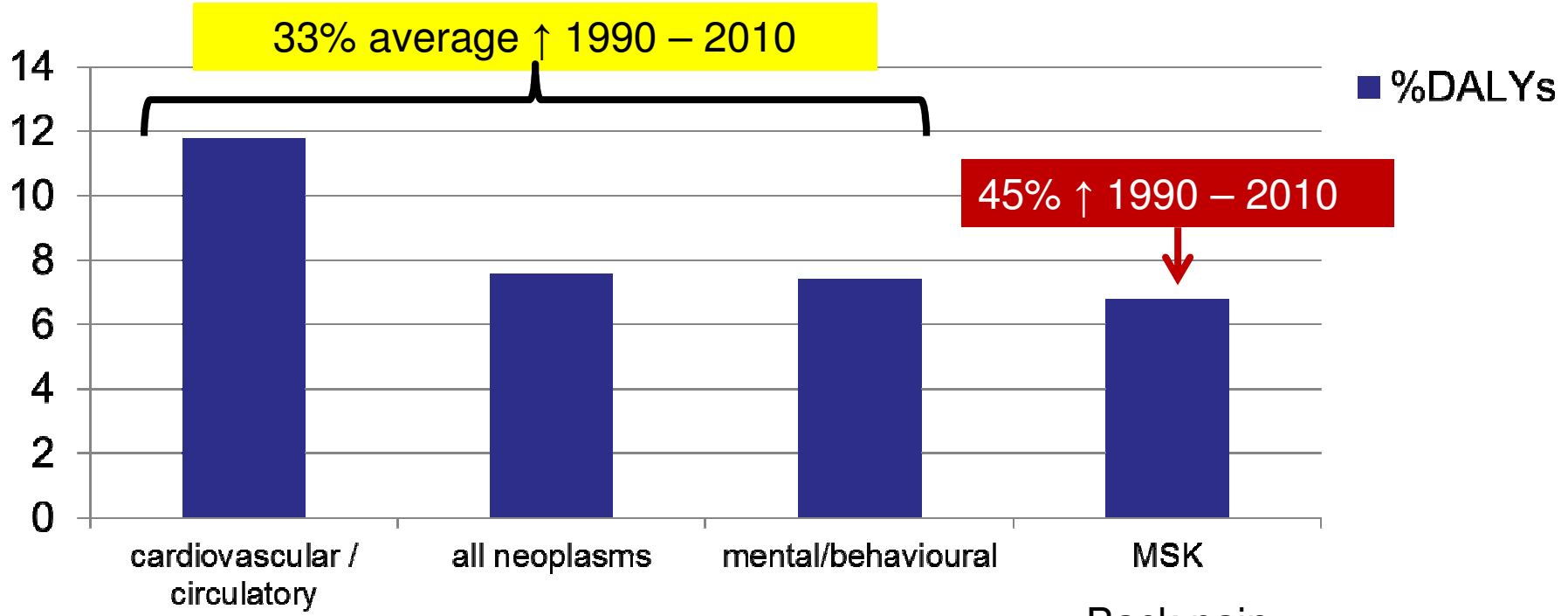
- Brief introduction
- Discuss impact of OA as a comorbid condition on management & outcomes of other conditions
- Review the evidence linking OA to metabolic syndrome
  (diabetes, hypertension, hyperlipidemia, obesity)
    - Metabolic OA phenotype

- Globally, aging populations & growing prevalence of obesity → increased population risk for hypertension, dyslipidemia, diabetes, cardiovascular disease…

  … & osteoarthritis (OA)

OA is the fastest growing major health condition

Ranking of Major Causes of Death and Disability (%DALYs)



Lancet 15 December 2012

Major Challenges to Dx & Mgmt of OA

- Societal attitudes / beliefs about OA
- Physician knowledge / awareness
- Attitudes and beliefs about ‘pain killers’
- Co-existent medical problems
  - Competing demands
  - Contraindications to OA therapies

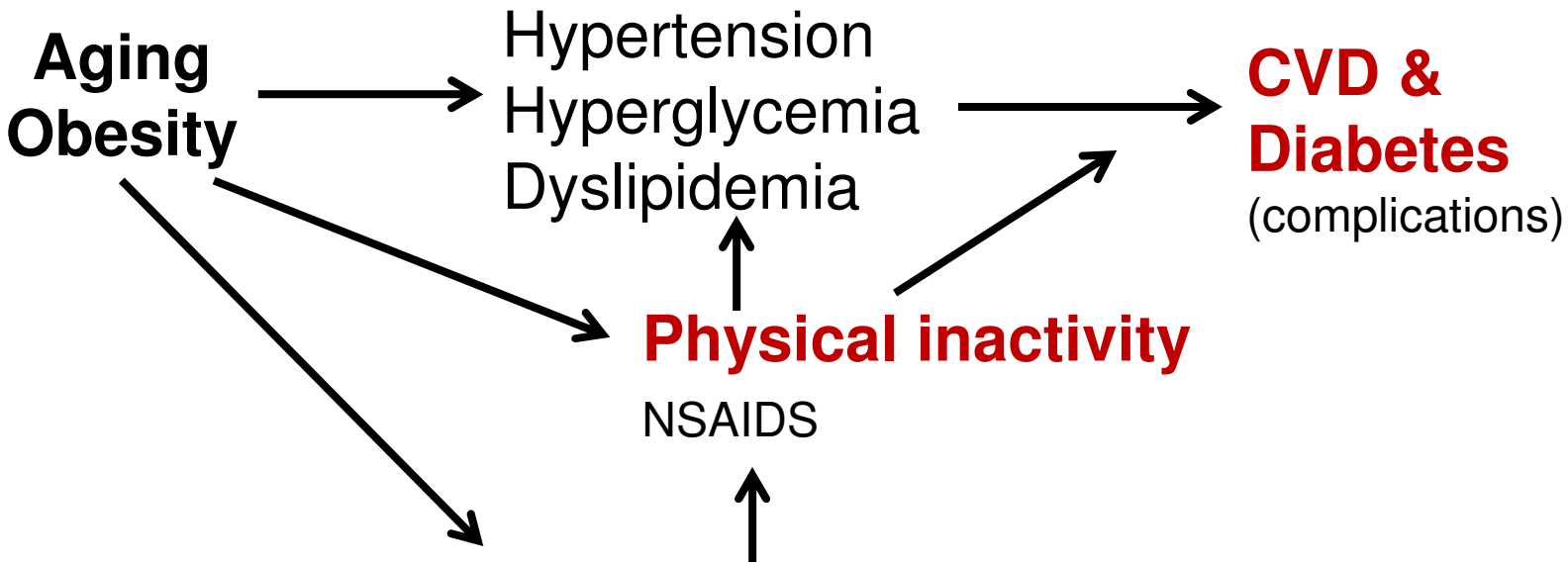
Co-Existent Medical Conditions

- 90% of people 65+ years with OA have ≥ 1 other chronic condition (common risk factors: aging, obesity)
  - Most commonly cardiovascular disease (CVD), *type 2 diabetes*, hypertension
    - + depressed mood (~ 1/3) - impacts adherence / effectiveness of therapies

US Medicare & Medicaid Report, 2012 Edition. Baltimore, MD.
Trelle S et al (2011) BMJ 342:c7086.
Hackam DG et al 2010. Can J Cardiol 26: 249-258.
Nieves Plaza et al J Clin Rheum 2013
K Magnusson et al Arthritis Care & Res 2014

Clustering of Common Chronic Conditions

Potential Explanations - 1

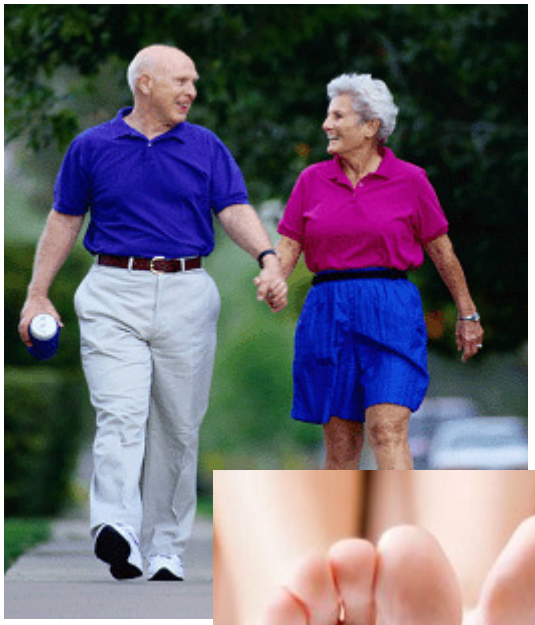


What is the evidence that OA impacts physical activity?

- Surveys
  - US men aged 66-74 years – 60% reported activity limitations due to chronic back, hip or knee pain and most managing their pain with sedentary activities / rest
- Qualitative studies:
  - People with OA frequently manage joint pain by giving up activities (risk of taking pain killers, not offered other options)
  - In setting of multiple health conditions
    - Patients prioritize the condition(s) seen as 'more severe' or with worse future implications
    - To balance health care issues, most frequently dropped activity was exercise
  - In patients with diabetes
    - Arthritis cited as a barrier to CVD risk factor control (physical activity self-management)

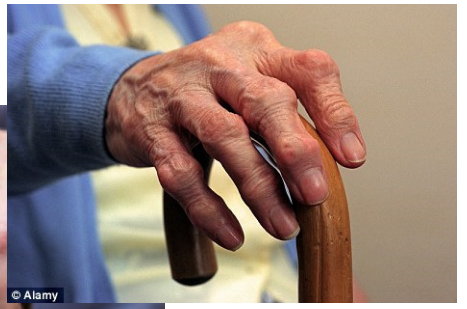
Impact of OA on outcomes of other common conditions?

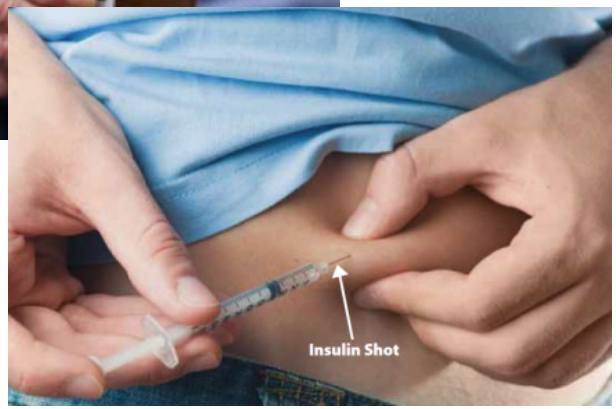
Hip and Knee OA



Chronic disease management

Hand OA

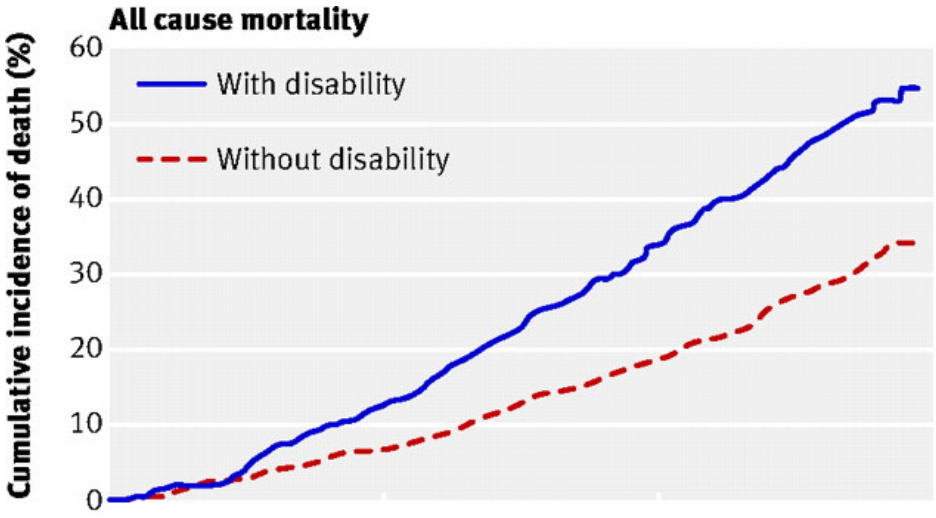


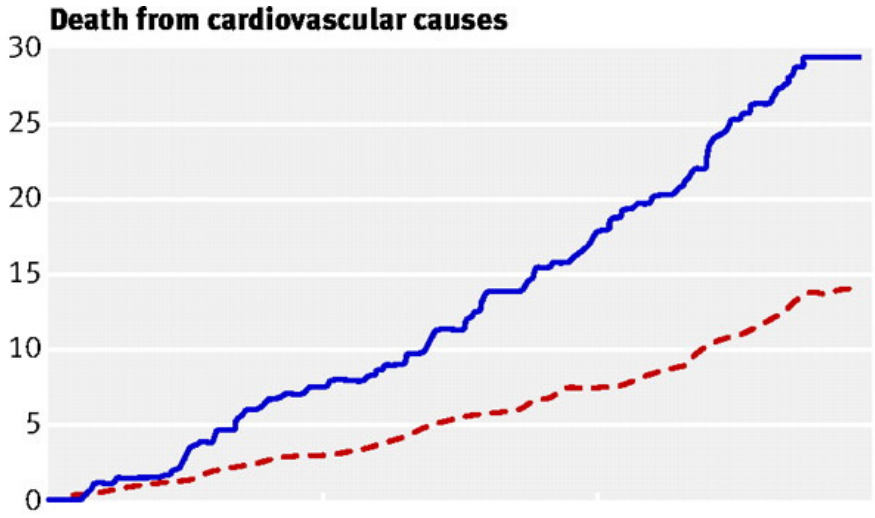


Helmrich et al, N Engl J Med 1991
Appel et al, JAMA. 2003
Cheraghi-Sohi *Arthritis Care & Res* 2013

Walking disability and mortality risk

- Population based cohort 35+ years with symptomatic hip/knee OA recruited 1994-5 from 40 English general practices (n=2,703)
- Examined survival status & cause of death to February 2009 using data from National Statistics
- Controlling for age, sex, diabetes, cancer, CVD, walking disability (1.48, 1.17 to 1.86) predicted ↑ all-cause death (mainly from CVD causes)





Neusch et al BMJ 2011

Grip strength, walking disability and risk for CVD & diabetes complications

- Population cohort 55+ years, symptomatic hip/knee OA recruited 1996-98 using tax records (n=2,156)
    - HAQ walking & grip strength (0-3)

- Whole cohort:
  - Examined hospital admission for CVD (AMI, CABG or PCI, CHF, stroke or TIA) & survival to Feb 2012 using provincial administrative databases

- Subset with diabetes at baseline:
  - Examined hospital admission for diabetes-specific complication (hypo- or hyperglycemia, soft tissue infection, amputation, end-stage renal disease)

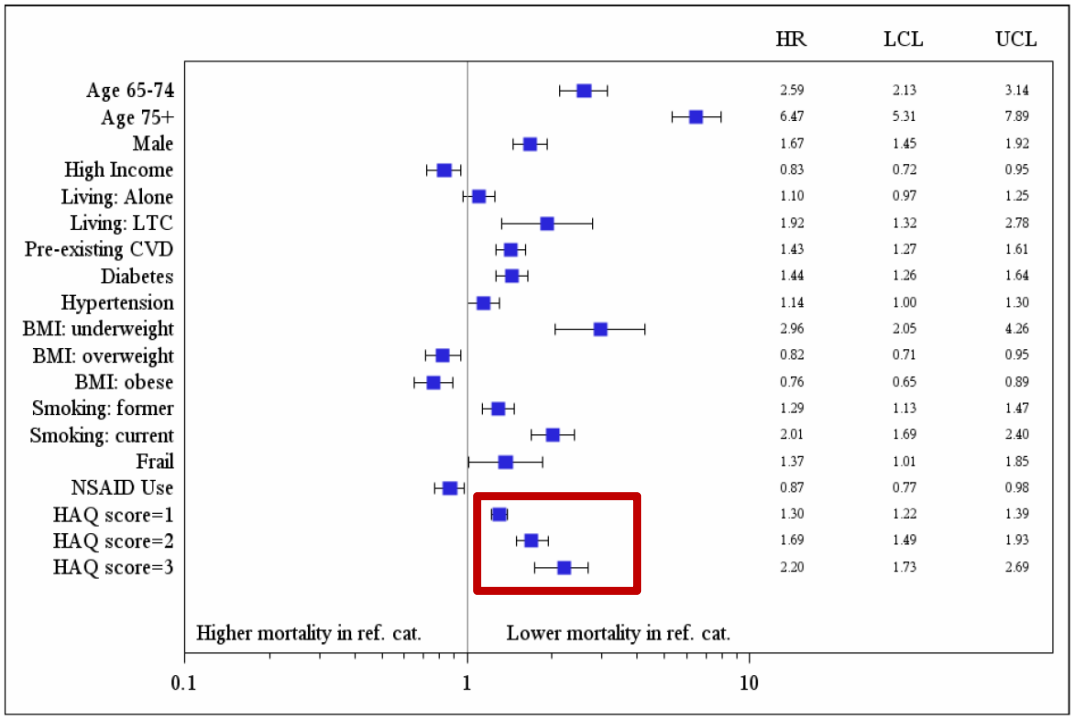
Hawker G et al *PLOS ONE 2014*

Grip strength, walking disability and risk for CVD & diabetes complications

Outcome	Median Follow-Up	%
All-cause death (n=2156)	13.2 years	57%
Composite CVD outcome (n=2156)	9.2 years	38%
Diabetes complication* (n=357)	6.5 years	37%

*102 experienced at least one infection; 47 hypoglycemia; 10 amputations; 11 hyperglycemia; and 4 initiated chronic dialysis

Grip strength, walking disability and risk for CVD & diabetes complications



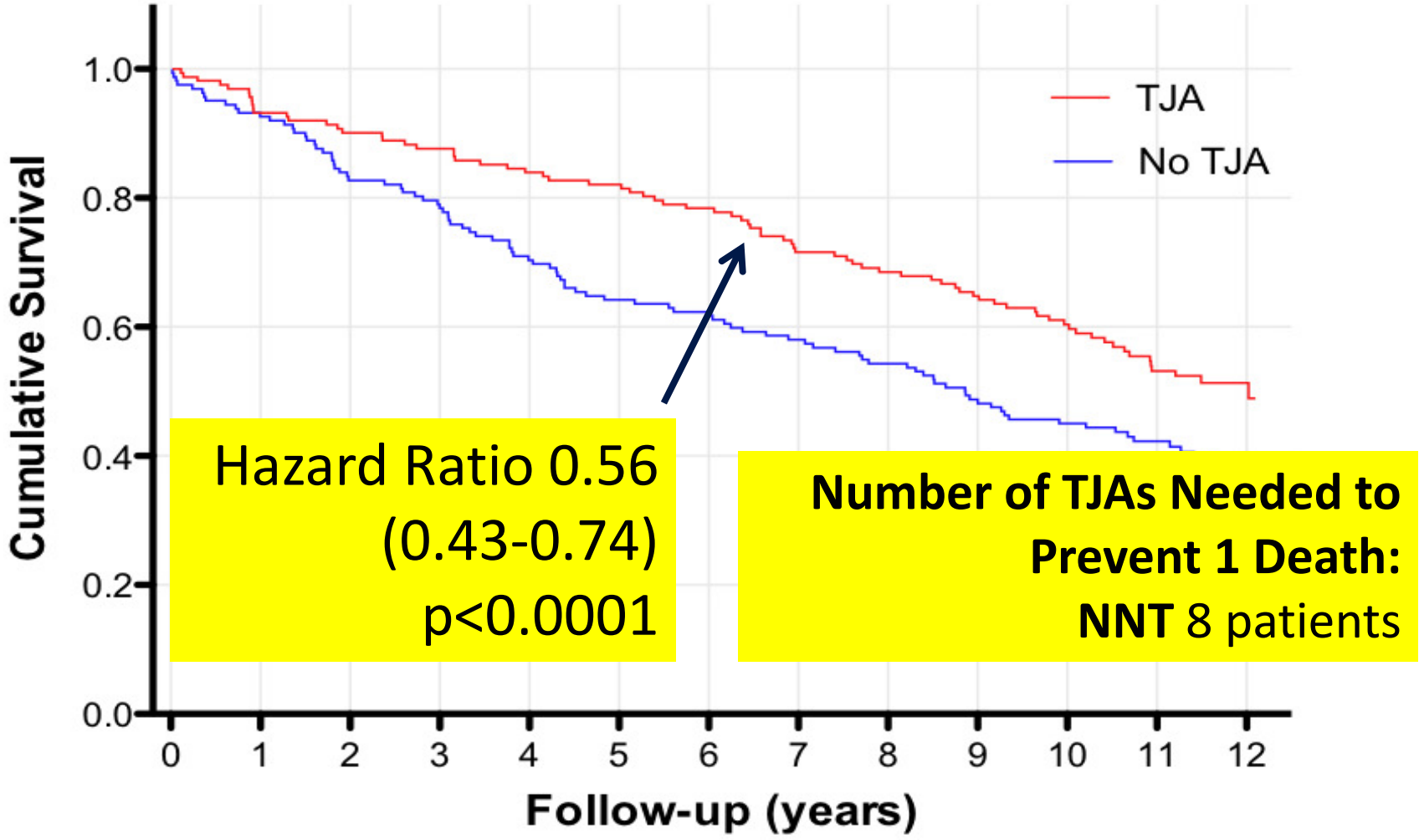
Walking disability predicted ↑ all-cause death (aHR 1.30, 1.22-1.39, p<0.001) & ↑ CVD events (aHR 1.17, 1.08-1.27, p=0.001)

*Covariates: age, sex, income, diabetes, hypertension, smoking, NSAIDs, frailty, pre-existing CVD

Subgroup OA + DM:

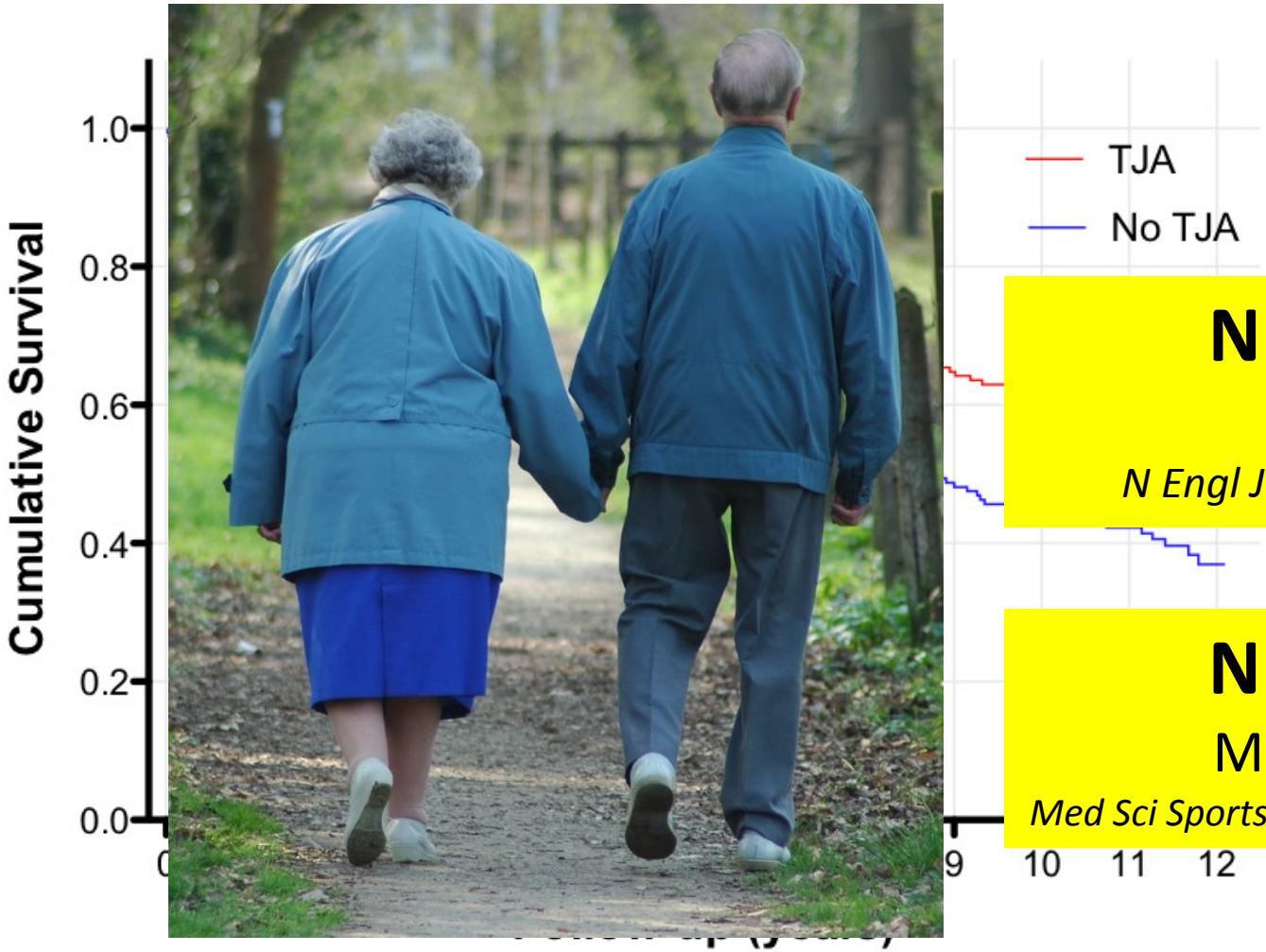
Walking disability *and* grip strength predicted ↑ diabetes complications: aHR per HAQ walking score 1.25 (1.01-1.55), p=0.04; aHR per HAQ grip strength score 1.21 (1.01-1.45), p=0.04

Survival curves for those who did and did not receive a primary, elective hip or knee replacement



Ravi B et al BMJ 2014

Comparative Effects: Physical Activity



NNT: 7 patients

Diabetes

N Engl J Med 2002; 346:393-403

NNT: 3 patients

Metabolic syndrome

Med Sci Sports Exerc. 2003;35(10):1703-9.

Summary

- Large well-controlled observational studies show consistent independent relationship between walking disability and future CVD events, diabetes complications & all cause death
  - Risk for all-cause death:
    - UK study: adj. HR for self-reported walking disability =1.48 (1.17-1.86)
    - Canadian study: adj. HR for HAQ walking score ≥ 2 = 1.51 (1.34-1.70)
- Possible explanations
  - Unmeasured confounding
  - Physical inactivity due to disabling OA
  - Stress (pain, depressed mood)
  - NSAIDs
  - Systemic inflammation? *Metabolic OA Phenotype*

OA Pathogenesis:

Influence of Aging and Obesity

Hand OA 2X more common in obese than non-obese

Yusuf E et al, Ann Rheum Dis 2010

Joint Destruction

Biomechanical Stress

Systemic Factors

inflammation

Matrix destruction
Aberrant repair response
Mechanical failure

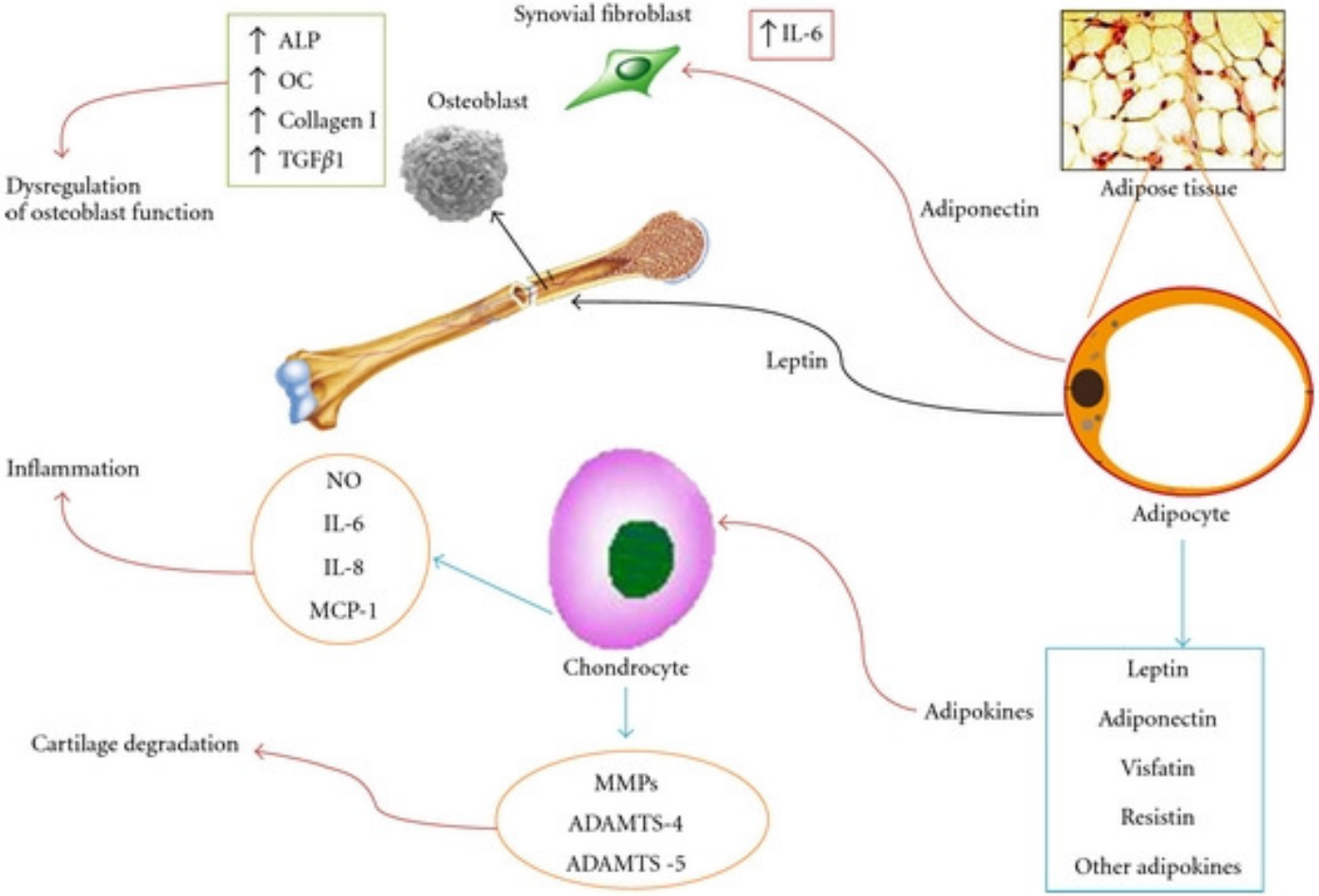
Metabolic syndrome

- Cluster of cardiac risk factors:
  - Abdominal obesity
  - Dyslipidemia
  - Impaired fasting glucose
  - Hypertension (atherosclerosis)

- Visceral adiposity → abnormal lipid metabolism + generation of inflammatory mediators (adipokines) → activation of renin-angiotensin-aldosterone system, ++ catecholamine production, insulin resistance, endothelial dysfunction

Adipokines influence all joint tissues

e.g., infra-patellar fat pad



Produces chrondrocyte activation similar to that seen with mechanical stress

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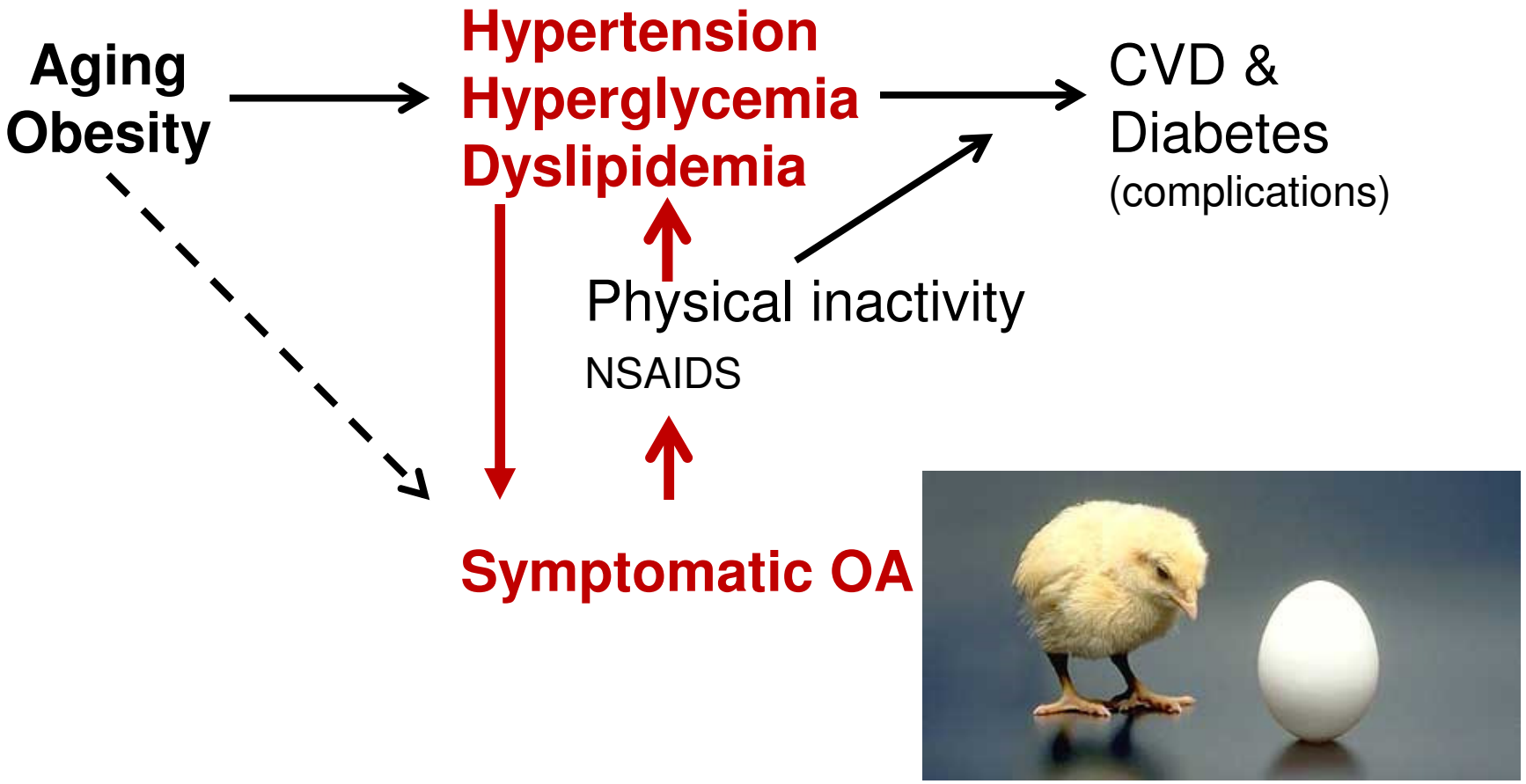
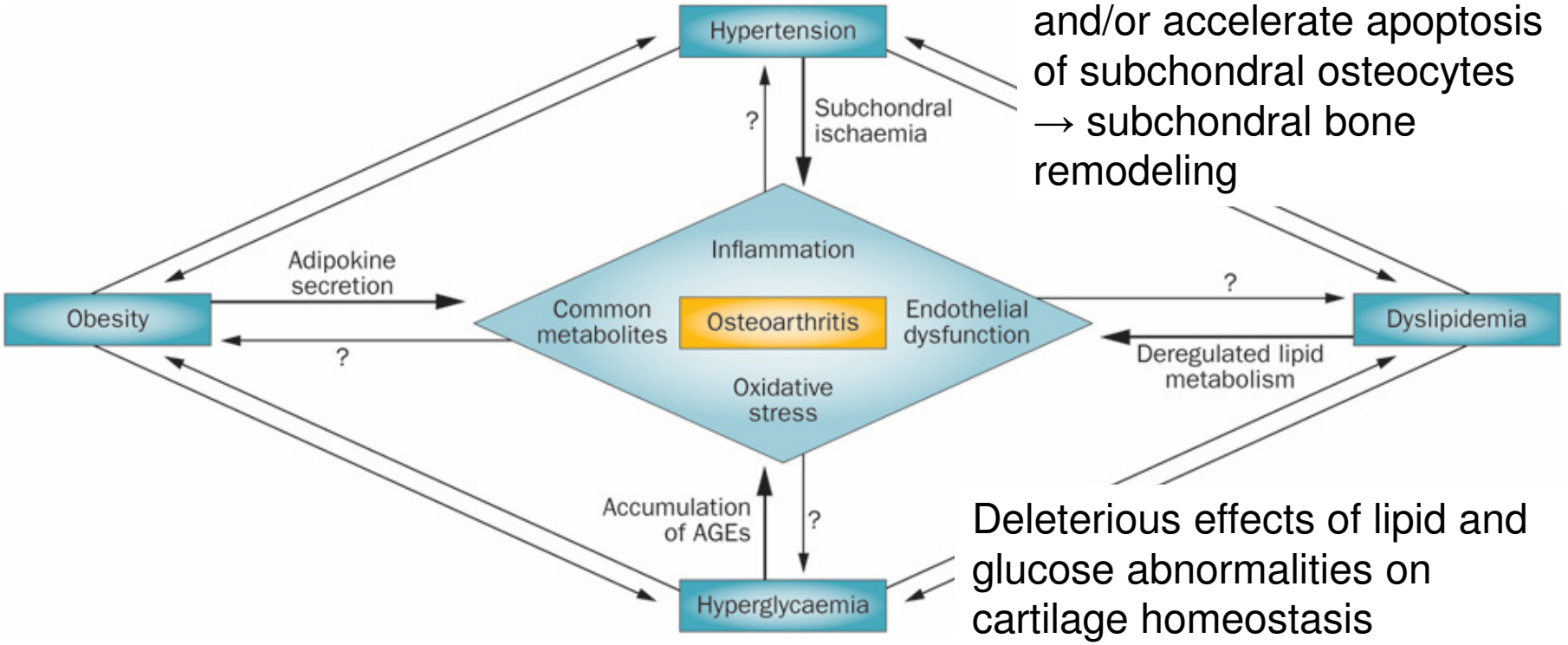
Conde J et al *Arthritis* 2011
Sellem J & Berenbaum F *Joint Bone Spine* 2013

Clustering of Common Chronic Conditions

Potential Explanations - 2



Metabolic OA:
5th component of MetS?



Reduced blood flow in subchondral vessels may reduce nutrient/O_2 supply and/or accelerate apoptosis of subchondral osteocytes → subchondral bone remodeling

Deleterious effects of lipid and glucose abnormalities on cartilage homeostasis

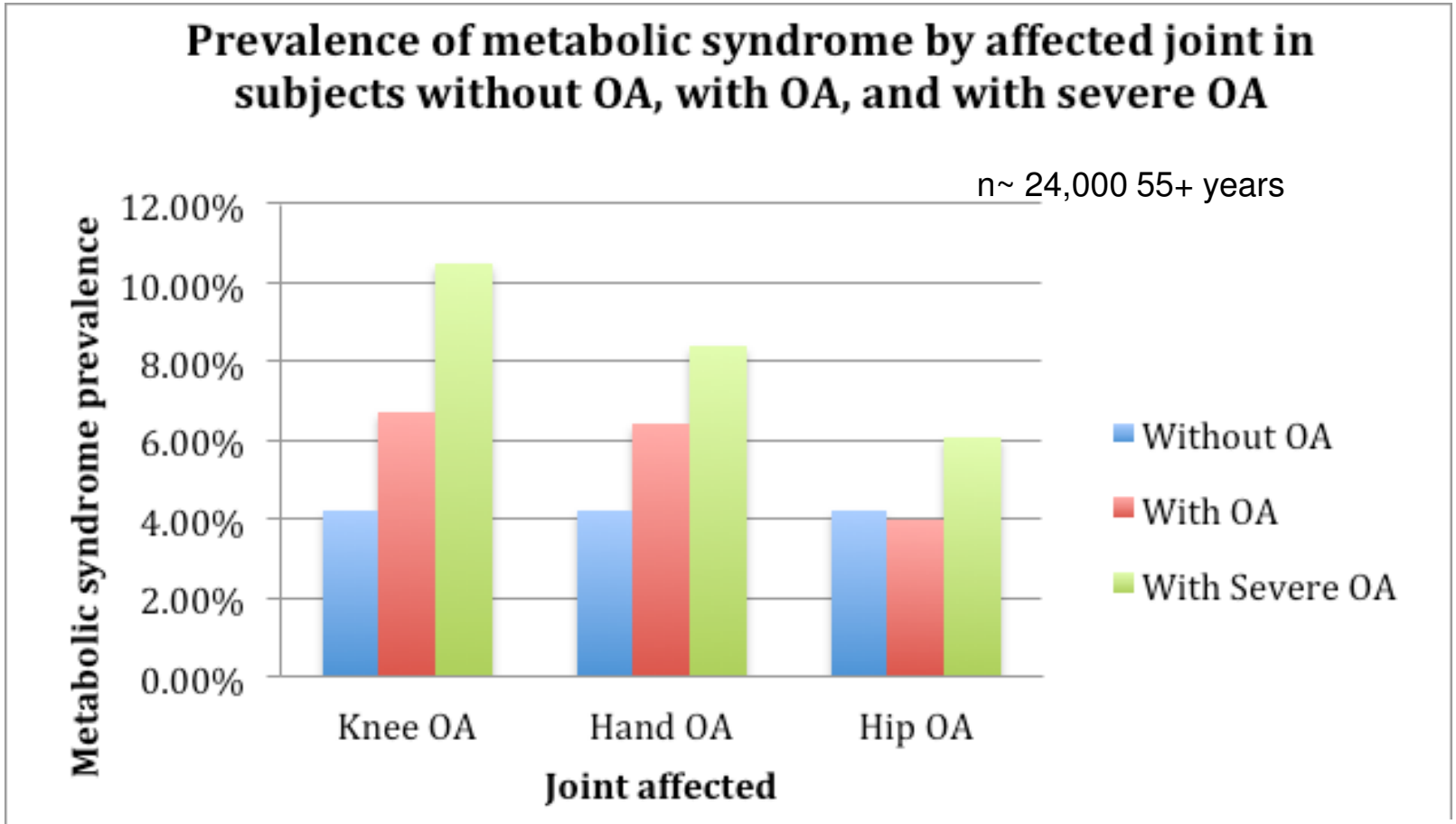
Zhuo, Q. *et al.* (2012) Metabolic syndrome meets osteoarthritis *Nat. Rev. Rheumatol.* doi:10.1038/nrrheum.2012.135

Metabolic syndrome and OA

- Adjusting for *age and BMI*:
  - ~ 3X > MetS in OA vs general population; relationship stronger in < 65 years
  - OA patients more sedentary (accelerometers), > more MetS
  - Number of MetS components predicted risk of development & progression of knee OA, hand OA

NHANES III: Puenpatom RA et al *Postgrad Med* 2009
Liu et al, *Arthritis Care Res*
Yoshimura N et al *OA&C* 2012 – ROAD study
Sowers M et al *Arthritis Rheum* 2009

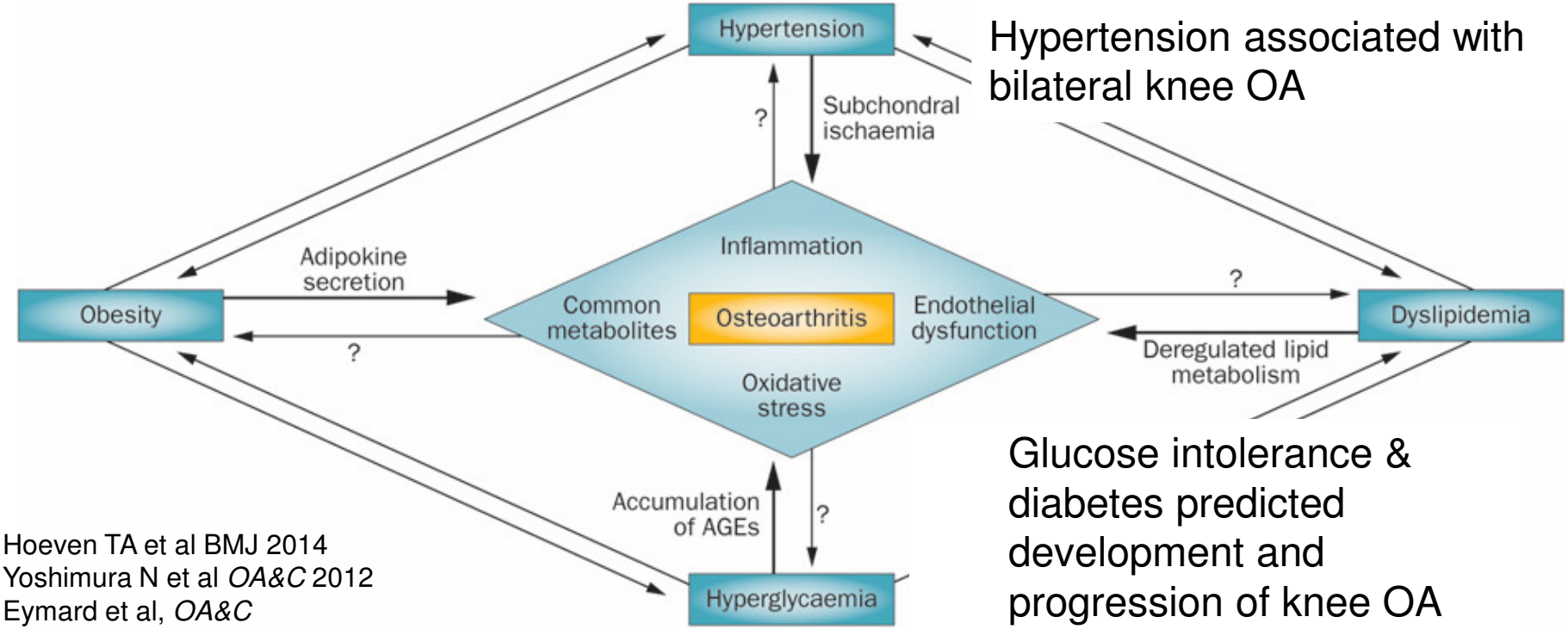
Relationship stronger for knees and hands than hips



Metabolic syndrome = 2+ of hypertension, diabetes, obesity, hyperlipidemia
OA = pain, swelling, stiff in hips/knees or hands for at least 6 weeks in past 3 months
Severe OA = OA with functional limitations, e.g. difficulty walking

Metabolic OA:
5th component of MetS?

Atherosclerosis (carotid intima media thickness, carotid placque) independently associated with knee & hand, not hip OA



Hypertension associated with bilateral knee OA

Glucose intolerance & diabetes predicted development and progression of knee OA

Hoeven TA et al BMJ 2014
Yoshimura N et al *OA&C* 2012
Eymard et al, *OA&C*
Nieves Plaza et al *J Clin Rheum* 2013
Schett G et al *Diabetes Care* 2013
Magnusson N *Arthritis Care & Res* 2015

Summary

- Independent associations between MetS and its components with OA (knee, hand, women, younger adults > hip, men, older adults?)
- Sy… …ity, re… …CVD ar…
- Limitations:
  - Variable definitions of MetS and OA
  - Variable control for key confounders (age, obesity, smoking, alcohol, etc)

What is the relative contribution of disability versus systemic inflammation?

Interactions Between OA & Other Common Conditions

CLINICAL IMPLICATIONS

Pivotal role of physical activity

combination of aerobic, resistance, balance + flexibility exercises

- ↓ Metabolic Alterations
  - accumulation of advanced glycation end-products [AGEs]
  - lipid metabolism
  - excess adipose tissues/fatty acids
  - hyperglycemia
  - systemic inflammation
    - Walking + weight loss in OA reduced IL-6 levels – Messier et al JAMA 2013
- ↓ Physical Impairments
  - activity/mobility limitations
  - deconditioning
  - excess body weight/joint loads
  - joint stiffness
  - muscle weakness/loss of lean muscle mass
  - poor balance/falls

Positive effect of PA on depressed mood…sleep

Piva SR et al, Clin Geriatr Med 2015

Clinical Implications

- OA is a risk factor for CVD?
  - Impact on treatment decisions (e.g. NSAIDs)

Core treatments

Appropriate for all individuals

Land-based exercise
Water-based exercise
Weight management
Self-management & education
Strength training

Knee OA *with* other health problems

Biomechanical interventions
Intra-articular corticosteroids
Topical NSAIDs

Multi-joint OA *with* other health problems

Biomechanical interventions
Intra-articular corticosteroids
Oral Cox-2 inhibitors (selective NSAIDs)
Duloxetine

Future directions

- Larger, prospective studies to confirm/examine temporal relationships & elucidate mechanisms beyond age & BMI
  - OA incidence and progression
  - Structure versus symptoms
  - Weight-bearing vs non weight-bearing joints
- Clinical trials of impact of Rx of metabolic syndrome / components on OA incidence and progression
  - Modifiable risk factors for OA?
- Clinical trials of impact of Rx of OA disability on outcomes for other conditions associated with MetS

Thanks


AND DON'T LET HIM SWEET-TALK YOU ABOUT DIET AND EXERCISE. I WANT PILLS!