Multimorbid Rheumatoid Arthritis

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VA | U.S. Department of Veterans Affairs

UNMC

Disclosures

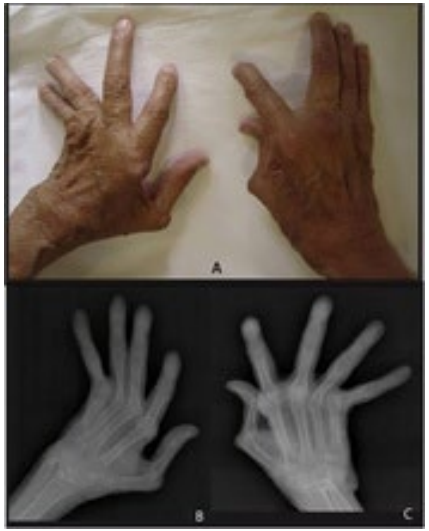
Consulting to Boehringer Ingelheim

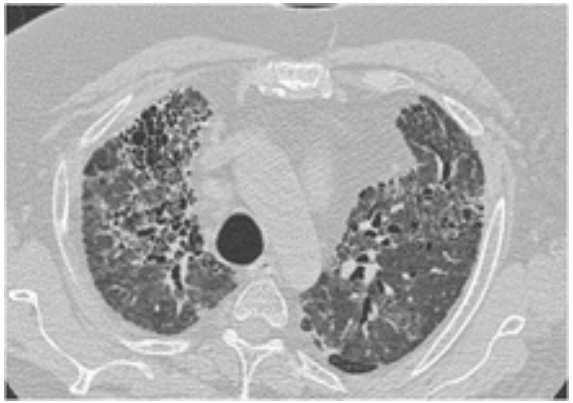
Royalties from UpToDate

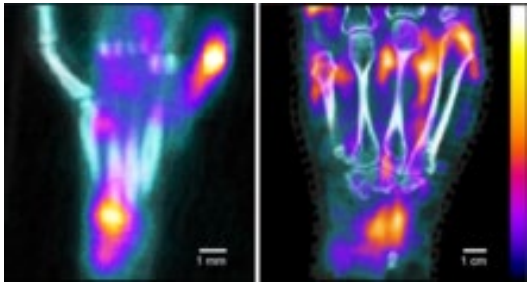
VA | U.S. Department of Veterans Affairs

Rheumatoid Arthritis

What's missing?







Images from ACR Image Library

Patient with RA (#1)

From a RA commercial

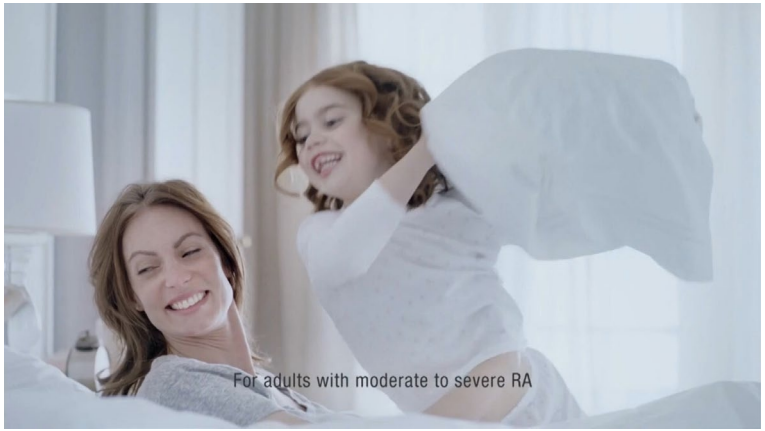
Patient with RA (#2)

***Not** from a RA commercial*

Quiz: Match Description to Picture

A. “TV RA”
B. “Real RA”

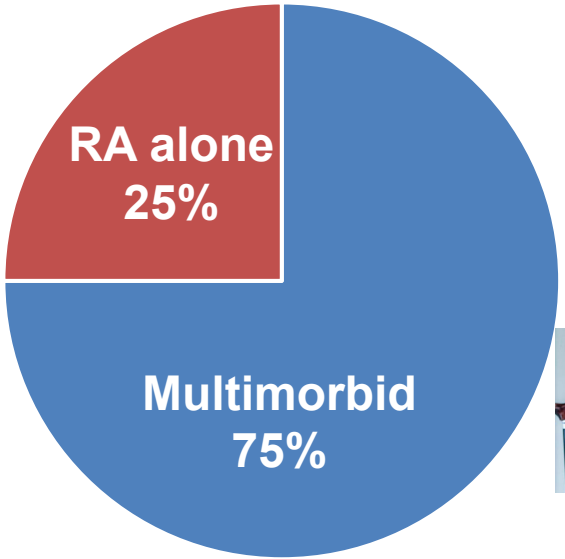
Patient with RA #1



Patient with RA #2

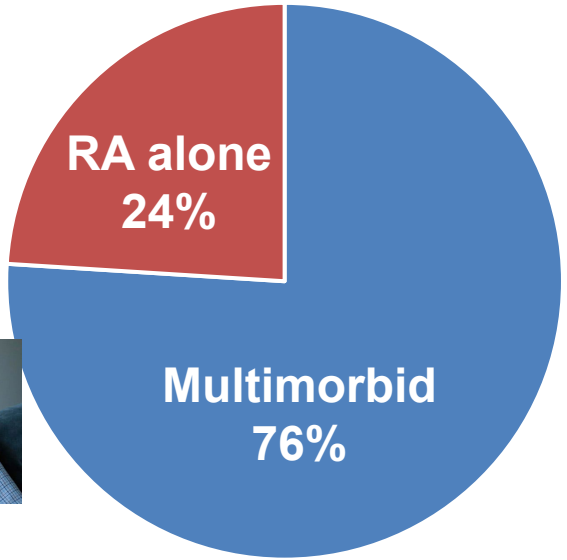
What does “Real RA” really look like?

VA RA Veterans Affairs Rheumatoid Arthritis Registry



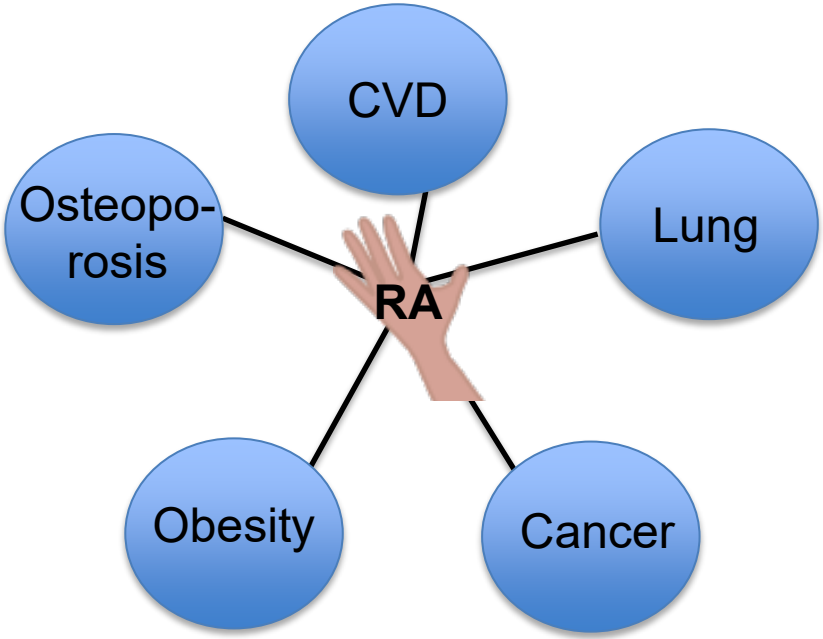
“Real” RA

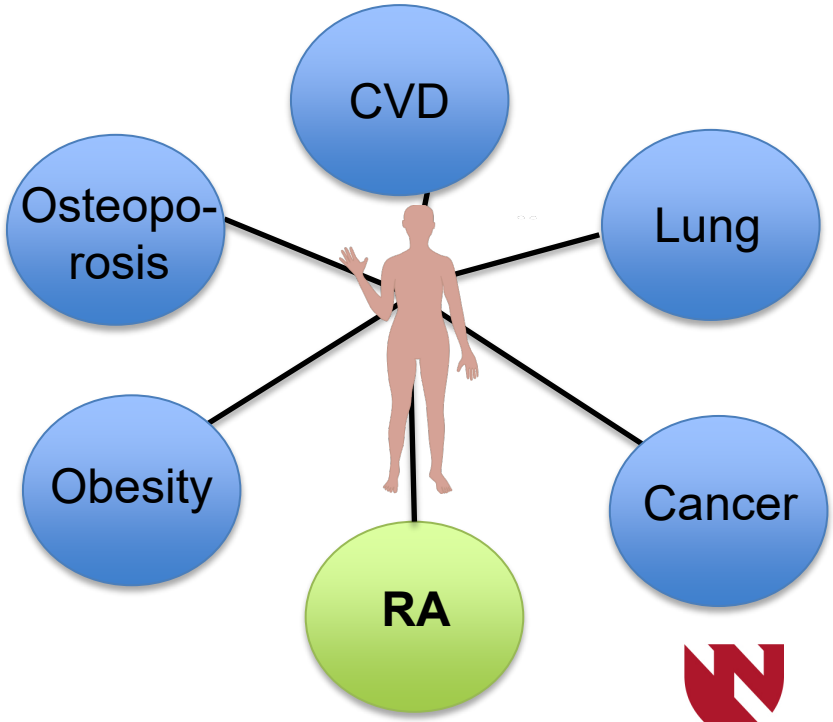
FORWARD The National Databank for Rheumatic Diseases



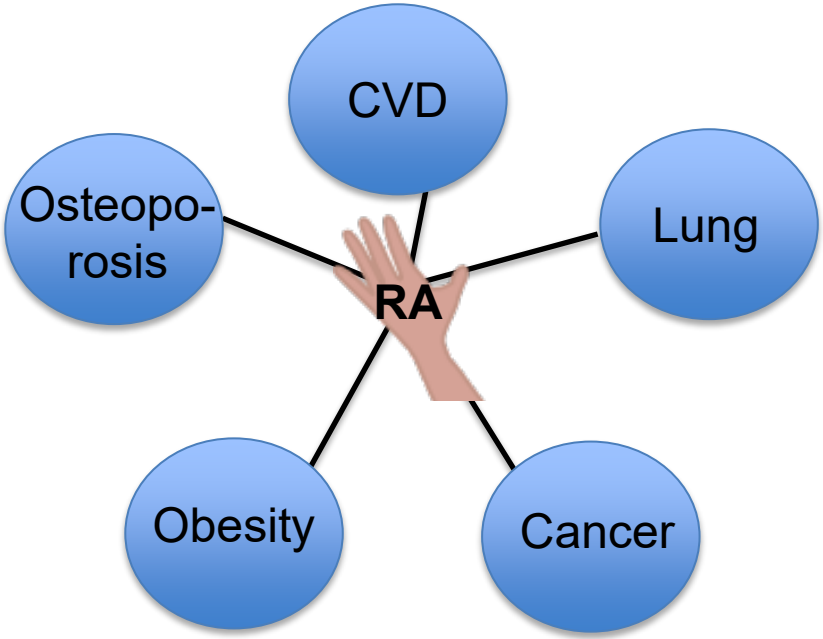
Defined as ≥1 condition in Rheumatic Disease Comorbidity Index

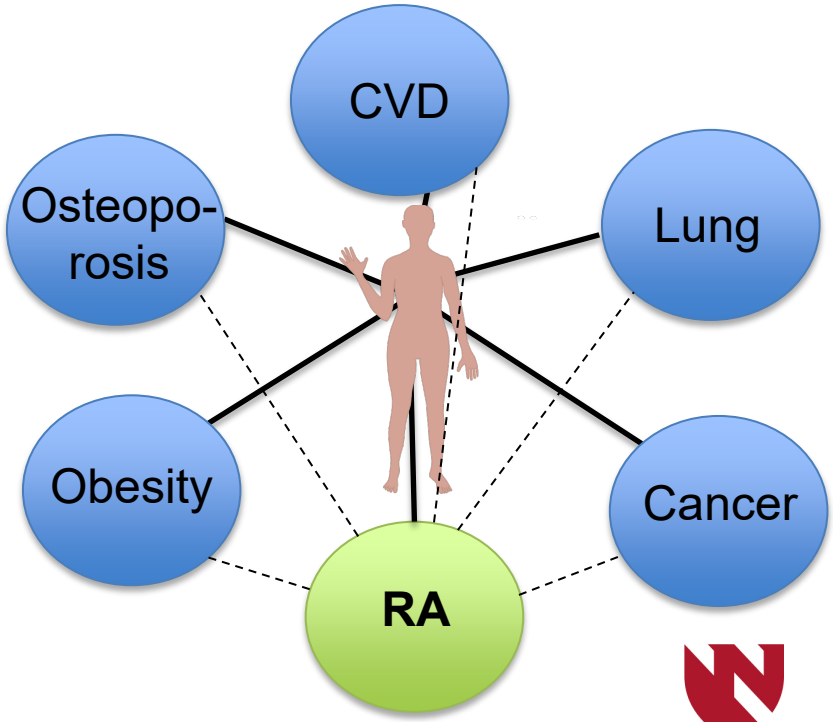
Comorbidity vs. Multimorbidity in RA



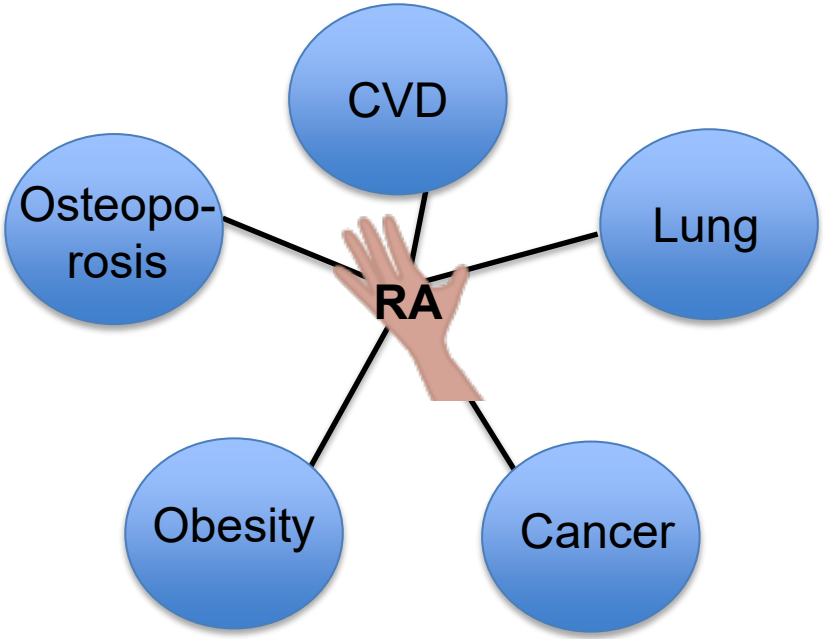


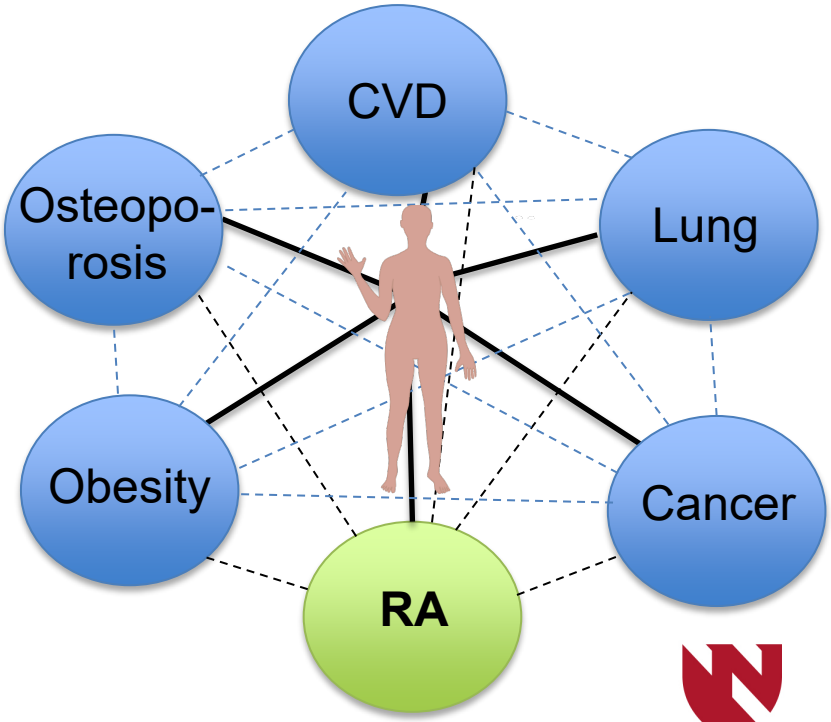
Comorbidity vs. Multimorbidity in RA





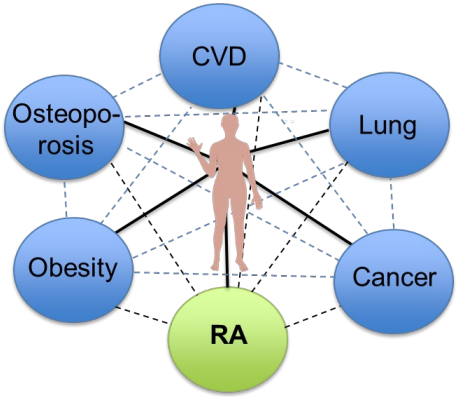
Comorbidity vs. Multimorbidity in RA



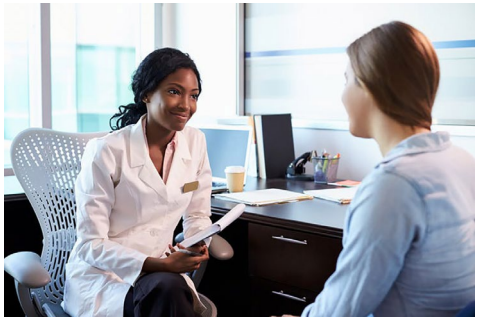


Multimorbidity: For Specialists Too!

1. Drive onset & progression of multimorbidity



3. MM Changes disease management



2. Poor long-term outcomes (e.g. MM-related outcomes)

Shortened lifespan

Reduced quality of life

Increased healthcare use

Expensive

Burden & Trajectory of Multimorbidity in RA

MarketScan database 2006-2015

- Overall cohort (n=277k)

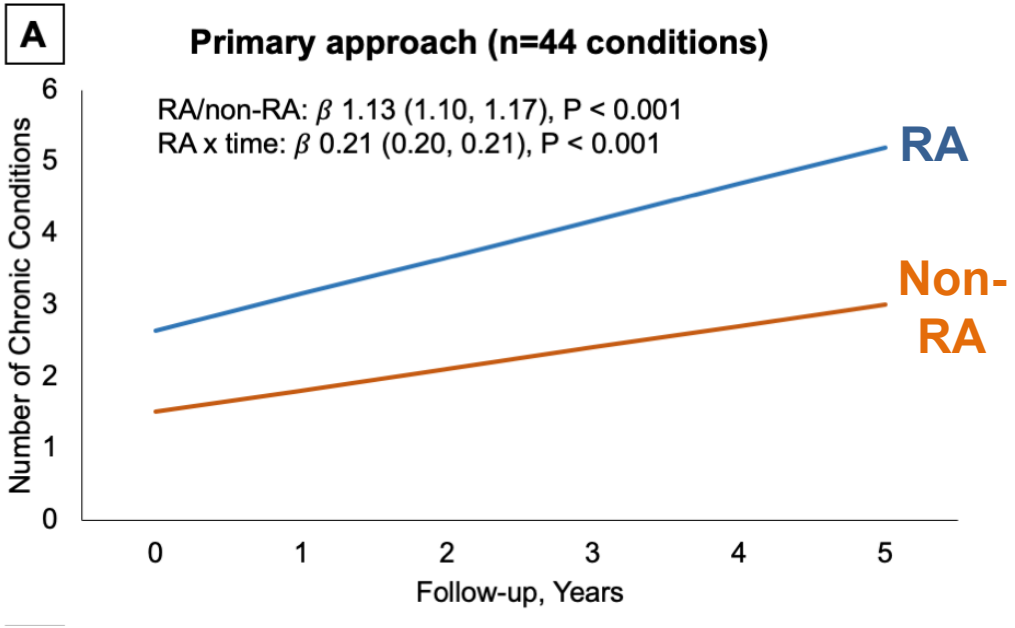
  Matched 1:1 RA:Non-RA
- Multimorbidity (≥2 / 44 conditions)

  RA: 34% (**51% at 1yr**)

  Non-RA: 21%

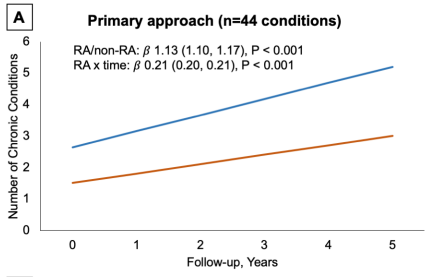
  OR: 2.29 (2.25-2.34)

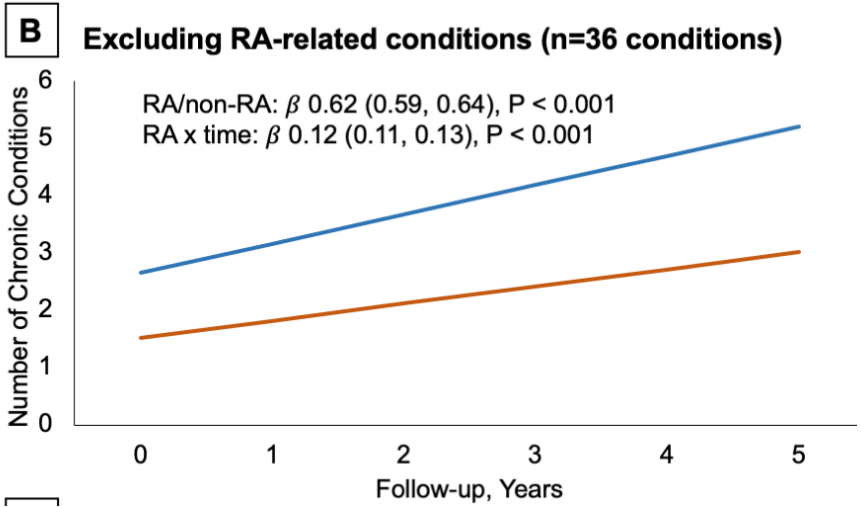
Incident cohort (n=61k)



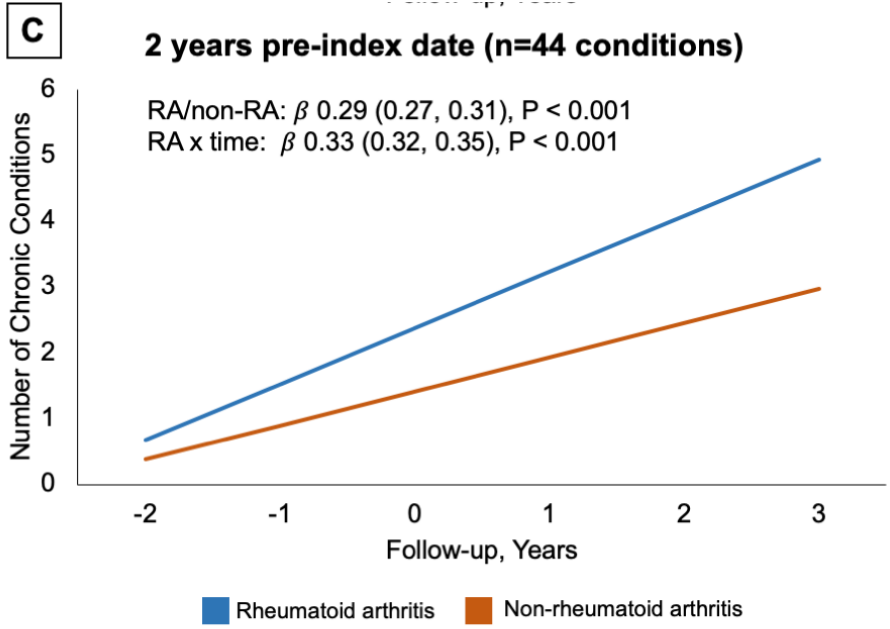
England BR et al. Ann Rheum Dis, 2020.

Multimorbidity Trajectory in RA





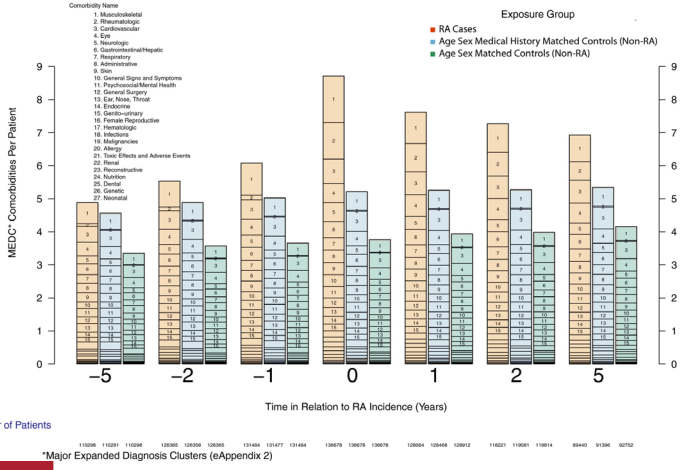
Excluded: anemia, osteoarthritis, fibromyalgia, interstitial lung disease, chronic back pain, gout, osteoporosis, inflammatory skin disorders

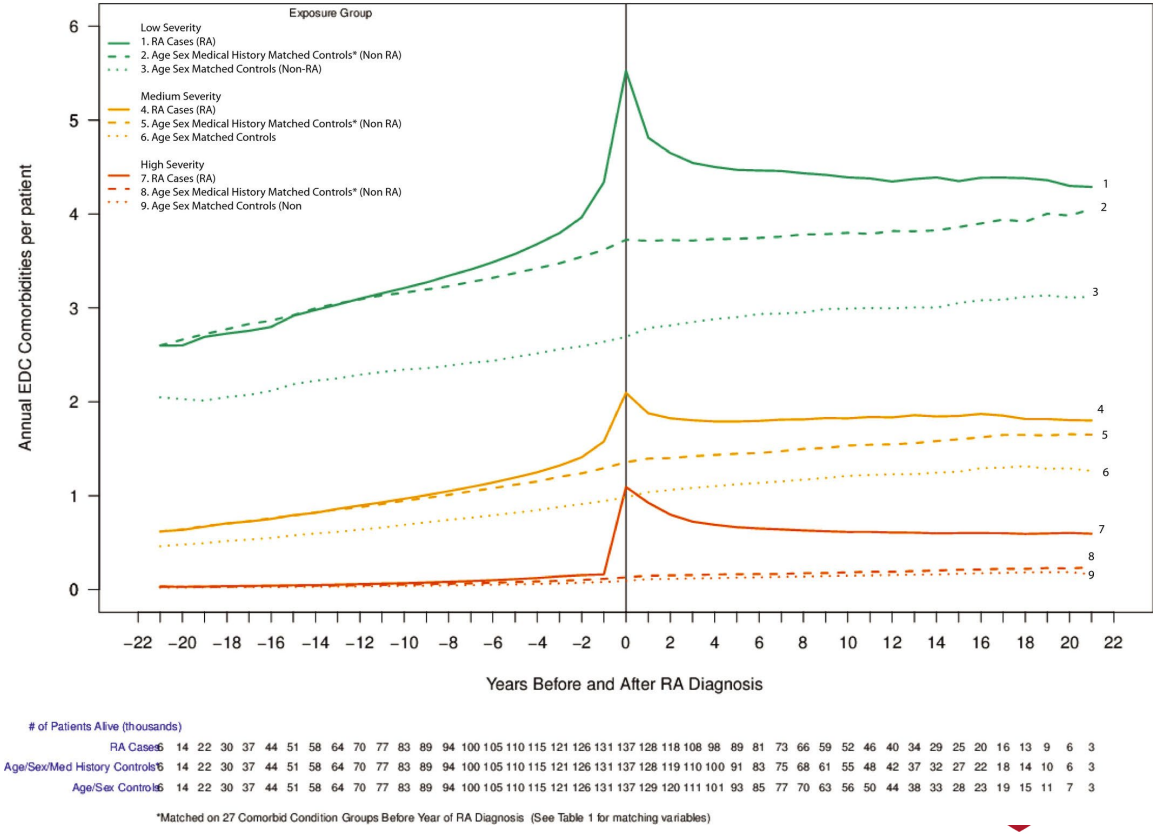


England BR et al. Ann Rheum Dis, 2020.

Multimorbidity Trajectory in RA

- Ontario, Canada (1995-2016)
- N=27 Johns Hopkins EDC conditions
- Year of diagnosis:
  131% increase vs. control
  67% increase vs. medical history matched





Tatangelo MR et al. ACR Open, 2020.

Identifying Multimorbidity Patterns with Factor Analysis

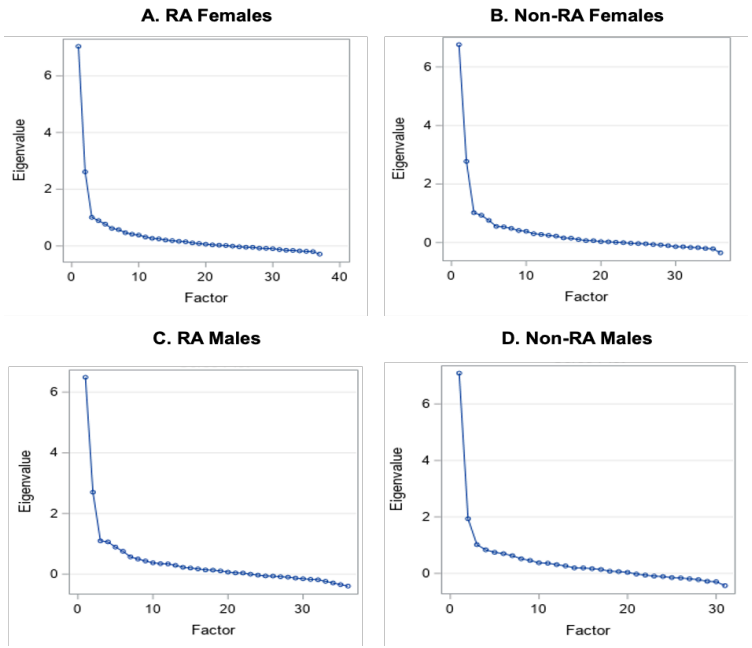
N=226,850 (1:1 RA, non-RA)
76% female
Mean age: F53, M58
MTX, 62%
b/tsDMARDs, 32%

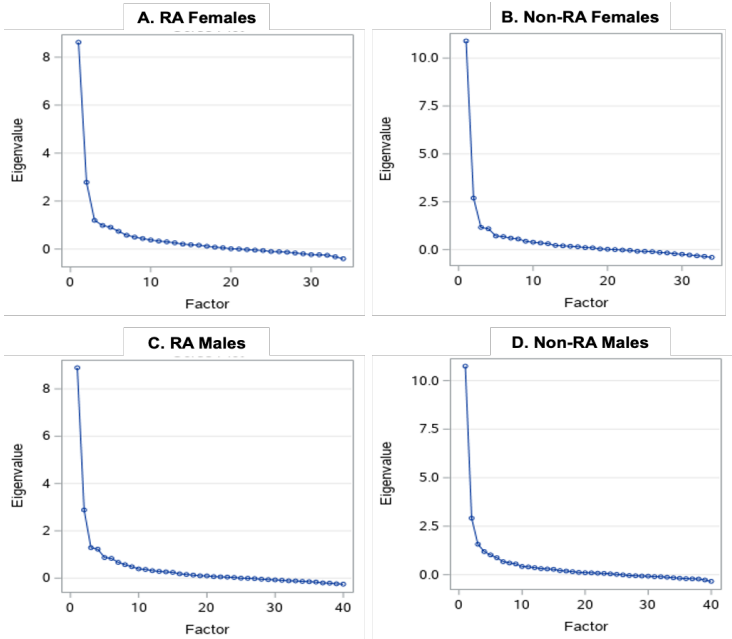
MarketScan

Assessed n=44 chronic conditions

VA

N=120,780 (1:1 RA, non-RA)
89% male
Mean age: F53, M64
MTX, 57%
b/tsDMARDs, 14%





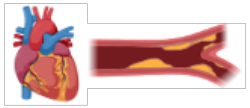
England BR et al. Arth Care Res, 2022.

Identifying Multimorbidity Patterns with Factor Analysis

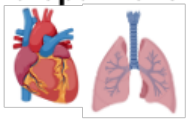
	MarketScan		VA	
	RA	**Non-RA**	**RA**	**Non-RA**
Females	Cardiopulmonary (0.47) Mental Health & Chronic Pain (0.17) Cardiometabolic (0.07)	Cardiopulmonary & metabolic (0.46) Mental Health & Chronic Pain (0.19) Vascular (0.07)	Mental Health & Chronic Pain (0.52) Cardiovascular (0.17) Metabolic (0.07)	Mental Health & Chronic Pain (0.59) Cardiovascular (0.15) Metabolic (0.06) Mental Health & Substance Abuse (0.06)
Males	Cardiometabolic (0.44) Mental Health & Chronic Pain (0.18) Cardiopulmonary (0.07) Mental Health & Substance Abuse (0.07)	Cardiovascular (0.50) Mental Health & Chronic Pain (0.14) Metabolic (0.07)	Mental Health & Substance Abuse (0.48) Cardiovascular (0.15) Chronic Pain (0.07) Metabolic (0.07)	Chronic pain (0.51) Cardiovascular (0.14) Metabolic (0.07) Mental Health & Substance Abuse (0.06) Cancer (0.05)

Primary Patterns

Cardiometabolic



Cardiopulmonary

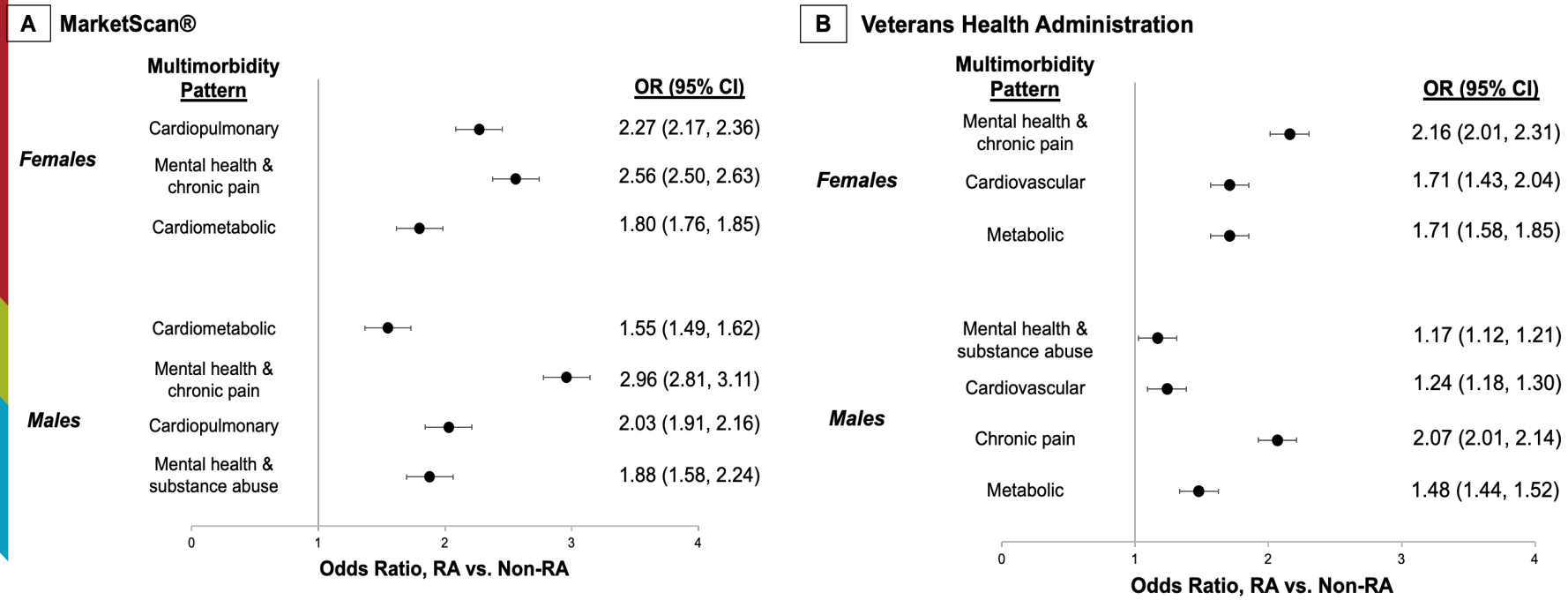


Mental health & chronic pain

Factors selected based on Eigenvalue ≥1

England BR et al. Arth Care Res, 2022.

Prevalence of Multimorbidity Patterns RA vs. Non-RA

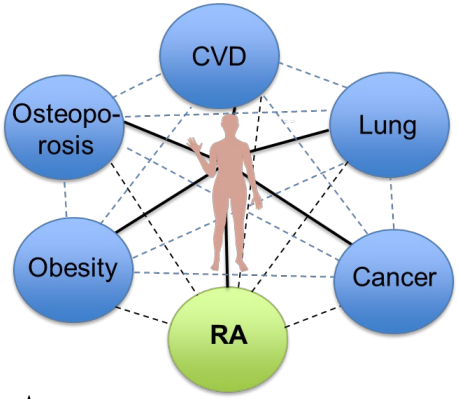


Multimorbidity patterns were considered present if at least two conditions from that pattern were present. Patterns depicted are those identified from RA patients in each dataset.

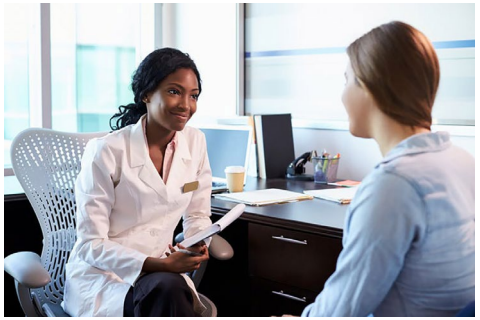
England BR et al. Arth Care Res, 2022.

Multimorbidity: For Specialists Too!

1. Drive onset & progression of multimorbidity



3. MM Changes disease management



2. Poor long-term outcomes (e.g. MM-related outcomes)

Shortened lifespan

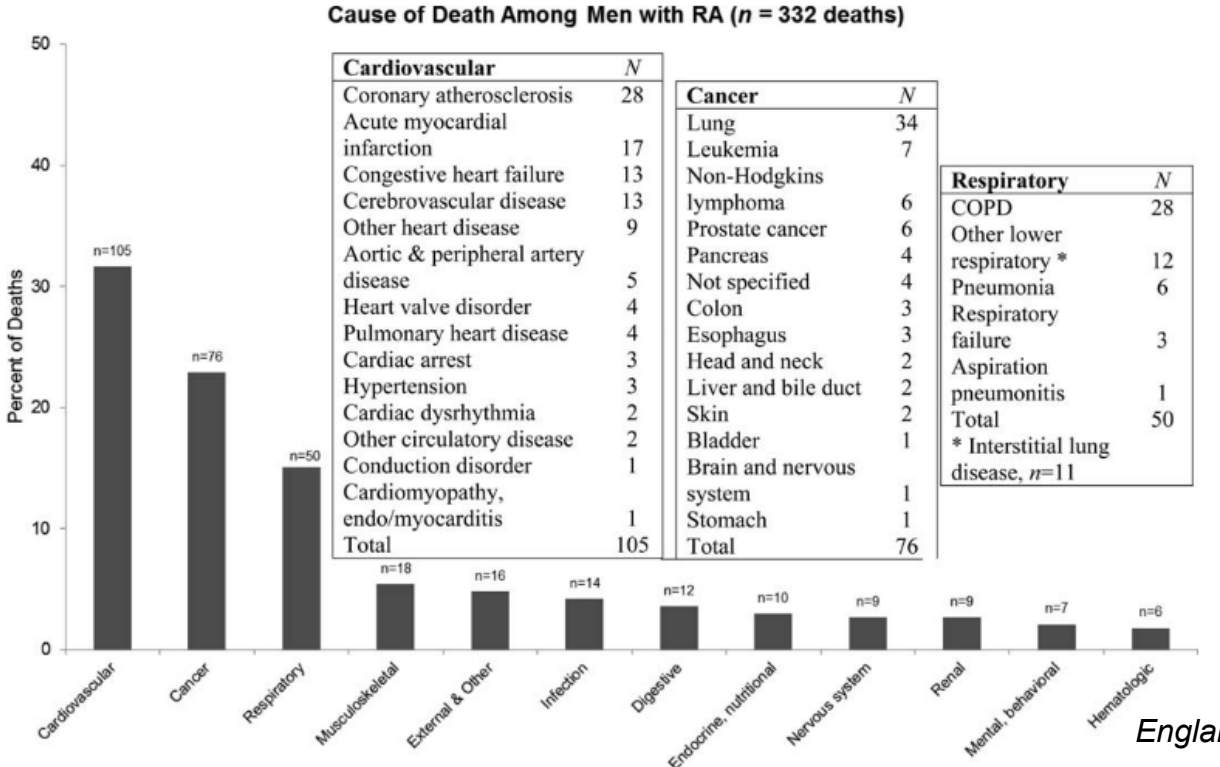
Reduced quality of life

Increased healthcare use

Expensive

Increased Mortality Rates in RA

95% of Deaths *Not* Attributed Directly to RA



Cardiovascular	N
Coronary atherosclerosis	28
Acute myocardial infarction	17
Congestive heart failure	13
Cerebrovascular disease	13
Other heart disease	9
Aortic & peripheral artery disease	5
Heart valve disorder	4
Pulmonary heart disease	4
Cardiac arrest	3
Hypertension	3
Cardiac dysrhythmia	2
Other circulatory disease	2
Conduction disorder	1
Cardiomyopathy, endo/myocarditis	1
Total	105

Cancer	N
Lung	34
Leukemia	7
Non-Hodgkins lymphoma	6
Prostate cancer	6
Pancreas	4
Not specified	4
Colon	3
Esophagus	3
Head and neck	2
Liver and bile duct	2
Skin	2
Bladder	1
Brain and nervous system	1
Stomach	1
Total	76

Respiratory	N
COPD	28
Other lower respiratory *	12
Pneumonia	6
Respiratory failure	3
Aspiration pneumonitis	1
Total	50
* Interstitial lung disease, *n*=11	

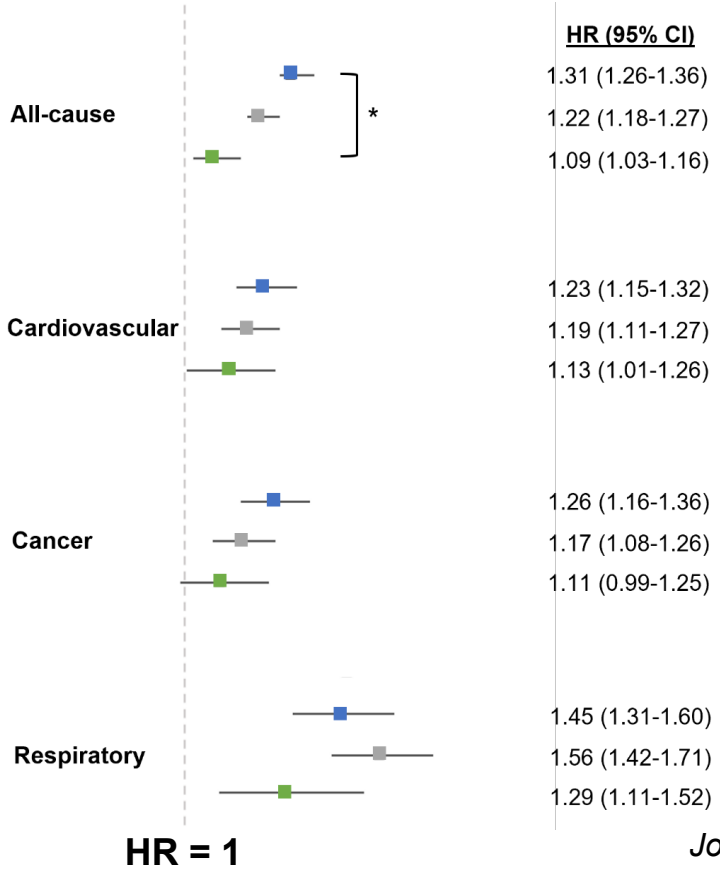
VA RA Veterans Affairs Rheumatoid Arthritis Registry

1700 men
>6,000 PY f/u
Registry linked to NDI

England BR et al. Arth Care Res, 2016.

Mortality Gap Narrowed, But Still Persists

2000-2005
2006-2011
2012-2017



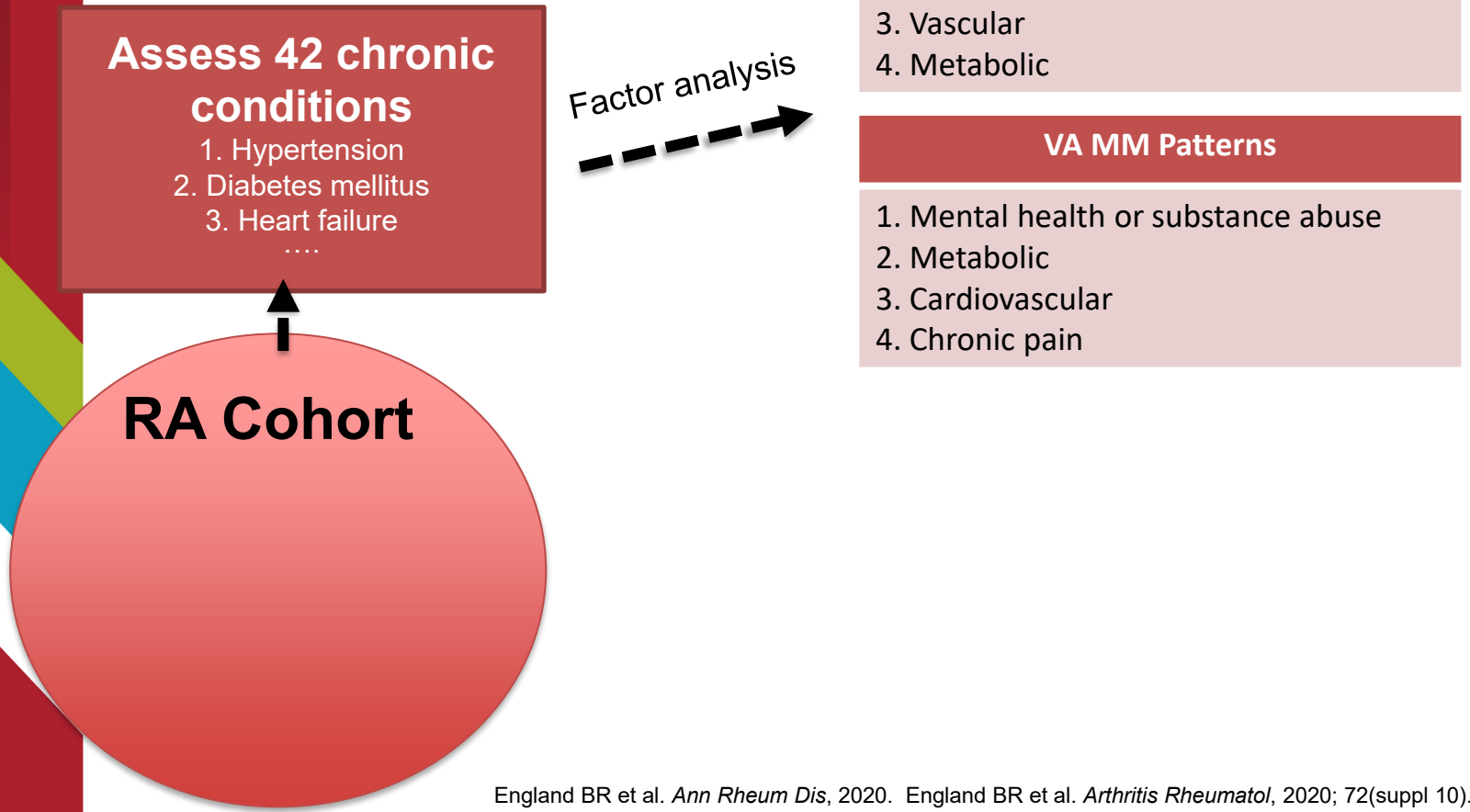
N=29,779 incident RA
N=245,285 non-RA

Johnson TM et al. ACR Convergence 2021.

Outcomes from Multimorbidity in RA

- Multimorbidity accounted some of the excess all-cause and cardiovascular **mortality** in RA
  - Nurses Health Study (1k RA, 10k matched non-RA)
  - Multimorbidity weighted index (n=61 conditions)
  - HR 1.5 -> 1.2 with adjustment for multimorbidity burden
- Multimorbidity associated with poor **HRQOL**
  - Derived in BRASS, validated in COMORA cohort
  - Multimorbidity index (MMI; n=40 conditions)
  - Weighted and unweighted MMI outperformed Charlson for predicting EQ-5D

Yoshida K et al. Arth Care Res, 2019.
Radner H et al. Sem Arth Rheum, 2015.



England BR et al. *Ann Rheum Dis*, 2020. England BR et al. *Arthritis Rheumatol*, 2020; 72(suppl 10). Abstract #0179.

Assess 42 chronic conditions

1. Hypertension
2. Diabetes mellitus
3. Heart failure
….

Factor analysis

MarketScan® MM Patterns

1. Mental health & chronic pain
2. Cardiopulmonary
3. Vascular
4. Metabolic

VA MM Patterns

1. Mental health or substance abuse
2. Metabolic
3. Cardiovascular
4. Chronic pain

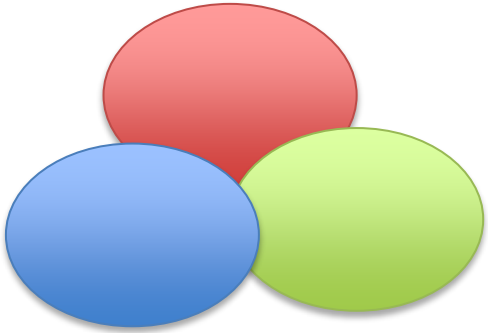
Apply patterns

RA Cohort

Pt	MHCP	CP	Vasc	Met
1	7	3	12	1
2	2	36	4	0
3	42	3	1	6
…				

K-means clustering of RA patients based on multimorbidity patterns

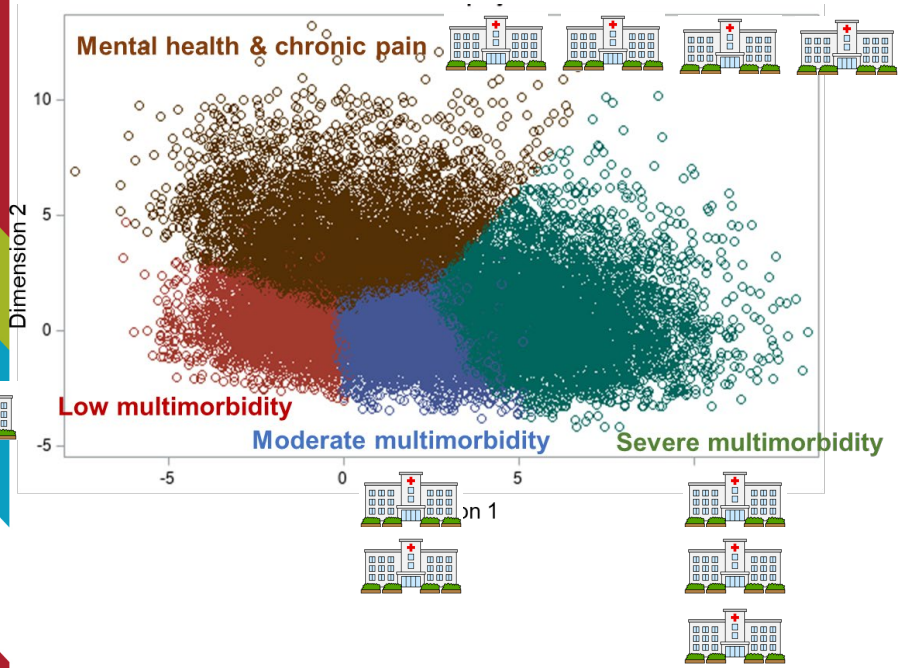
Clusters of RA Patients



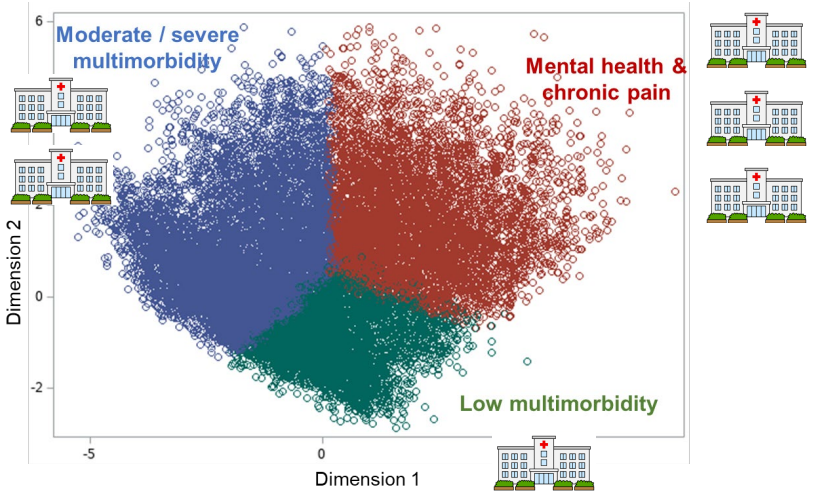
England BR et al. *Ann Rheum Dis*, 2020. England BR et al. *Arthritis Rheumatol*, 2020; 72(suppl 10). Abstract #0179.

Multimorbidity Patterns & Health Care Utilization

MarketScan (n=113,425)



VA (n=32,640)



England BR et al. ACR Convergence 2021

Multimorbidity & RA Disease Course

Veterans Affairs Rheumatoid Arthritis

N=2
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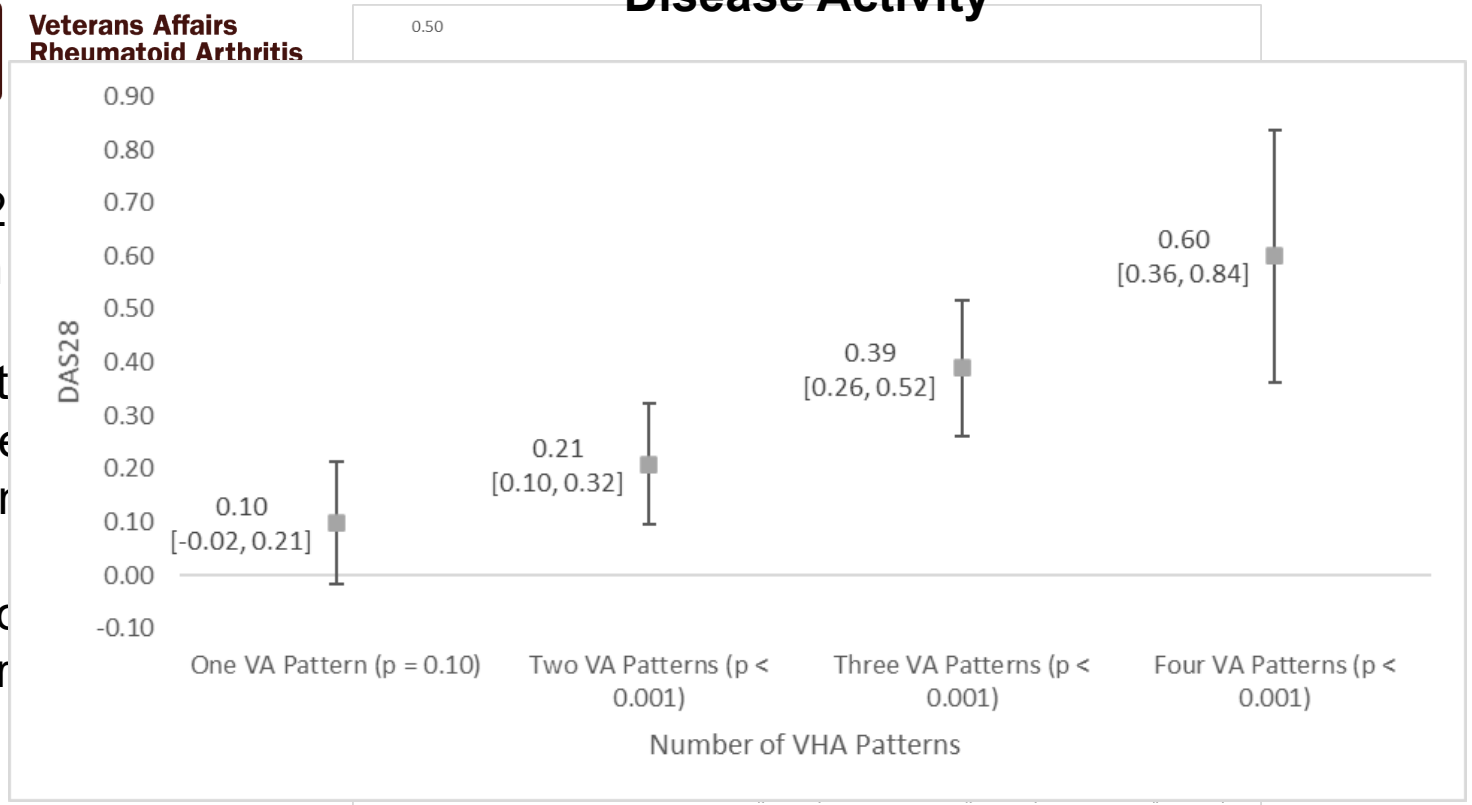

Dutt S et al. In preparation.

Multimorbidity: For Specialists Too!

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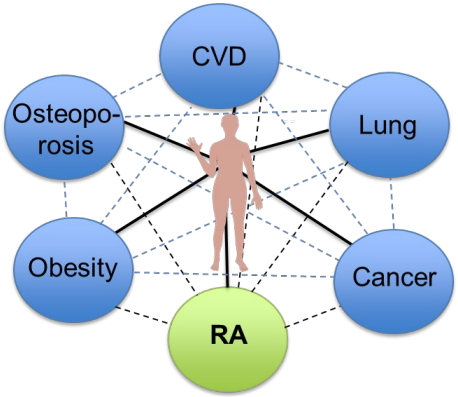

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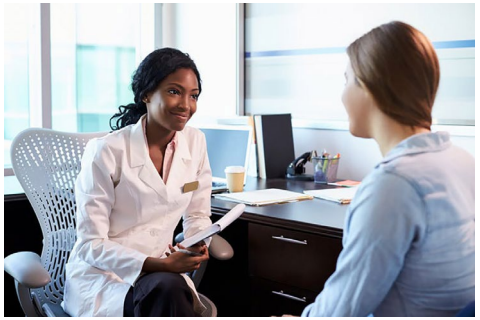


2. Poor long-term outcomes (e.g. MM-related outcomes)

Shortened lifespan

Reduced quality of life

Increased healthcare use

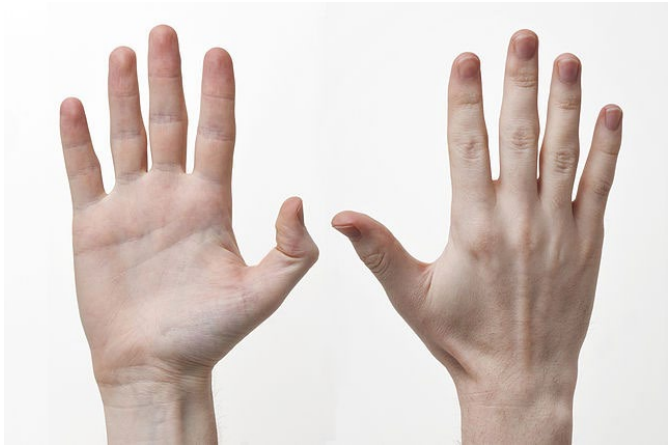
Expensive

Not All Doom & Gloom: RA Advancements

THEN

NSAIDs
Glucocorticoids
Methotrexate
Sulfasalazine
Hydroxychloroquine
Minocycline
~~Gold~~
~~Penicillamine~~
Azathioprine
~~Cyclosporine~~
~~Cyclophosphamide~~
Combination DMARDs

NOW



Glucocorticoids
Methotrexate
Sulfasalazine
Hydroxychloroquine
Minocycline
Azathioprine
Combination DMARDs
Leflunomide
Etanercept
Infliximab
Adalimumab
Golimumab
Certolizumab
Anakinra
Abatacept
Rituximab
Tocilizumab
Sarilumab
Tofacitinib
Baricitinib
Upadicitinib
Biosimilars

2021 ACR RA Treatment Guidelines

Table 6. Specific patient populations*

Recommendations	Certainty of evidence	Based on the evidence report(s) of the following PICO(s)	Evidence table(s), in Supp. App. 2
Subcutaneous nodules			
Methotrexate is **conditionally** recommended over alternative DMARDs for patients with subcutaneous nodules who have moderate-to-high disease activity.	Very low	PICO 64	p. 427
Switching to a non-methotrexate DMARD is **conditionally** recommended over continuation of methotrexate for patients taking methotrexate with progressive subcutaneous nodules.	Very low	PICO 65	p. 428
Pulmonary disease			
Methotrexate is **conditionally** recommended over alternative DMARDs for the treatment of inflammatory arthritis for patients with clinically diagnosed mild and stable airway or parenchymal lung disease who have moderate-to-high disease activity.	Very low	PICO 67	p. 430
Heart failure			
Addition of a non–TNF inhibitor bDMARD or tsDMARD is **conditionally** recommended over addition of a TNF inhibitor for patients with NYHA class III or IV heart failure and an inadequate response to csDMARDs.	Very low	PICO 70	p. 435
Switching to a non–TNF inhibitor bDMARD or tsDMARD is **conditionally** recommended over continuation of a TNF inhibitor for patients taking a TNF inhibitor who develop heart failure.	Very low	PICO 71	p. 436
Lymphoproliferative disorder			
Rituximab is **conditionally** recommended over other DMARDs for patients who have a previous lymphoproliferative disorder for which rituximab is an approved treatment and who have moderate-to-high disease activity.	Very low	PICO 75 and PICO 76	p. 446–7
Hepatitis B infection			
Prophylactic antiviral therapy is **strongly** recommended over frequent monitoring alone for patients initiating rituximab who are hepatitis B core antibody positive (regardless of hepatitis B surface antigen status).	Very low	PICO 82	p. 459
Prophylactic antiviral therapy is **strongly** recommended over frequent monitoring alone for patients initiating any bDMARD or tsDMARD who are hepatitis B core antibody positive and hepatitis B surface antigen positive.	Very low	PICO 83	p. 464
Frequent monitoring alone is **conditionally** recommended over prophylactic antiviral therapy for patients initiating a bDMARD other than rituximab or a tsDMARD who are hepatitis B core antibody positive and hepatitis B surface antigen negative.	Very low	PICO 84	p. 471
Nonalcoholic fatty liver disease			
Methotrexate is **conditionally** recommended over alternative DMARDs for DMARD-naive patients with nonalcoholic fatty liver disease, normal liver enzymes and liver function tests, and no evidence of advanced liver fibrosis who have moderate-to high disease activity.	Very low	PICO 87	p. 489
Persistent hypogammaglobulinemia without infection			
In the setting of persistent hypogammaglobulinemia without infection, continuation of rituximab therapy for patients at target is **conditionally** recommended over switching to a different bDMARD or tsDMARD.	Very low	PICO 66	p. 429
Previous serious infection			
Addition of csDMARDs is **conditionally** recommended over addition of a bDMARD or tsDMARD for patients with a serious infection within the previous 12 months who have moderate-to-high disease activity despite csDMARD monotherapy.	Very low	PICO 88	p. 490
Addition of/switching to DMARDs is **conditionally** recommended over initiation/dose escalation of glucocorticoids for patients with a serious infection within the previous 12 months who have moderate-to-high disease activity.	Very low	PICO 90 and PICO 91	p. 496–7
Nontuberculous mycobacterial lung disease			
Use of the lowest possible dose of glucocorticoids (discontinuation if possible) is **conditionally** recommended over continuation of glucocorticoids for patients with nontuberculous mycobacterial lung disease.	Very low	No relevant PICO	
Addition of csDMARDs is **conditionally** recommended over addition of a bDMARD or tsDMARD for patients with nontuberculous mycobacterial lung disease who have moderate-to-high disease activity despite csDMARD monotherapy.	Very low	PICO 92	p. 498
Abatacept is **conditionally** recommended over other bDMARDs and tsDMARDs for patients with nontuberculous mycobacterial lung disease who have moderate-to-high disease activity despite csDMARDs.	Very low	PICO 93	p. 499

Fraenkel L et al. Arth Rheum, 2021.

2021 ACR RA Treatment Guidelines

Only considered 9 chronic conditions

What if a patient has multiple chronic conditions?

Table 6. Specific patient populations*

Recommendations	Certainty of evidence	Based on the evidence report(s) of the following PICO(s)	Evidence table(s), in Supp. App. 2
Subcutaneous nodules			
Methotrexate is **conditionally** recommended over alternative DMARDs for patients with subcutaneous nodules who have moderate-to-high disease activity.	Very low	PICO 64	p. 427
Switching to a non-methotrexate DMARD is **conditionally** recommended over continuation of methotrexate for patients taking methotrexate with progressive subcutaneous nodules.	Very low	PICO 65	p. 428
Pulmonary disease			
Methotrexate is **conditionally** recommended over alternative DMARDs for the treatment of inflammatory arthritis for patients with clinically diagnosed mild and stable airway or parenchymal lung disease who have moderate-to-high disease activity.	Very low	PICO 67	p. 430
Heart failure			
Addition of a non–TNF inhibitor bDMARD or tsDMARD is **conditionally** recommended over addition of a TNF inhibitor for patients with NYHA class III or IV heart failure and an inadequate response to csDMARDs.	Very low	PICO 70	p. 435
Switching to a non–TNF inhibitor bDMARD or tsDMARD is **conditionally** recommended over continuation of a TNF inhibitor for patients taking a TNF inhibitor who develop heart failure.	Very low	PICO 71	p. 436
Lymphoproliferative disorder			
Rituximab is **conditionally** recommended over other DMARDs for patients who have a previous lymphoproliferative disorder for which rituximab is an approved treatment and who have moderate-to-high disease activity.	Very low	PICO 75 and PICO 76	p. 446–7
Hepatitis B infection			
Prophylactic antiviral therapy is **strongly** recommended over frequent monitoring alone for patients initiating rituximab who are hepatitis B core antibody positive (regardless of hepatitis B surface antigen status).	Very low	PICO 82	p. 459
Prophylactic antiviral therapy is **strongly** recommended over frequent monitoring alone for patients initiating any bDMARD or tsDMARD who are hepatitis B core antibody positive and hepatitis B surface antigen positive.	Very low	PICO 83	p. 464
Frequent monitoring alone is **conditionally** recommended over prophylactic antiviral therapy for patients initiating a bDMARD other than rituximab or a tsDMARD who are hepatitis B core antibody positive and hepatitis B surface antigen negative.	Very low	PICO 84	p. 471
Nonalcoholic fatty liver disease			
Methotrexate is **conditionally** recommended over alternative DMARDs for DMARD-naive patients with nonalcoholic fatty liver disease, normal liver enzymes and liver function tests, and no evidence of advanced liver fibrosis who have moderate-to high disease activity.	Very low	PICO 87	p. 489
Persistent hypogammaglobulinemia without infection			
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Previous serious infection			
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Nontuberculous mycobacterial lung disease			
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Abatacept is **conditionally** recommended over other bDMARDs and tsDMARDs for patients with nontuberculous mycobacterial lung disease who have moderate-to-high disease activity despite csDMARDs.	Very low	PICO 93	p. 499

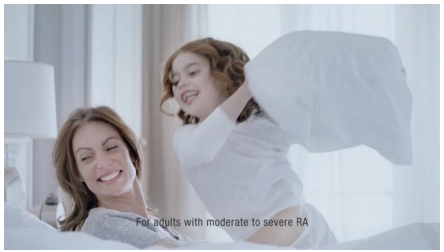
Certainty of evidence: Very Low

Fraenkel L et al. Arth Rheum, 2021.

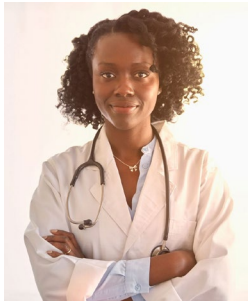
Or Paradox?

The Process of Evidence Based Medicine

"TV" RA

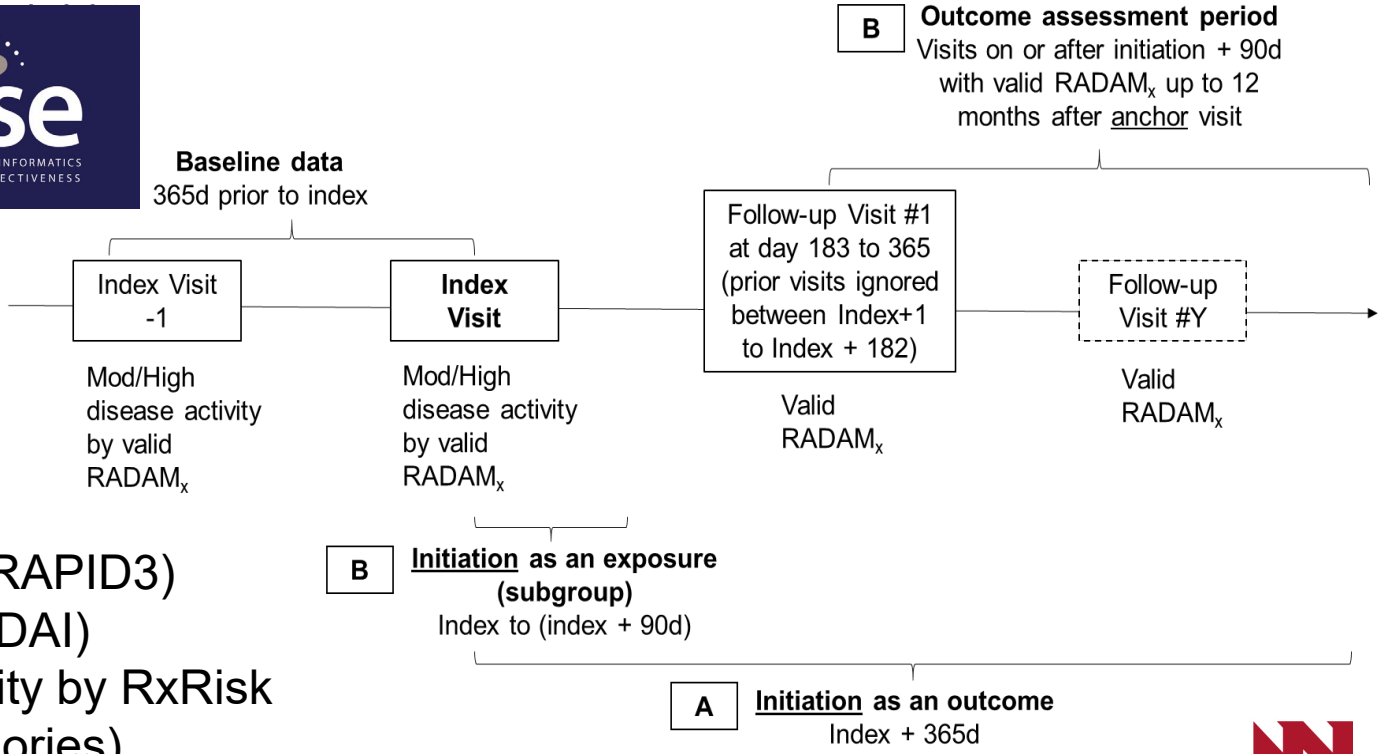


DBRCT



"Real" RA

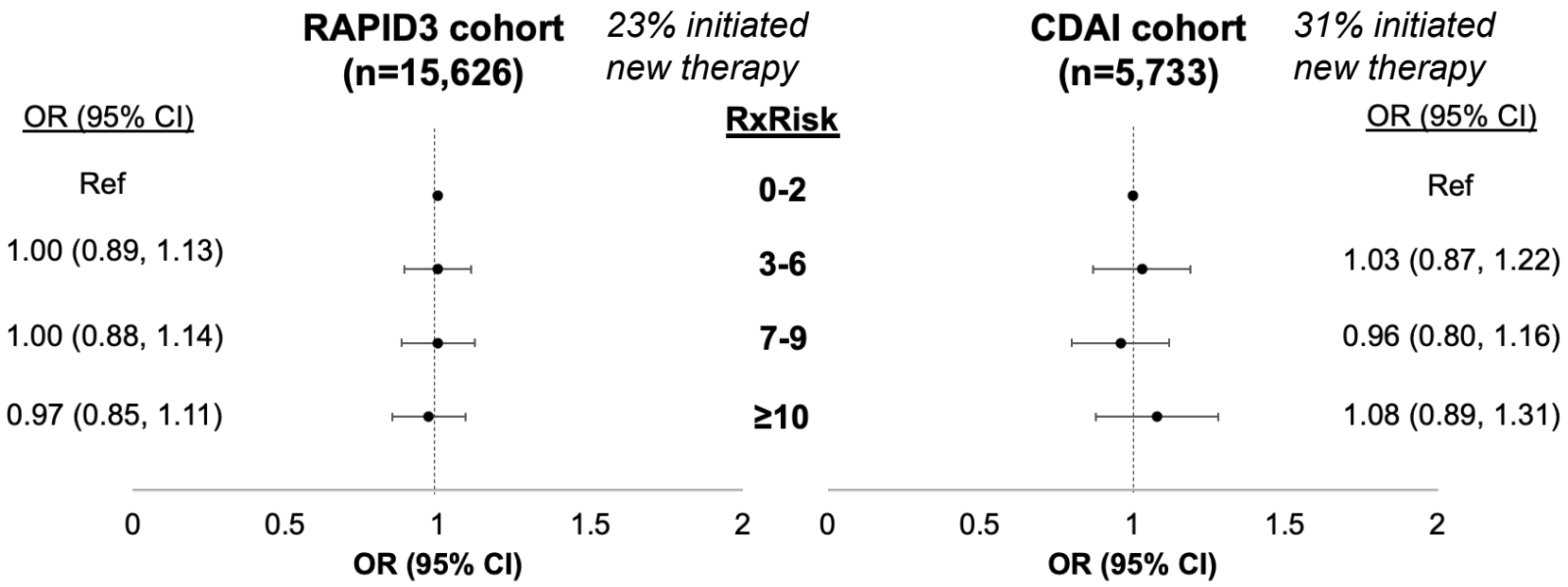
Multimorbidity & RA Treatment: Real-World Data



- N=15,626 (RAPID3)
- N=5,733 (CDAI)
- Multimorbidity by RxRisk (n=46 categories)
- Mean RxRisk 6-7

England BR et al. Arth Care Res, 2021.

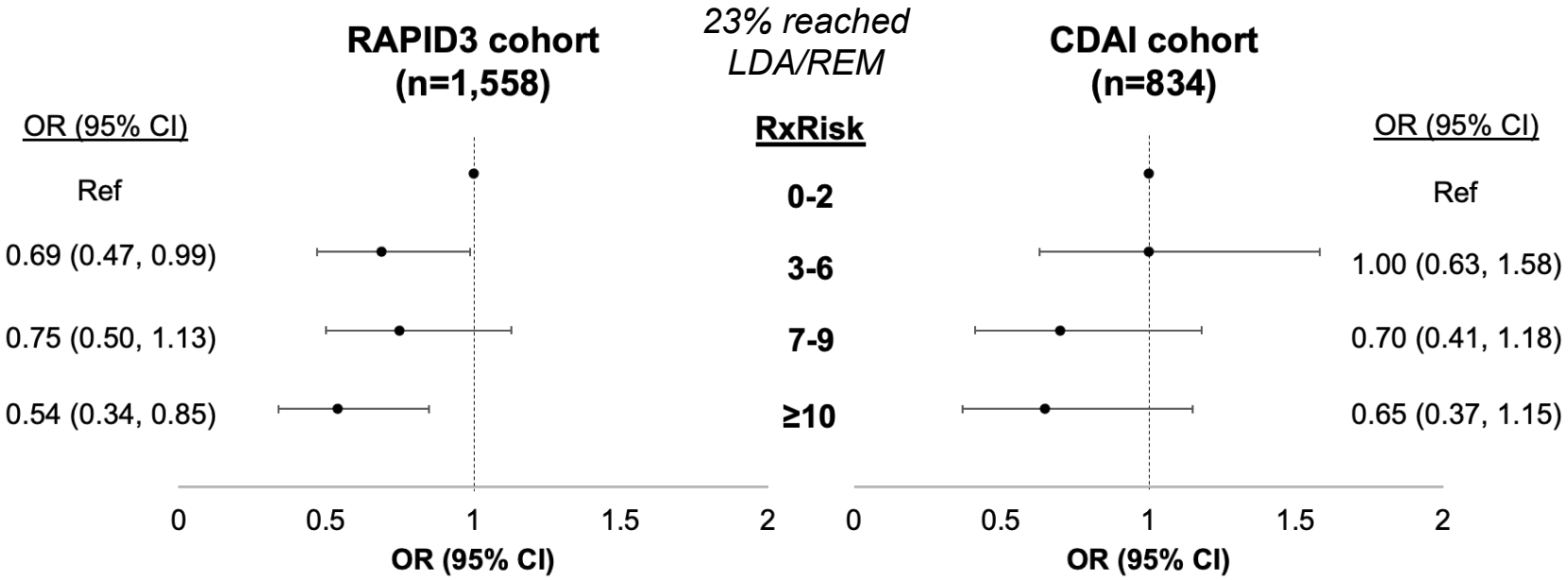
Multimorbidity & Initiating RA Treatment



Adjusted for age, sex, race, U.S. region, insurance status, seropositivity, number of visits, csDMARDs, bDMARDs, and oral steroids

England BR et al. Arth Care Res 2021.

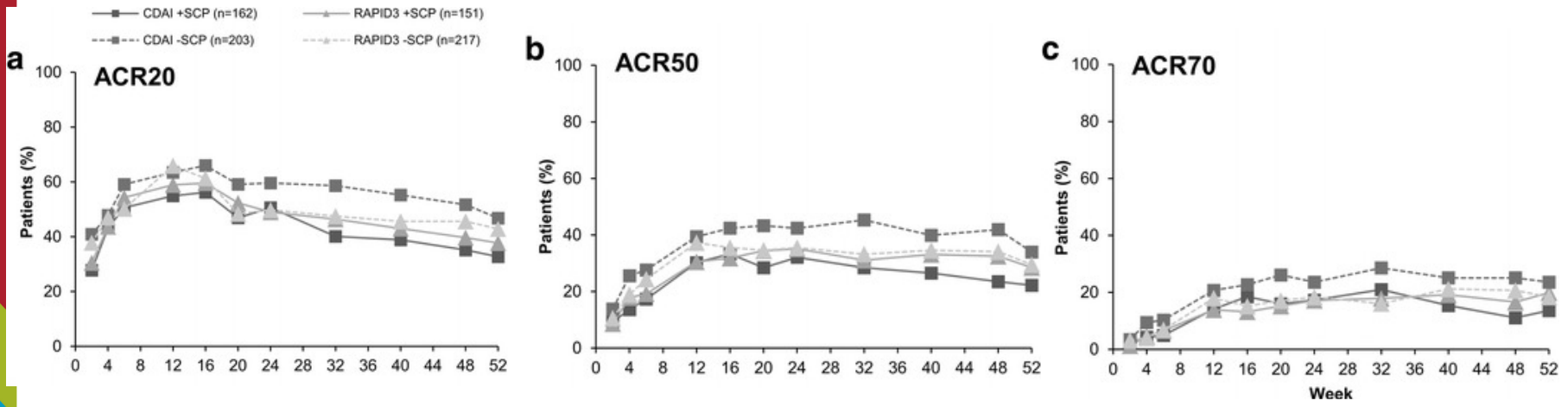
Multimorbidity & Achieving RA Target



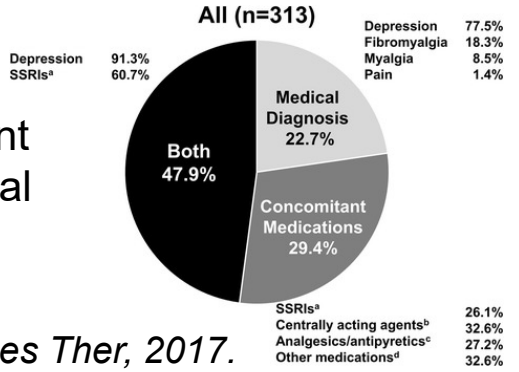
Adjusted for age, sex, race, U.S. region, insurance status, seropositivity, number of visits, oral steroids, number of prior csDMARDs, number of prior bDMARDs, number of prior tsDMARDs, baseline disease activity category, treatment being initiated (cDMARD, TNFi, non-TNFi bDMARD, tsDMARD)

England BR et al. Arth Care Res, 2021.

Somatization Comorbidity Phenotype & Treatment Response

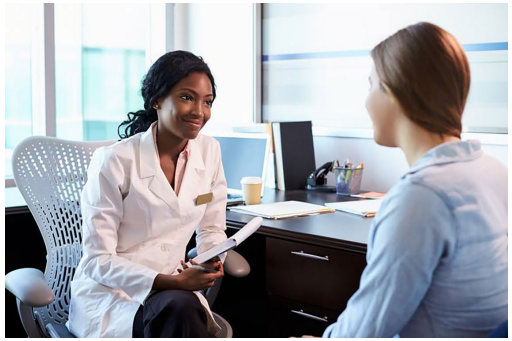


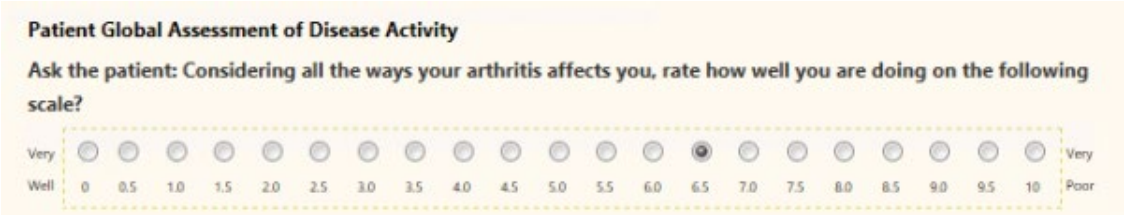
- RCT of RAPID3 vs. CDAI assessment of certolizumab response
- **SCP** = use of concomitant medications indicated for the treatment of depression, anxiety, or neuropathic pain –OR- baseline medical diagnosis of depression, chronic pain, fibromyalgia, or myalgias



Curtis JR et al. Arth Res Ther, 2017.

Multimorbidity & Shared Decision Making





- Treat-to-target, still the best option?
  - Are measures valid in multimorbid individuals?
  - Lower effectiveness of medications?
  - Higher risk of medications?
  - Will I meet quality metrics for reimbursement?
- Other health conditions may be the priority
- Are their arthritis symptoms limiting their function/QOL?
- Polypharmacy
- Expensive medications/healthcare

Example 1: RA and CVD prevention

58 y/o female with RA has lipid panel drawn:

- LDL 92 mg/dL
- ASCVD risk 4%
- Low risk, no statin initiated

High RA disease activity at last rheumatology visit:

- RA associated with 1.5-fold increased risk of CVD (risk calculators underestimate risk)
- Lipid paradox (LDL low during active inflammation)
- Taking prednisone 7.5 mg daily

Who runs the CVD prevention show?

PCP – understands CVD prevention, but ? RA impact
Rheum – understands RA impact, but? CVD prevention
Cardiology?
Both?

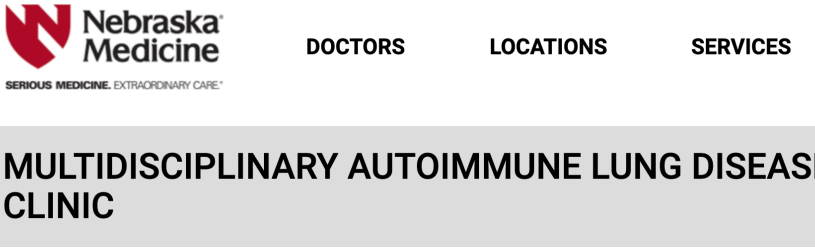
Example 2: RA and ILD

67 y/o male with RA reports mild, non-productive cough:

- CT shows reticulation in subpleural region, bilateral lung bases
- PFT reveals normal FVC, DLCO
- Disease activity moderate
- Regimen: methotrexate, etanercept

Who runs the show?

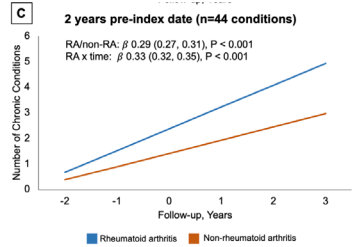
Rheum – change etanercept to rituximab, see pulm
Pulm – stop methotrexate and enbrel, start nintedanib, see rheum
PCP - ?

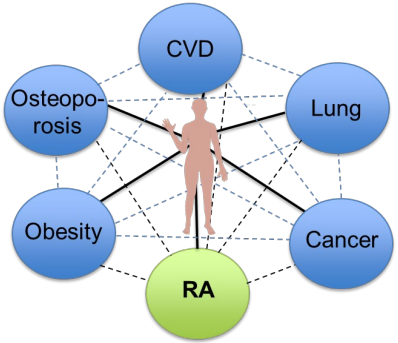


Multimorbid RA

- “Real RA” patients are multimorbid
- RA drives multimorbidity onset and progression <u>early</u> in the disease course
- Multimorbidity causes bad things to happen and changes the RA treatment landscape
- Understanding the patterns/networks of RA multimorbidity may allow for targeted intervention
- Research needs: A LOT – identification, assessment, pathophysiology, management, patient preferences, care delivery models

“Real RA”





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Rheumatology Research Foundation
Advancing Treatment | Finding Cures

Scientist Development Award

GREAT PLAINS IDeA | Clinical and Translational Research

Patients participating in clinical registries:

VA RA Veterans Affairs Rheumatoid Arthritis Registry

RHEUMATOID ARTHRITIS INVESTIGATIONAL RAIN NETWORK

FORWARD The National Databank for Rheumatic Diseases

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