



# Osteo-arthritis and Cardiovascular Diseases

21th of Oktober 2016

Prof Dr Willem F Lems,  
Reumatologist in VUmc (and Reade)



# DISCLOSURES

- Speaker's fee: Amgen, Eli Lilly, Merck.
- Advisory boards: Amgen, Eli Lilly, Merck.
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# Osteoporosis and cardiovascular diseases



- Prof Dr Willem F Lems
- Department of Rheumatology
- EULAR Centre of Excellence:
- VU University medical centre and Reade,  
Amsterdam, the Netherlands

# Cardiovascular events and osteoporotic fractures



Part 4

- Fracture risk is elevated in patients with cardiovascular diseases, particularly after stroke;
- Atherosclerotic manifestations occur more often in patients with osteoporosis.

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# Cardiovascular events and osteoporotic fractures



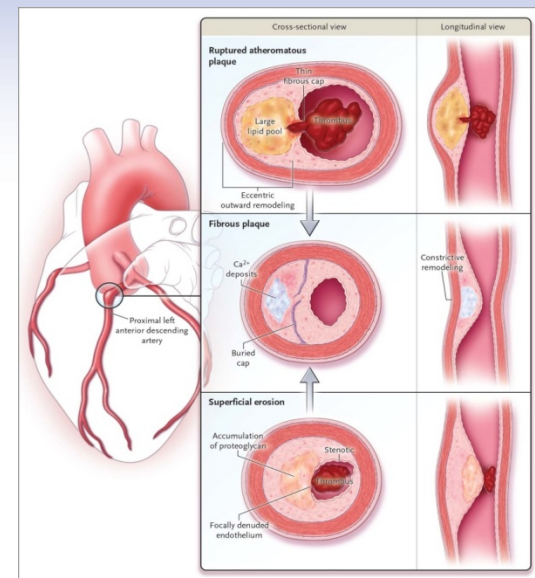
Part 4

- Several common risk factors for CVD and osteoporosis, particularly systemic inflammation;
- Co-occurrence of CVD and osteoporosis may occur in patients with systemic inflammatory rheumatic diseases.





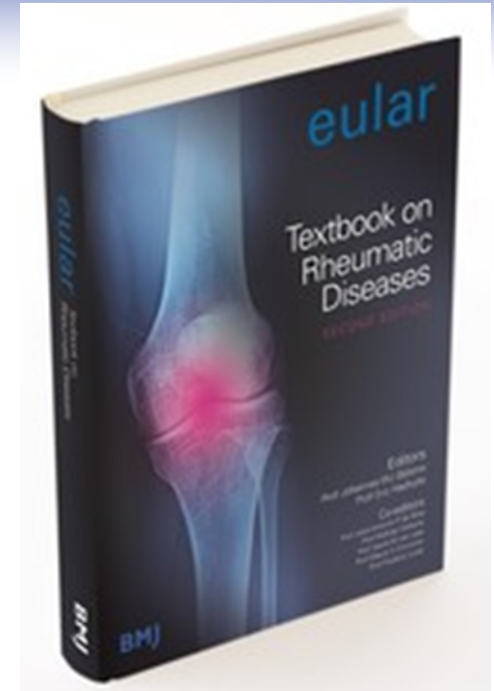
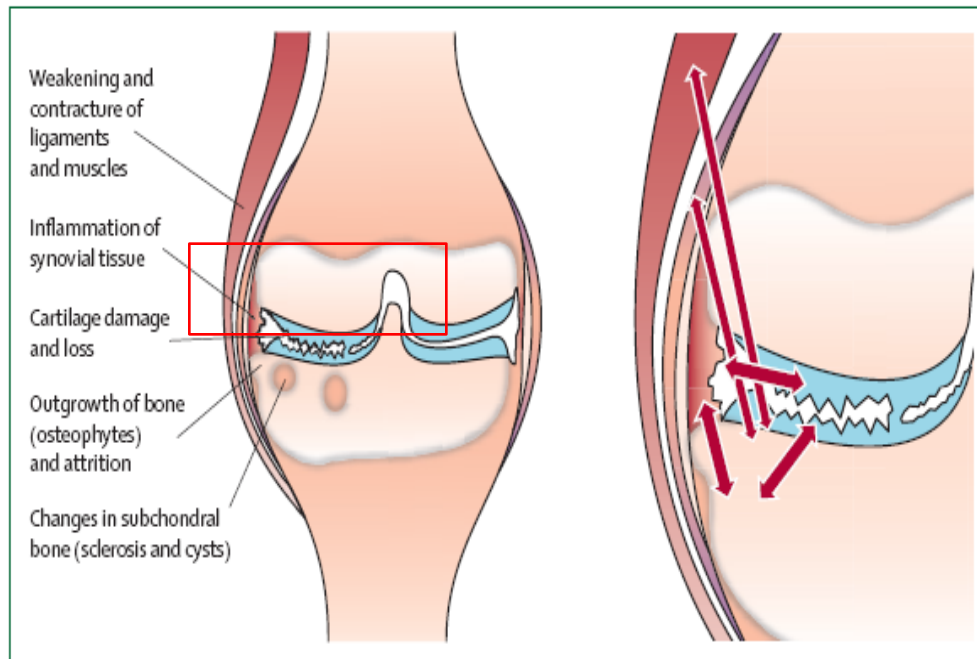
# Osteo-arthritis and Cardiovascular Diseases/Mortality



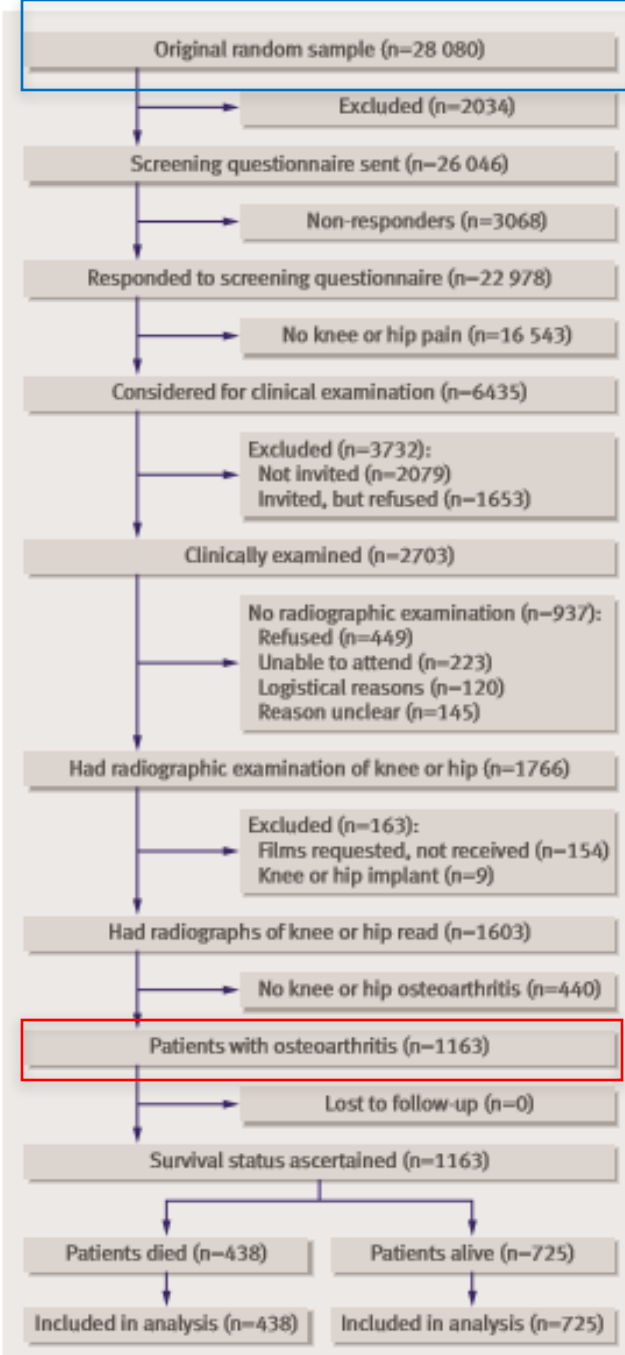
# Arthritis 1

## Osteoarthritis: an update with relevance for clinical practice

Johannes W J Bijlsma, Francis Berenbaum, Floris P J G Lafeber







## All cause and disease specific mortality in patients with knee or hip osteoarthritis: population based cohort study

Eveline Nüesch, research fellow,<sup>1,2</sup> Paul Dieppe, professor of clinical education research,<sup>3</sup> Stephan Reichenbach, rheumatologist and senior research fellow,<sup>1,4</sup> Susan Williams, research associate,<sup>5</sup> Samuel Iff, research fellow,<sup>1,2</sup> Peter Jüni, professor of clinical epidemiology<sup>1,2</sup>

BMJ 2011;342:d1165

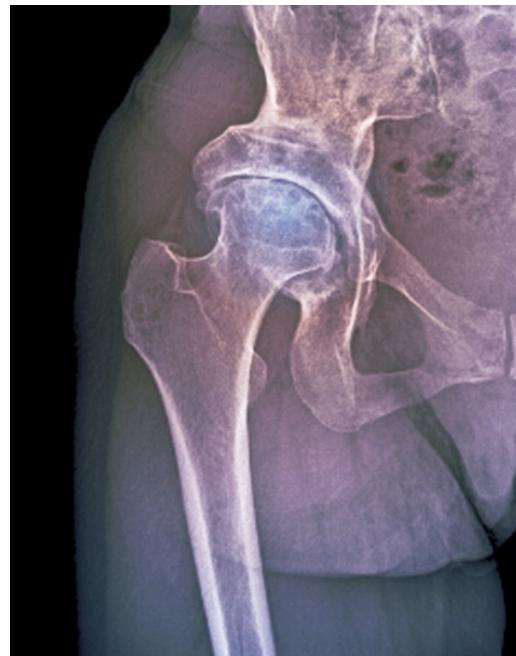
Fig 1 | Flow of participants through different stages of study



## Excess mortality in osteoarthritis

Provides evidence for a unified approach to musculoskeletal ageing

Standardised Mortality: 1.55, (95% c.i. 1.41-1.70)

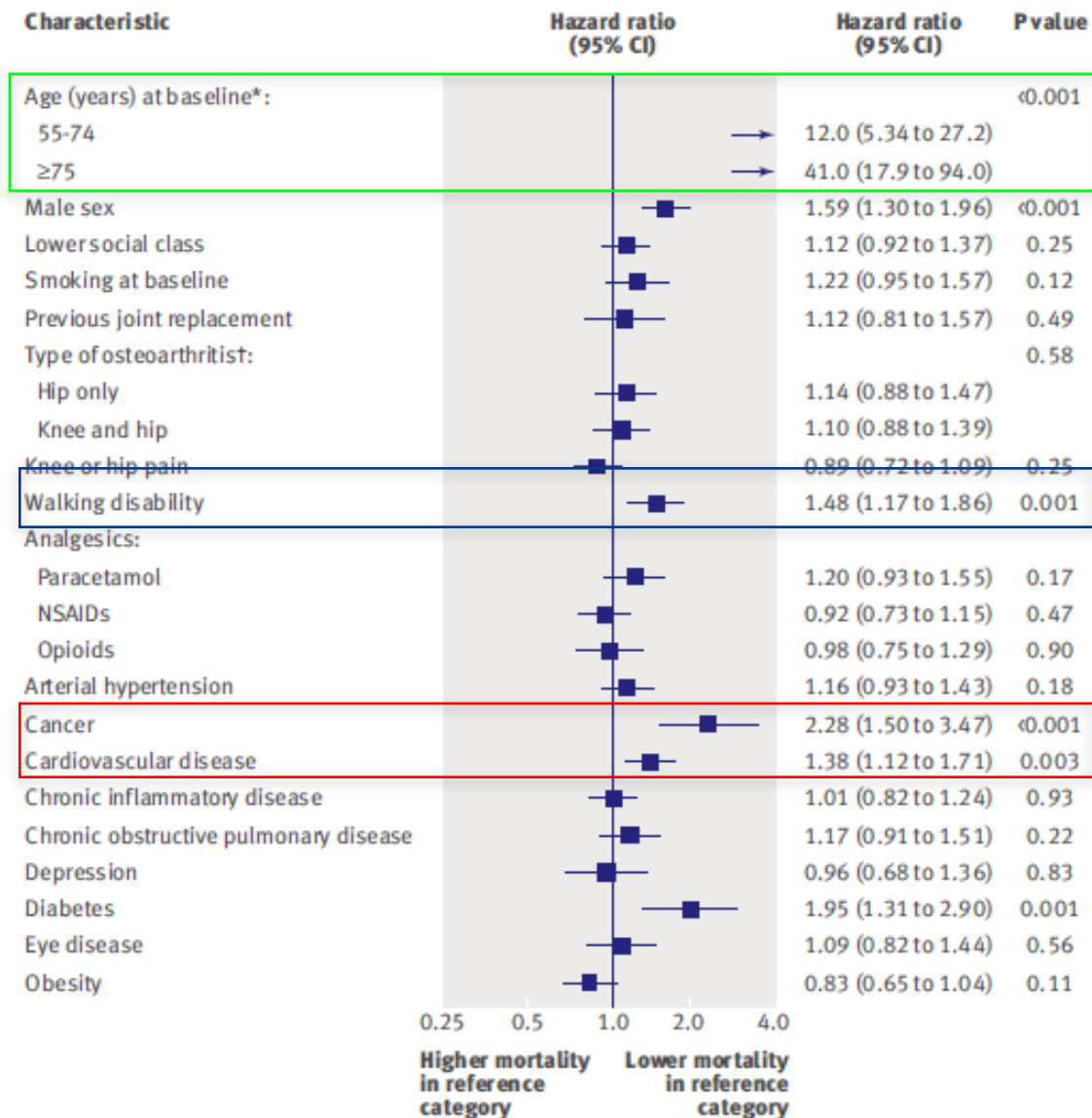


Cooper et al, BMJ 2011

# All cause and disease specific mortality in patients with knee or hip osteoarthritis: population based cohort study



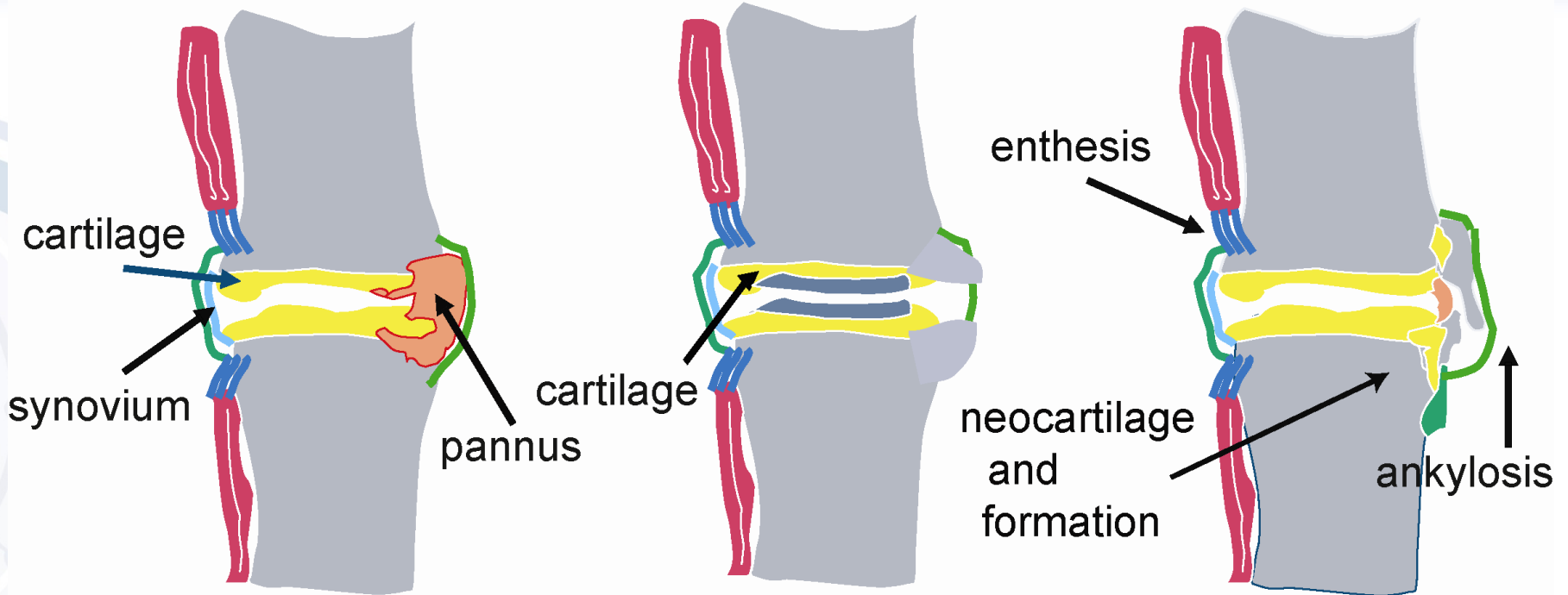
Eveline Nüesch, research fellow,<sup>1,2</sup> Paul Dieppe, professor of clinical education research,<sup>3</sup> Stephan Reichenbach, rheumatologist and senior research fellow,<sup>1,4</sup> Susan Williams, research associate,<sup>5</sup> Samuel Iff, research fellow,<sup>1,2</sup> Peter Jüni, professor of clinical epidemiology<sup>1,2</sup>



# Metabolic Bone Changes in Rheumatic Diseases



rheumatoid arthritis    osteoarthritis    spondyloarthritis



# Risk of Cardiovascular Disease in Patients With Osteoarthritis: A Prospective Longitudinal Study

M. MUSHFIQUR RAHMAN,<sup>1</sup> JACEK A. KOPEC,<sup>1</sup> ASLAM H. ANIS,<sup>2</sup> JOLANDA CIBERE,<sup>1</sup> AND CHARLIE H. GOLDSMITH<sup>3</sup>



**Table 2. Baseline characteristics of OA cases and non-OA individuals by exposure status\***

	Exposed (OA)	Nonexposed (non-OA)
N	12,745	36,886
Age, mean $\pm$ SD years	58.2 $\pm$ 14.5	57.5 $\pm$ 14.3
Women	60	59
Body mass index, kg/m <sup>2</sup>		
<18.5	1.6	2.3
18.5–24.9	31.9	44.3
25.0–29.9	32.1	36.7
$\geq 30.0$	34.4	17.7
Socioeconomic status		
1 (low)	16.0	15.1
2	17.7	17.0
3	19.3	18.1
4	21.4	21.1
5 (high)	24.0	25.2
Missing	1.6	3.5
COPD	10.6	6.9
Hypertension	19.7	16.4
Hyperlipidemia	6.0	4.9
Diabetes mellitus	5.2	4.7
Charlson score, mean $\pm$ SD	0.41 $\pm$ 0.92	0.35 $\pm$ 0.98

\* Values are the percentage unless indicated otherwise. OA = osteoarthritis; COPD = chronic obstructive pulmonary disease.

Physician diagnosed OA;  
Follow-up up to 18 years;  
First longitudinal study  
observing OA and CVD.

# Risk of Cardiovascular Disease in Patients With Osteoarthritis: A Prospective Longitudinal Study

M. MUSHFIQUR RAHMAN,<sup>1</sup> JACEK A. KOPEC,<sup>1</sup> ASLAM H. ANIS,<sup>2</sup> JOLANDA CIBERE,<sup>1</sup> AND CHARLIE H. GOLDSMITH<sup>3</sup>



Table 3. RRs and 95% CIs of cardiovascular disease for OA cases by age and sex\*

Variables	Total, RR (95% CI)	Men, RR (95% CI)		Women, RR (95% CI)	
		Age <65 years	Age ≥65 years	Age <65 years	Age ≥65 years
Exposure to OA					
Unadjusted	1.23 (1.17–1.29)	1.19 (1.08–1.32)	1.21 (1.10–1.33)	1.51 (1.35–1.69)	1.23 (1.14–1.33)
Adjusted	1.13 (1.07–1.18)	1.08 (0.97–1.19)	1.15 (1.04–1.27)	1.26 (1.13–1.42)	1.17 (1.07–1.26)
Body mass index, kg/m <sup>2</sup>					
<18.5	1.29 (1.11–1.50)	1.04 (0.55–1.94)	1.56 (1.07–2.28)	0.95 (0.64–1.40)	1.45 (1.20–1.74)
18.5–24.9	Reference	Reference	Reference	Reference	Reference
25.0–29.9	1.09 (1.03–1.15)	1.33 (1.18–1.49)	1.02 (0.92–1.13)	1.26 (1.11–1.44)	0.99 (0.90–1.08)
≥30.0	1.40 (1.33–1.48)	1.93 (1.70–2.18)	1.14 (1.01–1.28)	1.88 (1.65–2.14)	1.17 (1.07–1.29)
SES					
1 (low)	1.07 (0.99–1.14)	1.09 (0.94–1.26)	1.00 (0.86–1.15)	1.20 (1.01–1.43)	1.10 (0.98–1.23)
2	1.03 (0.96–1.10)	1.00 (0.87–1.14)	1.06 (0.92–1.22)	1.19 (1.01–1.41)	0.97 (0.86–1.09)
3	1.05 (0.98–1.12)	0.97 (0.85–1.12)	1.08 (0.94–1.24)	1.14 (0.96–1.35)	1.05 (0.93–1.18)
4	1.05 (0.99–1.13)	0.87 (0.77–1.00)	1.04 (0.91–1.19)	1.29 (1.10–1.51)	1.04 (0.93–1.17)
5 (high)	Reference	Reference	Reference	Reference	Reference
COPD	1.17 (1.08–1.26)	1.23 (1.03–1.46)	1.06 (0.92–1.24)	1.31 (1.10–1.57)	1.08 (0.94–1.24)
Hypertension	1.43 (1.36–1.50)	1.93 (1.72–2.17)	1.32 (1.20–1.46)	2.23 (1.97–2.53)	1.49 (1.38–1.61)
Hyperlipidemia	1.02 (0.93–1.13)	1.26 (1.06–1.51)	0.98 (0.80–1.21)	1.27 (1.03–1.56)	0.79 (0.67–0.94)
Diabetes mellitus	1.73 (1.60–1.88)	2.05 (1.70–1.22)	1.50 (1.29–1.74)	2.30 (1.89–2.80)	1.79 (1.56–2.05)
Charlson score	1.05 (1.02–1.07)	1.15 (1.07–1.22)	1.06 (1.01–1.10)	1.14 (1.06–1.21)	1.07 (1.03–1.10)

\* RR = relative risk; 95% CI = 95% confidence interval; OA = osteoarthritis; SES = socioeconomic status; COPD = chronic obstructive pulmonary disease.

# Risk of Cardiovascular Disease in Patients With Osteoarthritis: A Prospective Longitudinal Study

M. MUSHFIQUR RAHMAN,<sup>1</sup> JACEK A. KOPEC,<sup>1</sup> ASLAM H. ANIS,<sup>2</sup> JOLANDA CIBERE,<sup>1</sup> AND CHARLIE H. GOLDSMITH<sup>3</sup>



Table 4. RRs and 95% CIs of specific cardiovascular diseases for osteoarthritis cases by age and sex\*

Outcome	Total, RR (95% CI)	Men, RR (95% CI)		Women, RR (95% CI)	
		Age <65 years	Age ≥65 years	Age <65 years	Age ≥65 years
IHD					
Unadjusted	1.49 (1.37–1.63)	1.17 (1.00–1.37)	1.41 (1.17–1.69)	1.94 (1.61–2.34)	1.54 (1.31–1.82)
Adjusted	1.30 (1.19–1.42)	1.07 (0.91–1.25)	1.33 (1.11–1.62)	1.66 (1.37–2.01)	1.45 (1.22–1.72)
CHF					
Unadjusted	1.43 (1.29–1.58)	1.47 (1.07–2.01)	1.28 (1.05–1.56)	1.56 (1.20–2.03)	1.25 (1.08–1.43)
Adjusted	1.15 (1.04–1.28)	1.35 (0.98–1.86)	1.25 (1.02–1.54)	1.29 (1.00–1.68)	1.20 (1.03–1.39)
MI					
Unadjusted	1.20 (1.09–1.32)	1.19 (0.99–1.42)	1.12 (0.92–1.36)	1.17 (0.93–1.48)	1.14 (0.97–1.35)
Adjusted	1.02 (0.92–1.12)	1.06 (0.88–1.28)	1.11 (0.91–1.36)	0.95 (0.75–1.21)	1.06 (0.89–1.26)
Stroke					
Unadjusted	1.15 (1.04–1.27)	1.10 (0.86–1.40)	0.95 (0.78–1.17)	1.34 (1.06–1.69)	1.07 (0.92–1.24)
Adjusted	0.96 (0.87–1.06)	0.99 (0.77–1.26)	0.96 (0.78–1.17)	1.13 (0.89–1.44)	1.02 (0.87–1.19)

\* RR = relative risk; 95% CI = 95% confidence interval; IHD = ischemic heart disease other than MI; CHF = congestive heart failure; MI = myocardial infarction.

# Disability and not osteoarthritis predicts cardiovascular disease: a prospective population-based cohort study

T A Hoeven,<sup>1,2</sup> M J G Leening,<sup>2,3</sup> P J Bindels,<sup>1</sup> M Castaño-Betancourt,<sup>2,4</sup> J B van Meurs,<sup>4</sup> O H Franco,<sup>2</sup> M Kavousi,<sup>2</sup> A Hofman,<sup>2</sup> M A Ikram,<sup>2,5,6</sup> J C M Witteman,<sup>2</sup> S M Bierma-Zeinstra<sup>1,7</sup>



**Table 1** Baseline characteristics of the study population

Variable	All (n=4648)	Knee OA* (n=336)	Hip OA* (n=134)	Hand OA* (n=339)
Age, years	67.6±7.9	71.0±8.2	72.0±7.7	69.8±7.6
Male gender, %	39	21	15	13
Body mass index, kg/m <sup>2</sup>	26.3±3.6	28.2±4.1	27.4±3.9	27.2±4.1
Cholesterol/HDL ratio	5.2±1.6	5.1±1.6	5.1±1.5	5.1±1.5
Diabetes, %	9	9	11	11
Current smoking, %	24	17	19	16
Hypertension, %	53	63	55	61
Disability, %	57	85	90	75
Radiographic knee OA†, %	21	100	19	53
Self-reported OA, %	18	56	63	19

Categorical variables are presented as percentages. Continuous variables are expressed as means and corresponding SDs.

\*Radiographic OA and reported complaints of the same joint during the last month.

†Kellgren–Lawrence score ≥2 in at least one joint.

HDL, high density lipoprotein; OA, osteoarthritis.



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**Table 2** Knee osteoarthritis and risk of incident cardiovascular disease

	HR (95% CI) Total CVD (n=1230)	p Value	HR (95% CI) Hard CVD (n=889)	p Value
<b>Radiographic OA*</b>				
Model 1†	1.00 (0.87 to 1.15)	0.96	1.03 (0.88 to 1.21)	0.72
Model 2‡	0.99 (0.86 to 1.15)	0.92	0.99 (0.84 to 1.17)	0.91
<b>Clinical OA§</b>				
Model 1†	1.08 (0.88 to 1.33)	0.45	0.99 (0.77 to 1.28)	0.95
Model 2‡	1.09 (0.88 to 1.34)	0.43	0.96 (0.75 to 1.24)	0.76
<b>Self-reported OA</b>				
Model 1†	1.08 (0.93 to 1.24)	0.32	1.07 (0.94 to 1.21)	0.33
Model 2‡	1.09 (0.94 to 1.26)	0.26	1.09 (0.95 to 1.24)	0.24

Total CVD=myocardial infarction, surgical or percutaneous coronary revascularisation, coronary mortality and stroke (ischaemic and haemorrhagic). Hard CVD=myocardial infarction, ischaemic stroke and coronary mortality.

\*Kellgren–Lawrence score  $\geq 2$  in at least one joint.

†Adjusted for age and sex.

‡Adjusted for age, sex, body mass index, diabetes, hypertension, total cholesterol/HDL cholesterol ratio and smoking.

§Kellgren–Lawrence score  $\geq 2$  and complaints in the same joint during the last month.

CVD, cardiovascular disease; OA, osteoarthritis.

## Disability and not osteoarthritis predicts cardiovascular disease: a prospective population-based cohort study

T A Hoeven,<sup>1,2</sup> M J G Leening,<sup>2,3</sup> P J Bindels,<sup>1</sup> M Castaño-Betancourt,<sup>2,4</sup> J B van Meurs,<sup>4</sup> O H Franco,<sup>2</sup> M Kavousi,<sup>2</sup> A Hofman,<sup>2</sup> M A Ikram,<sup>2,5,6</sup> J C M Witteman,<sup>2</sup> S M Bierma-Zeinstra<sup>1,7</sup>



**Table 3** Disability and risk of incident cardiovascular disease

	HR (95% CI)		HR (95% CI)	
	Total CVD (n=1230)	p Value	Hard CVD (n=889)	p Value
<b>Disability</b>				
Model 1*	1.30 (1.15 to 1.46)	<0.001	1.29 (1.12 to 1.49)	0.001
Model 2†	1.26 (1.12 to 1.42)	<0.001	1.22 (1.06 to 1.41)	0.007
<b>LL disability</b>				
Model 1*	1.22 (1.08 to 1.38)	0.002	1.26 (1.09 to 1.45)	0.002
Model 2†	1.19 (1.05 to 1.34)	0.008	1.18 (1.02 to 1.37)	0.03

Total CVD=myocardial infarction, surgical or percutaneous coronary revascularisation, coronary mortality and stroke (ischaemic and haemorrhagic). Hard CVD=myocardial infarction, ischaemic stroke and coronary mortality.

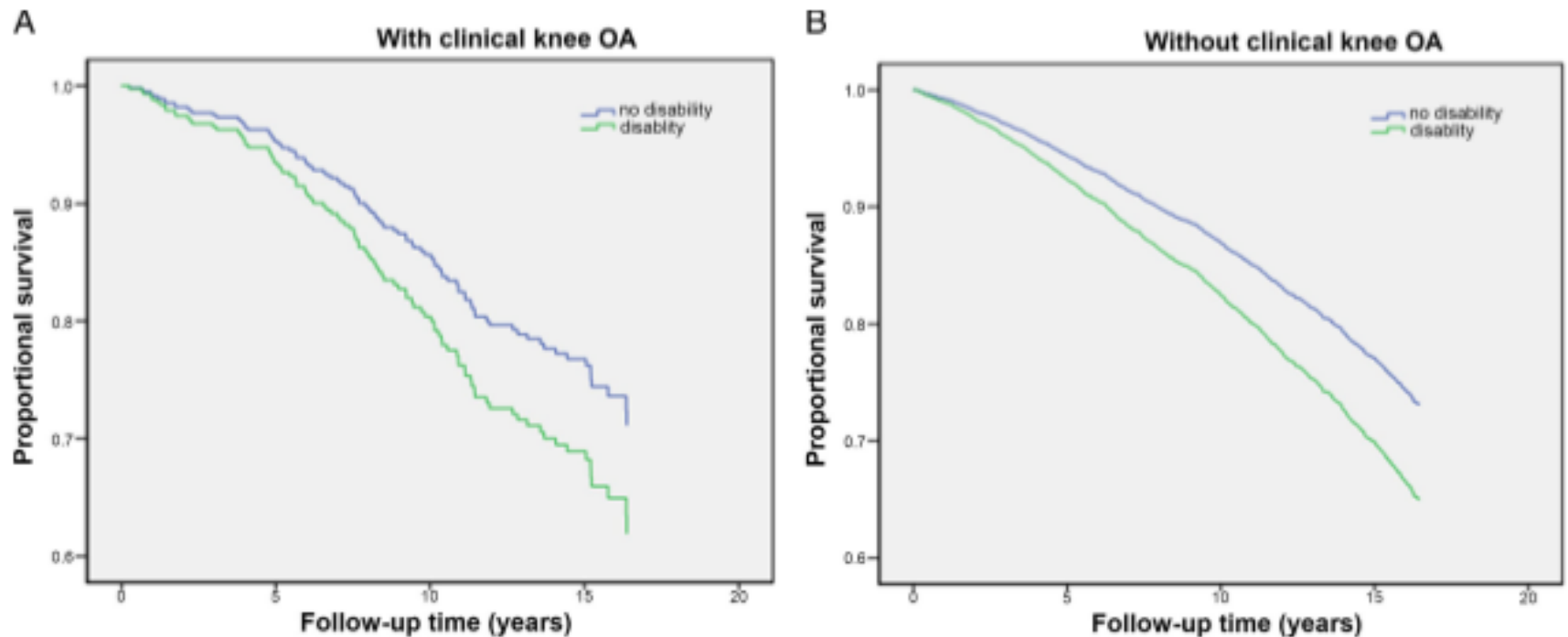
\*Adjusted for age and sex.

†Adjusted for age, sex, body mass index, diabetes, hypertension, total cholesterol/HDL cholesterol ratio and smoking.

CVD, cardiovascular disease; HDL, high-density lipoprotein; LL, lower limb.

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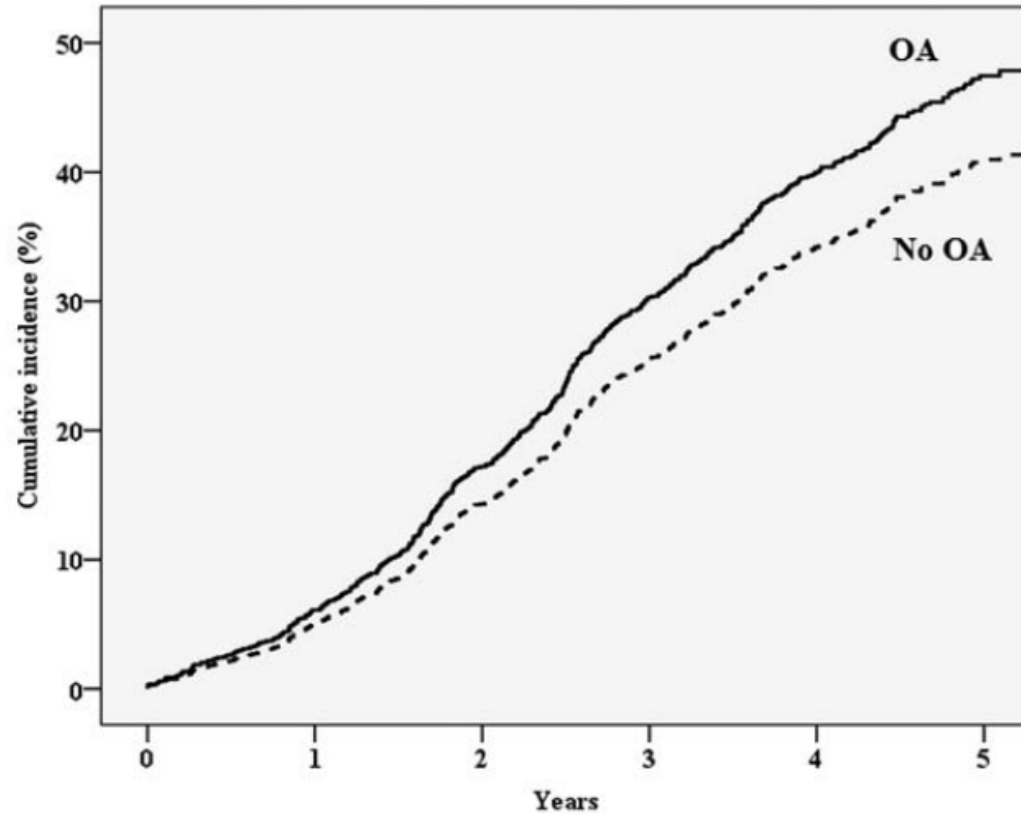


**Figure 1** (A, B) Age and gender adjusted cardiovascular disease-free survival curves for non-disabled and disabled participants in participants with clinical knee osteoarthritis (OA).

Association of Osteoarthritis With Increased Risk of  
Cardiovascular Diseases in the Elderly

Findings From the Progetto Veneto Anziano Study Cohort

Nicola Veronese,<sup>1</sup> Caterina Trevisan,<sup>1</sup> Marina De Rui,<sup>1</sup> Francesco Bolzetta,<sup>1</sup> Stefania Maggi,<sup>2</sup>  
Sabina Zambon,<sup>3</sup> Estella Musacchio,<sup>1</sup> Leonardo Sartori,<sup>1</sup> Egle Perissinotto,<sup>1</sup> Gaetano Crepaldi,<sup>2</sup>  
Enzo Manzato,<sup>3</sup> and Giuseppe Sergi<sup>1</sup>



No OA	822	743	630	527	437	123
OA	1336	1173	969	760	633	227

**Figure 1.** Cumulative incidence of cardiovascular disease according to the presence or absence of osteoarthritis (OA) at baseline in

(hazard ratio 1.22, 95% confidence interval 1.02-1.49;  $p = 0.04$ )

Mean follow-up 4 years, previous CV events excluded

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**Table 2.** Associations of OA with the onset of CVD events in all study participants at follow-up\*

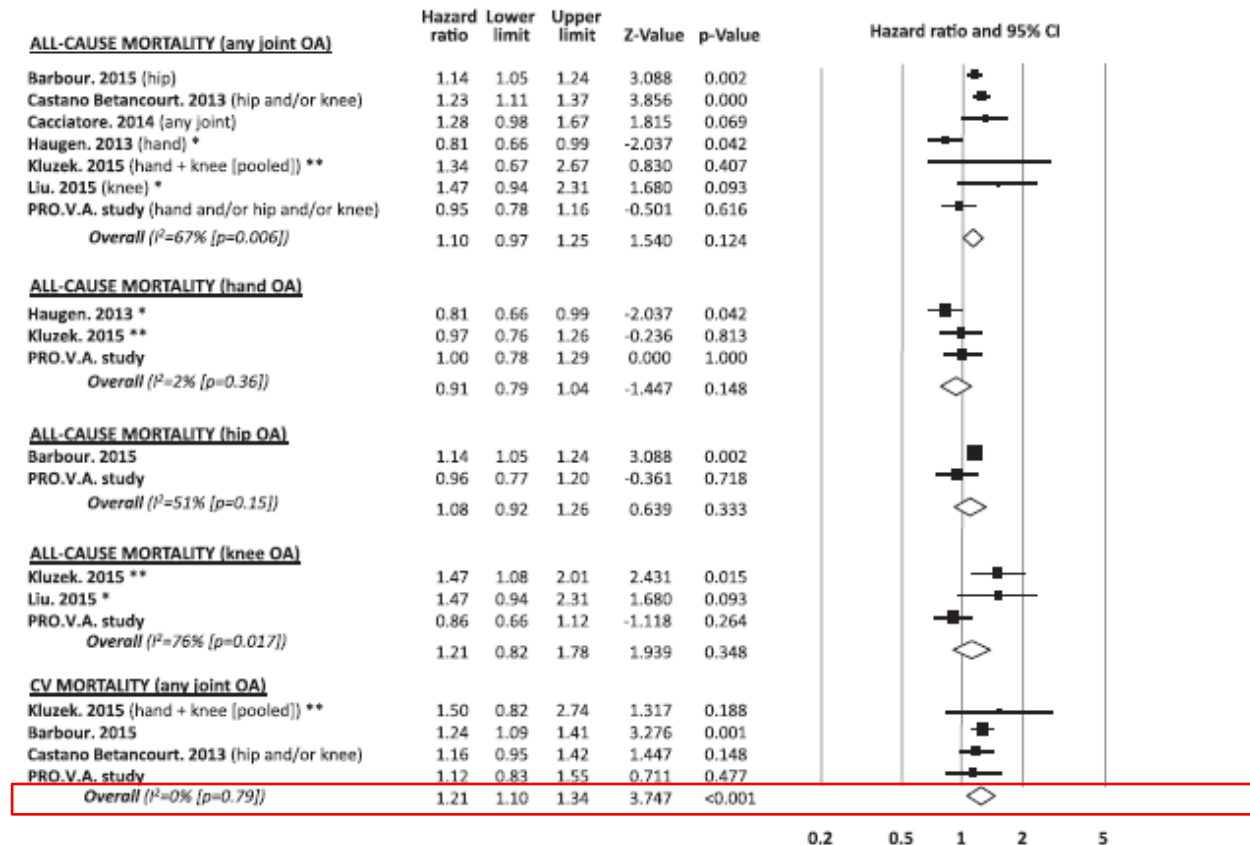
OA subset	No. of CVD events	No. of participants	Unadjusted model		Fully adjusted model	
			HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
No OA	340	822	Referent	–	Referent	–
Presence of OA	638	1,336	1.42 (1.16–1.76)	0.001	1.22 (1.02–1.49)	0.04
Hand OA	346	806	1.20 (0.97–1.48)	0.09	1.16 (0.82–2.10)	0.11
Hip OA	311	609	1.72 (1.39–2.13)	<0.0001	1.29 (1.01–1.64)	0.04
Knee OA	469	949	1.64 (1.34–1.99)	<0.0001	1.30 (1.05–1.62)	0.02
Monoarticular OA	283	593	1.45 (1.16–1.81)	0.001	1.23 (1.04–1.84)	0.03
Polyarticular OA†	355	742	1.53 (1.24–1.88)	<0.0001	1.31 (1.04–1.64)	0.02

\* Associations with cardiovascular disease (CVD) events are presented as the hazard ratio (HR) with 95% confidence interval (95% CI). Those without osteoarthritis (OA) at any site were the referent group



Nicola Veronese, MD<sup>a,1</sup>, Emanuele Cereda, MD<sup>b,1</sup>, Stefania Maggi, MD<sup>c</sup>,  
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 Michael Hurley, PhD<sup>i</sup>, Trevor Thompson, PhD<sup>k</sup>, Enzo Manzato, MD<sup>a,c</sup>, Giuseppe Sergi, MD<sup>a</sup>,  
 Brendon Stubbs, PhD<sup>l,m,\*</sup>

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0.2 0.5 1 2 5



# Cardiovascular Risk factors in OA

- Age
- Classical Cardiovascular Risk factors: hypertension, DM, overweight.
- Immobility
- Drugs: use of NSAIDs/COXIBs
- Low Grade inflammation?

# Changes in Mortality Patterns Following Total Hip or Knee Arthroplasty Over the Past Two Decades



A Nationwide Cohort Study

Arief Lalmohamed,<sup>1</sup> Peter Vestergaard,<sup>2</sup> Anthonius de Boer,<sup>3</sup> Hubertus G. M. Leufkens,<sup>3</sup>  
Tjeerd P. van Staa,<sup>4</sup> and Frank de Vries<sup>5</sup>

**Table 2.** Baseline characteristics of the 40,642 patients who underwent TKA, stratified by calendar period\*

	1989–1991 (n = 4,009)	1992–1996 (n = 7,220)	1997–2002 (n = 10,861)	2003–2007 (n = 18,552)
Followup, mean $\pm$ SD years	11.8 $\pm$ 5.6	10.5 $\pm$ 4.1	7.1 $\pm$ 2.2	2.4 $\pm$ 1.5
Age, mean $\pm$ SD years	70.2 $\pm$ 9.5	69.6 $\pm$ 10.0	68.1 $\pm$ 10.5	67.2 $\pm$ 10.4
Male, %	27.8	30.9	35.6	38.5
Hospital stay for TKA, mean $\pm$ SD days	17.6 $\pm$ 11.2	15.7 $\pm$ 7.5	12.9 $\pm$ 6.9	7.6 $\pm$ 4.9
Comorbidities, % <sup>†</sup>				
Previous acute MI	3.2	4.3	4.4	4.7
COPD	2.7	4.0	5.6	7.8
Cerebrovascular disease	3.6	4.3	5.9	7.1
Diabetes mellitus	2.6	3.3	4.0	6.7
Heart failure	2.0	2.5	3.1	3.6

\* TKA = total knee arthroplasty; MI = myocardial infarction; COPD = chronic obstructive pulmonary disease.

<sup>†</sup> More than 6 weeks before surgery.



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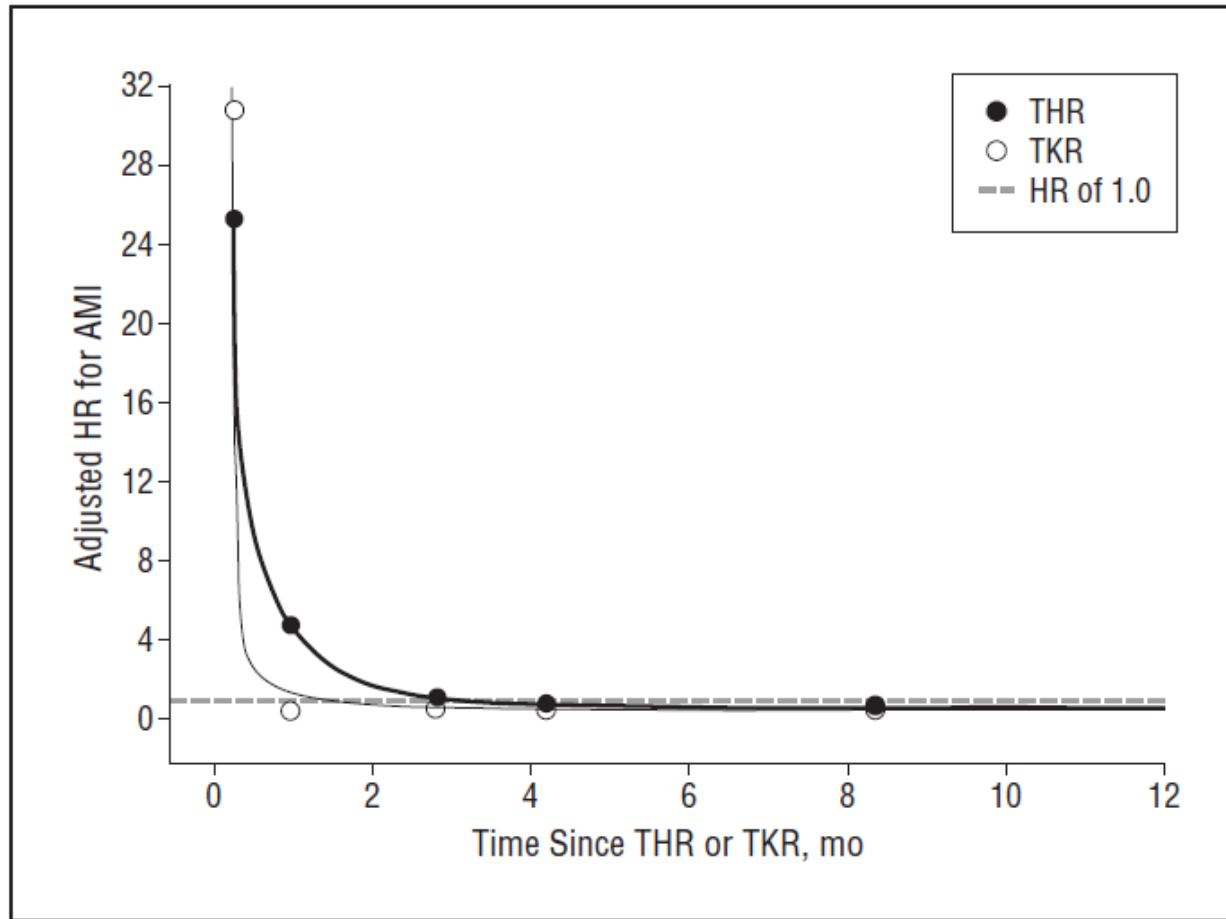
**Table 3.** Sixty-day all-cause and disease-specific mortality rate ratios following THA, stratified by calendar period, age, and sex\*

	1989–1991 (referent category)	Adjusted RR (95% CI) <sup>†</sup>			<i>P</i> for trend <sup>‡</sup>
		1992–1996	1997–2002	2003–2007	
General population	1.00	1.02 (0.96–1.09)	0.93 (0.87–0.99)	0.72 (0.67–0.77)	<0.01
Patients undergoing THA	1.00	0.66 (0.46–0.94)	0.51 (0.36–0.72)	0.40 (0.28–0.58)	<0.01
By age, years					
18–64	1.00	1.07 (0.31–3.67)	0.54 (0.15–1.92)	0.77 (0.24–2.47)	0.45
65–79	1.00	0.56 (0.33–0.92)	0.42 (0.25–0.69)	0.28 (0.16–0.48)	<0.01
≥80	1.00	0.72 (0.41–1.27)	0.62 (0.36–1.06)	0.48 (0.27–0.83)	0.24
By sex					
Male	1.00	0.63 (0.39–1.02)	0.53 (0.34–0.84)	0.44 (0.27–0.70)	<0.01
Female	1.00	0.70 (0.41–1.19)	0.47 (0.28–0.80)	0.36 (0.20–0.62)	<0.01
By cause of death					
Acute myocardial infarction	1.00	0.55 (0.27–1.12)	0.46 (0.23–0.90)	0.27 (0.13–0.58)	<0.01
Venous thromboembolism	1.00	0.35 (0.13–0.95)	0.25 (0.09–0.67)	0.04 (0.01–0.31)	<0.01
Pneumonia	1.00	1.02 (0.30–3.50)	0.24 (0.05–1.11)	0.15 (0.03–0.81)	<0.01
Gastrointestinal bleeding	1.00	–	–	–	–
Ischemic stroke	1.00	0.09 (0.01–0.75)	0.19 (0.05–0.73)	0.13 (0.03–0.61)	<0.01
Hemorrhagic stroke	1.00	0.15 (0.02–1.32)	0.18 (0.03–1.01)	0.07 (0.01–0.64)	0.02
None of the above	1.00	1.21 (0.67–2.17)	0.96 (0.55–1.70)	0.93 (0.53–1.63)	0.57

# Timing of Acute Myocardial Infarction in Patients Undergoing Total Hip or Knee Replacement

*A Nationwide Cohort Study*

Arief Lalmohamed, PharmD; Peter Vestergaard, MD, PhD, DMSc; Corinne Klop, PharmD; Erik Lerkevang Grove, MD, PhD; Anthonius de Boer, MD, PhD; Hubertus G. M. Leufkens, PhD; Tjeerd P. van Staa, MD, PhD; Frank de Vries, PharmD, PhD

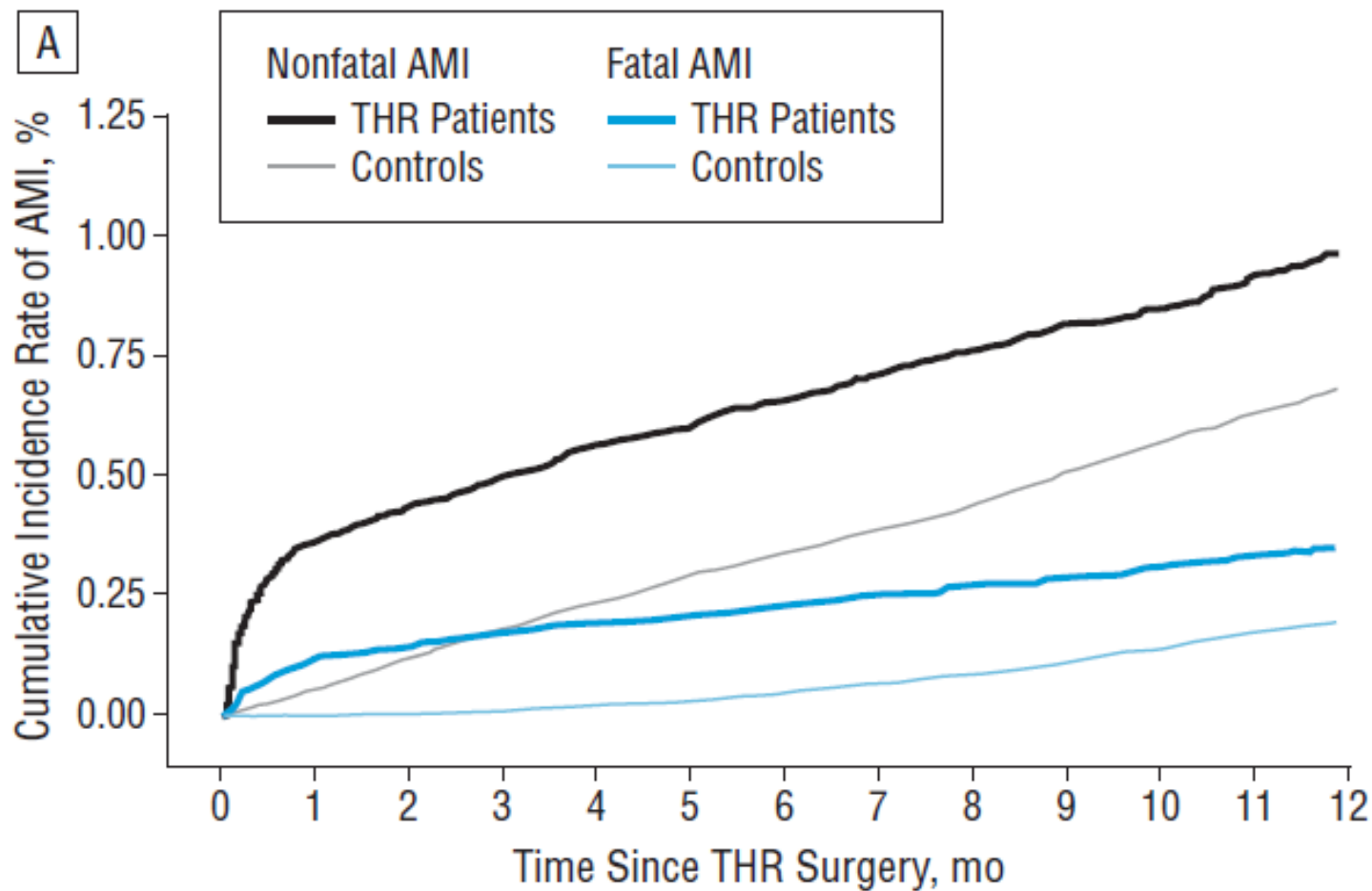


**Figure 1.** Adjusted hazard ratios (HRs) for acute myocardial infarction (AMI). THR indicates total hip replacement; TKR, total knee replacement.

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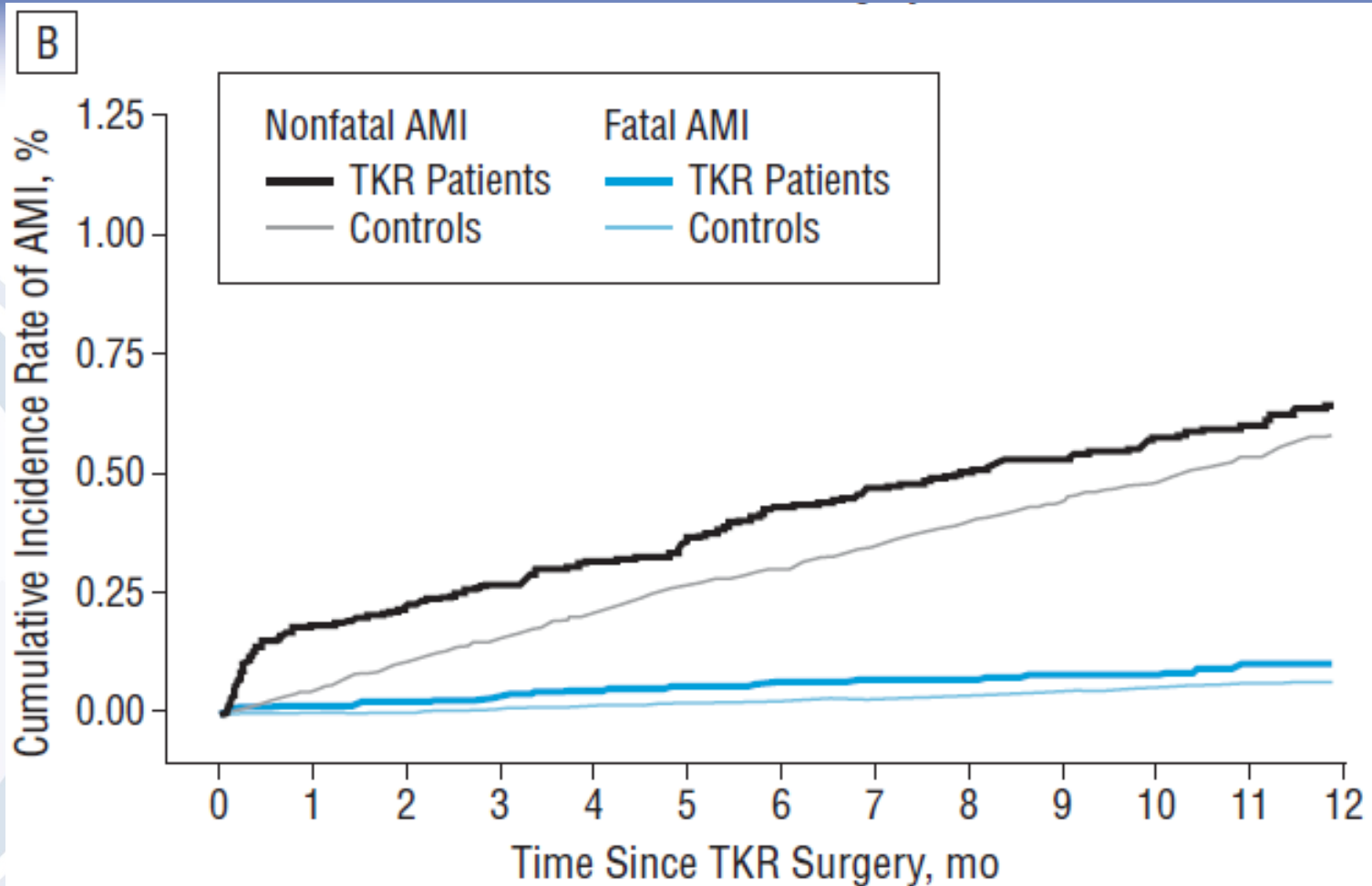
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# Cardiovascular risk in young women



Suppose a young woman suffers from SLE, which has a relative risk of Cardio Vascular Events of 9.  
Her background risk is low!

# Cardiovascular risk and mortality in the elderly



Mortality risk because of osteoarthritis is only 10-30% higher,  
But background risk in these patients is high!

# Summary, 1



Cardiovascular Risk is 10-30% elevated in  
Osteoarthritis.

This is substantial, since osteoarthritis predominantly  
occurs in the elderly.



## Summary, 2



Mechanisms of elevated cardiovascular risk not fully elucidated, but risk factors seem to play a role.

High Age

Comorbidity, including cardiovascular disease and  
overweight

Low Grade Inflammation

Immobility

Drugs-NSAIDs





## Risk factors for CVE in Osteoarthritis

High Age

Low Grade Systemic Inflammation

Comorbidity, including cardiovascular disease and  
overweight

Immobility

Drugs-NSAIDs

In Red: Modifiable factors





Thank you for your attention!

