New therapies in Osteoporosis, Sarcopenia, Frailty and Osteoarthritis

Jonathan D. Adachi MD, FRCPC
Actavis Chair for Better Bone Health in Rheumatology
Professor, Department of Medicine
Michael G. DeGroote School of Medicine
McMaster University

Disclosure of Commercial Support

- **Potential for conflict(s) of interest:**
  - Jonathan D. Adachi has received payment/funding from Amgen whose product is being discussed in this program.
  - Amgen developed romosozumab a product that will be discussed in this program.

Mitigating Potential Bias

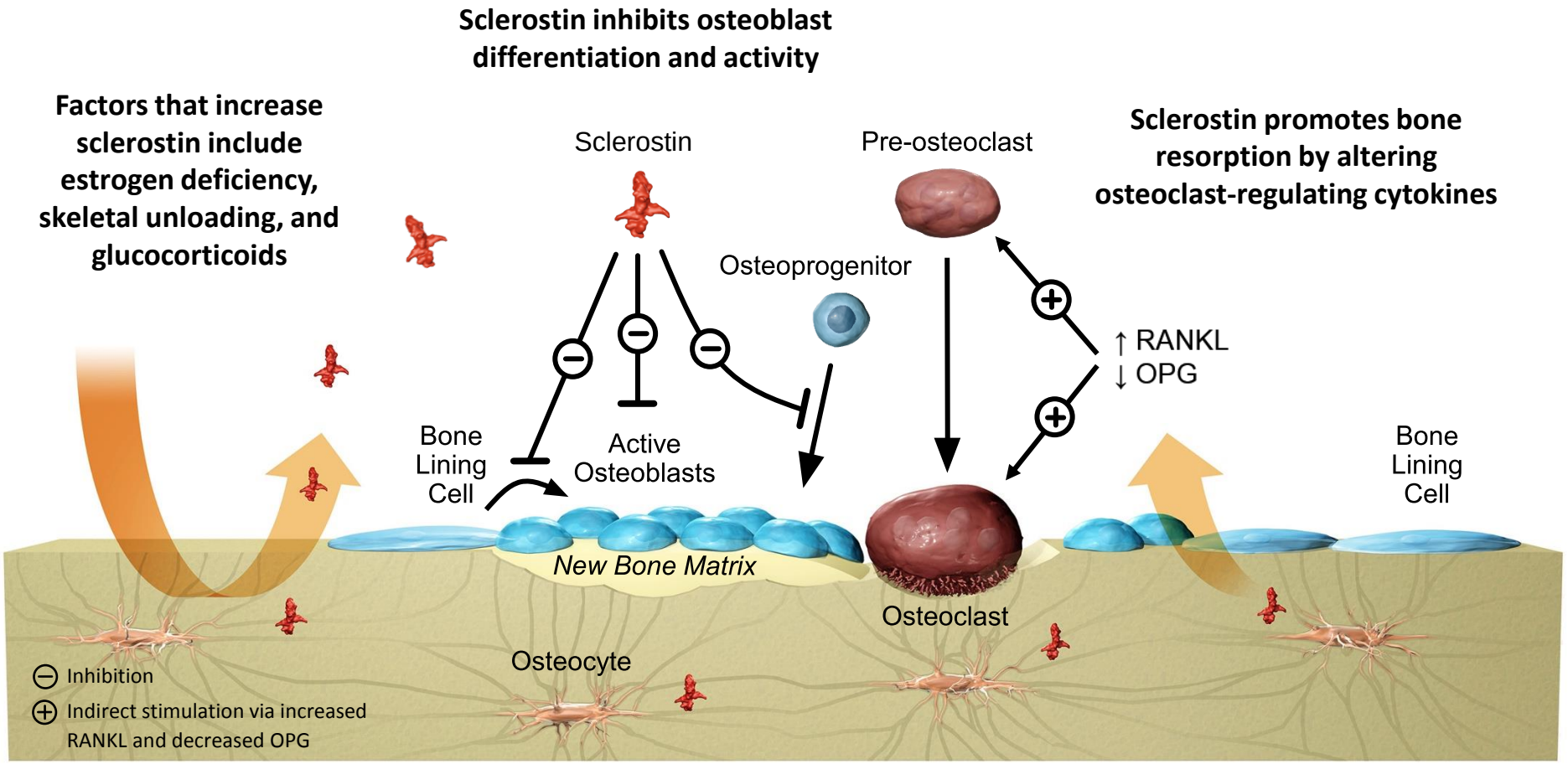
- Potential sources of bias identified in slides 1, have been mitigated by limiting evidence of benefit and side effects to a pivotal RCT

Objectives

- Understand the role of sclerostin in bone metabolism
- Review the results of anti-sclerostin therapy in osteoporosis
- Understand the role of diet and exercise in sarcopenia, frailty and osteoarthritis

What is the role of sclerostin?

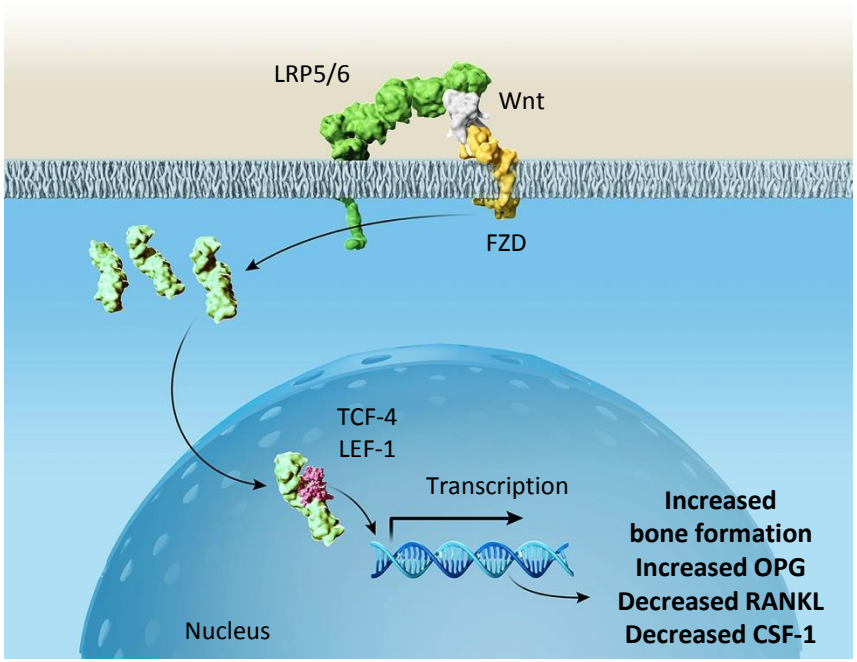
Sclerostin, primarily secreted by osteocytes, inhibits bone formation and increases bone resorption



Wijenayaka AR, et al. *PLoS One*. 2011;6(10):e25900; Taylor S, et al. Bone 2016;84:148-159; Nioi P, et al. *J Bone Miner Res*. 2015;30:1457-1467.

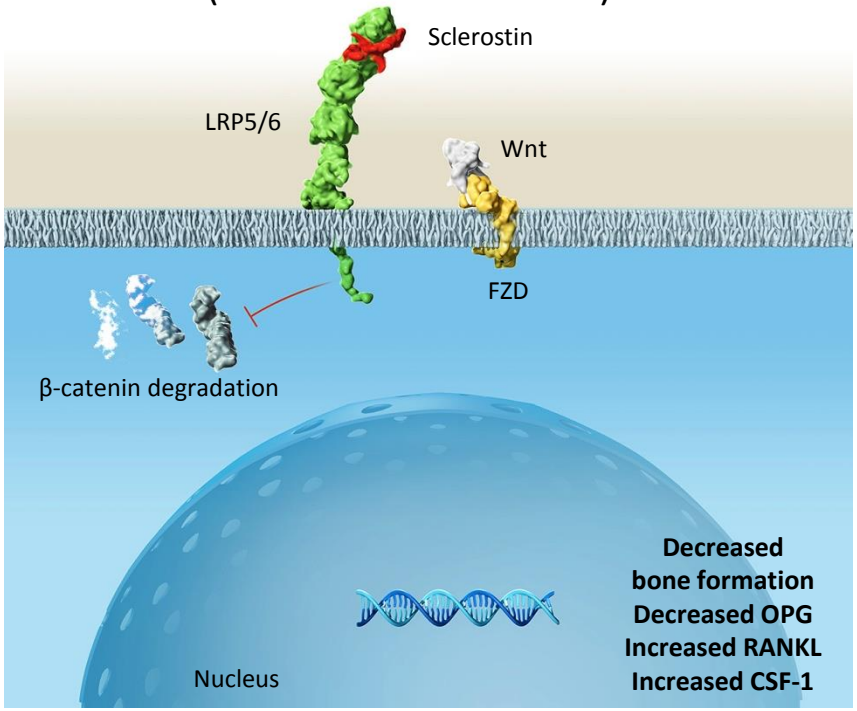
Sclerostin decreases bone formation and increases bone resorption by inhibiting Wnt signaling in the osteoblast lineage

Effects of Wnt Signaling in Bone
(Absence of Sclerostin)



Wnts activate the β-catenin pathway to increase bone formation and decrease bone resorption

Absence of Wnt Signaling in Bone
(Presence of Sclerostin)

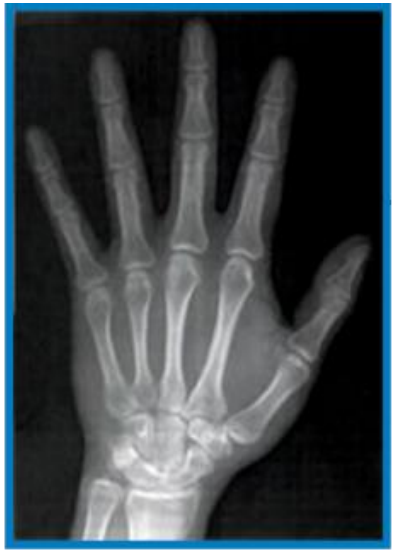


Sclerostin inhibits activation of the β-catenin pathway to decrease bone formation and promote bone resorption

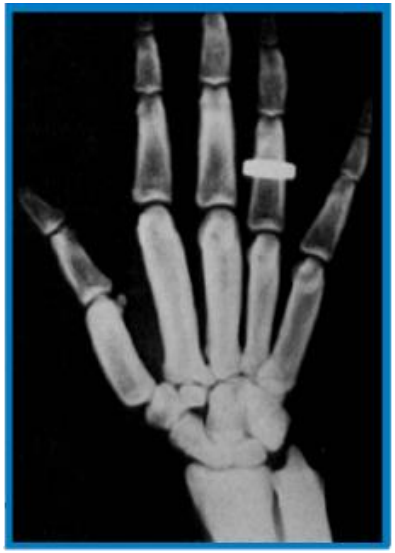
Li X, et al. *J Biol Chem.* 2005;280:19883-19887; Semënov M, et al. *J Biol Chem.* 2005; 280:26770-26775;
Glass D, et al. *Dev Cell.* 2005;8:751-764; Taylor S, et al. *Bone* 2016;84:148-159; Wijenayaka AR, et al. *PLoS One*. 2011;6(10):e25900.

Humans with genetic sclerostin deficiency have high bone mass

Normal[1]



Sclerosteosis[2]

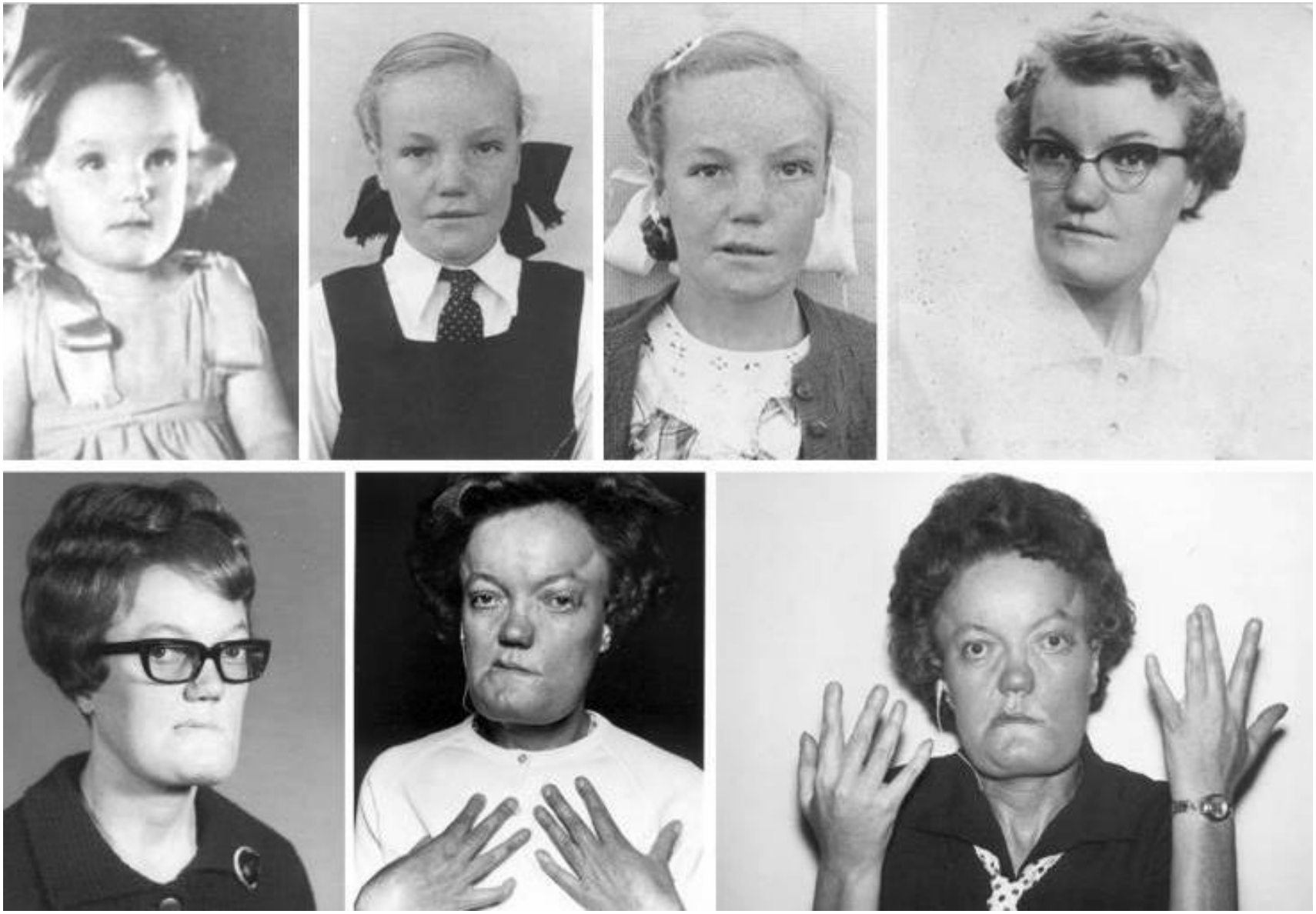


Sclerosteosis:

- Rare autosomal recessive disease[3]
- Mutations in the *SOST* gene result in the absence of functional sclerostin[4]
- Results in high bone mass with anecdotal evidence of fracture resistance[5]
- Heterozygous carriers have a milder high bone mass phenotype[6]
- In *SOST* knockout mice it was confirmed that high bone mass with sclerostin deficiency leads to greater bone strength[7]

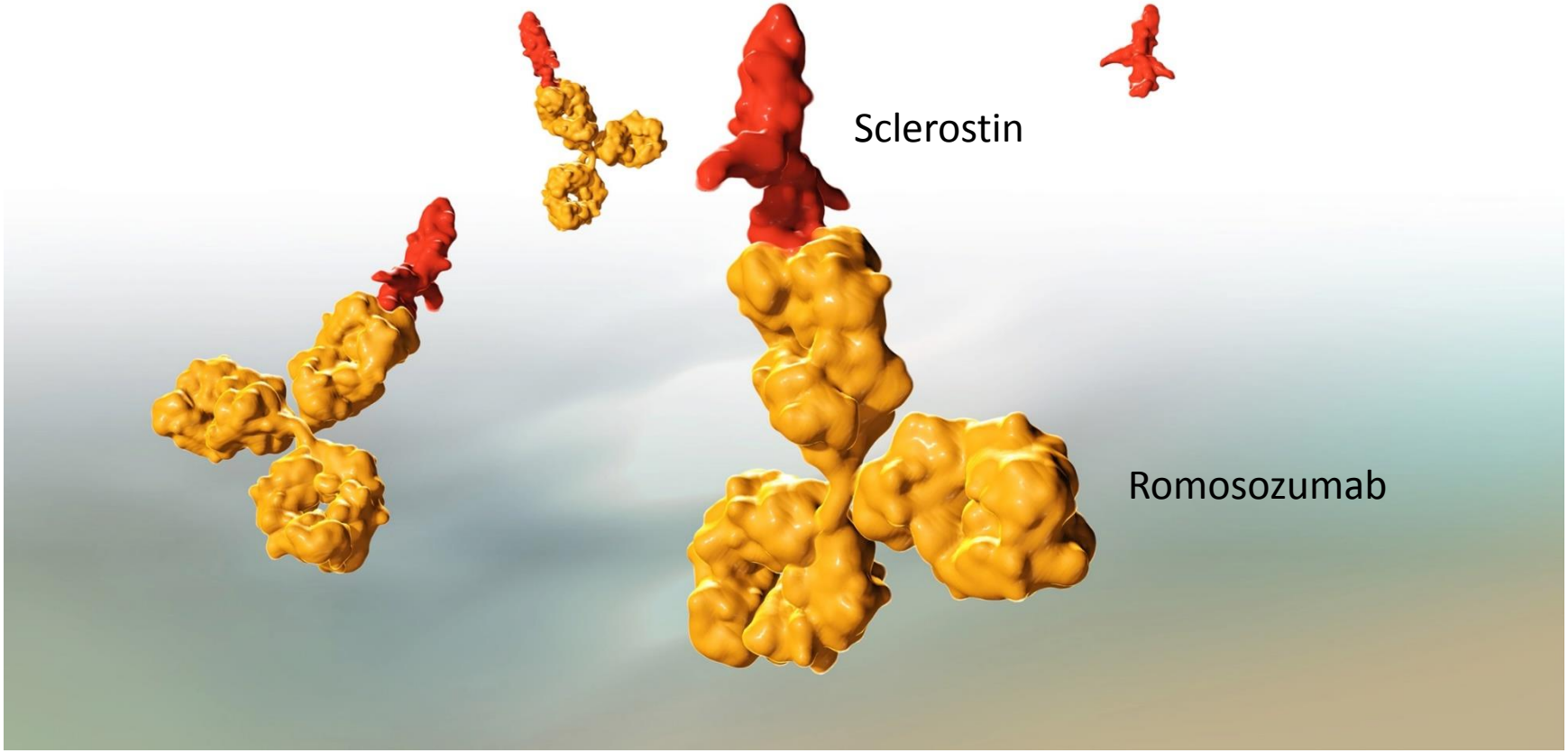
Genetically-induced reductions in sclerostin increase bone mass and bone strength, making sclerostin an attractive therapeutic target

1. Hochberg MC, et al. *Rheumatology* 4th Ed. Philadelphia, PA; Elsevier 2007: 318; 2. Beighton P, *Clin Genet* 1984;25:175-181;
3. Balemans W and van Hul W; *J Musculoskel Neuronal Interact* 2006;6:355-356;
4. Brunkow ME, et al. *Am J Hum Genet*. 2001;68:577-589; 5. Beighton P. *J Med Genet* 1988;25:200-203;
6. Gardner J, et al. *J Clin Endocrinol Metab* 2005;90:6392-6395; 7. Li X, et al. *J Bone Miner Res* 2008;23:860-869.



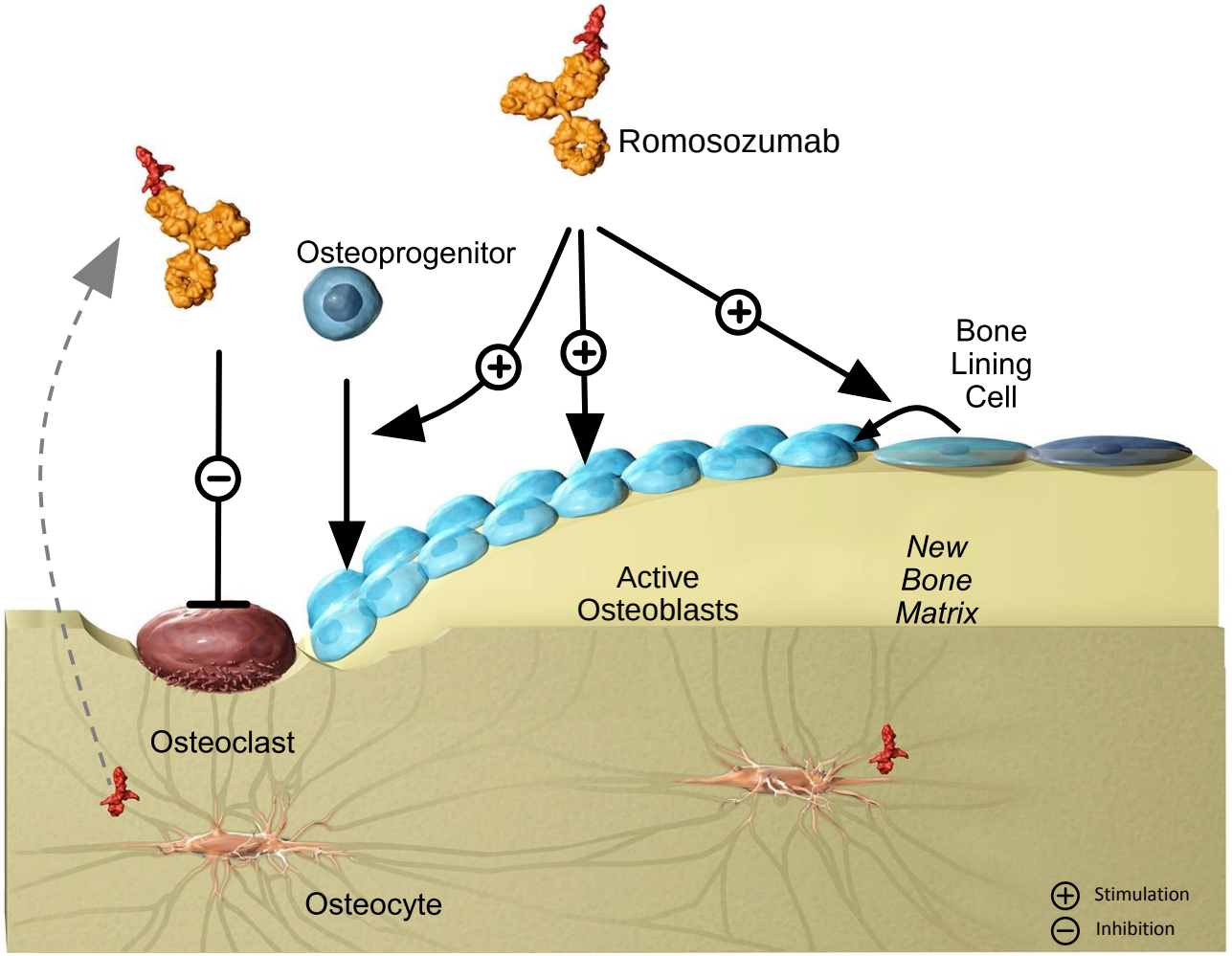
Calcif Tissue Int. 2010 Aug; 87(2): 99–107.

Romosozumab is a humanized monoclonal antibody that binds and inhibits sclerostin



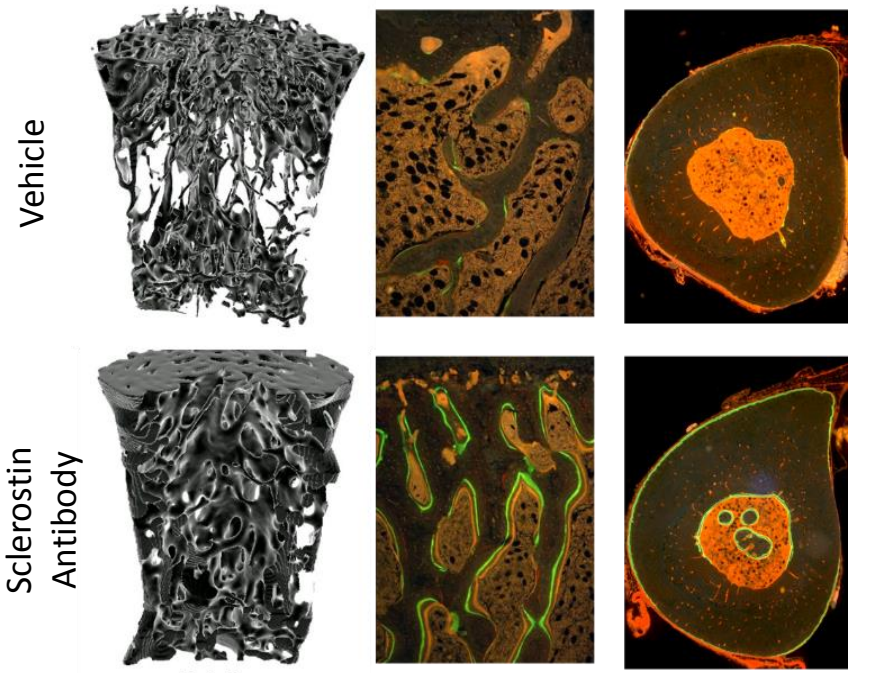
Amgen, Data on file (CARC publication, supplemental data); Paszty C, Robinson MK, Graham K, et al, inventors; UCB SA, Amgen Inc, assignees. US patent 7592429 B2. September 22, 2009.

Sclerostin inhibition by romosozumab increases bone formation and decreases bone resorption



Sclerostin antibody increased bone formation

Aged Rats Treated with Sclerostin Antibody[1]



Micro-computed tomography of vertebral trabecular bone

Fluorescence indicates trabecular bone formation

Fluorescence indicates periosteal and endocortical bone formation

In preclinical studies, sclerostin antibody:

- Increased activity of mature osteoblasts[2]
- Activated modeling-based bone formation by converting bone lining cells to osteoblasts[2,3]
- Recruited osteoblasts from osteoprogenitors[4]
- Increased bone formation on trabecular and cortical surfaces[3,4]
- Increased wall thickness in remodeling units[5]
- Rapidly increased bone formation markers[4]

In clinical studies, romosozumab:

- Rapidly increased bone formation markers[6]

1. Ke HZ, et al. Endocr Rev. 2012;33:747-783; 2. Nioi P, et al. *J Bone Miner Res*. 2015;30:1457-1467;
3. Ominsky MS, et al. *J Bone Miner Res*. 2014; 29:1424-1430; 4. Ominsky MS, et al. *Bone*. 2015;81:380–391;
5. Ominsky MS, et al. Abstract LB-MO0030, ASBMR annual meeting 2015. *J Bone Miner Res*. 30(Suppl 1):S503;
6. McClung MR, et al. *N Engl J Med*. 2014;370:412-420.

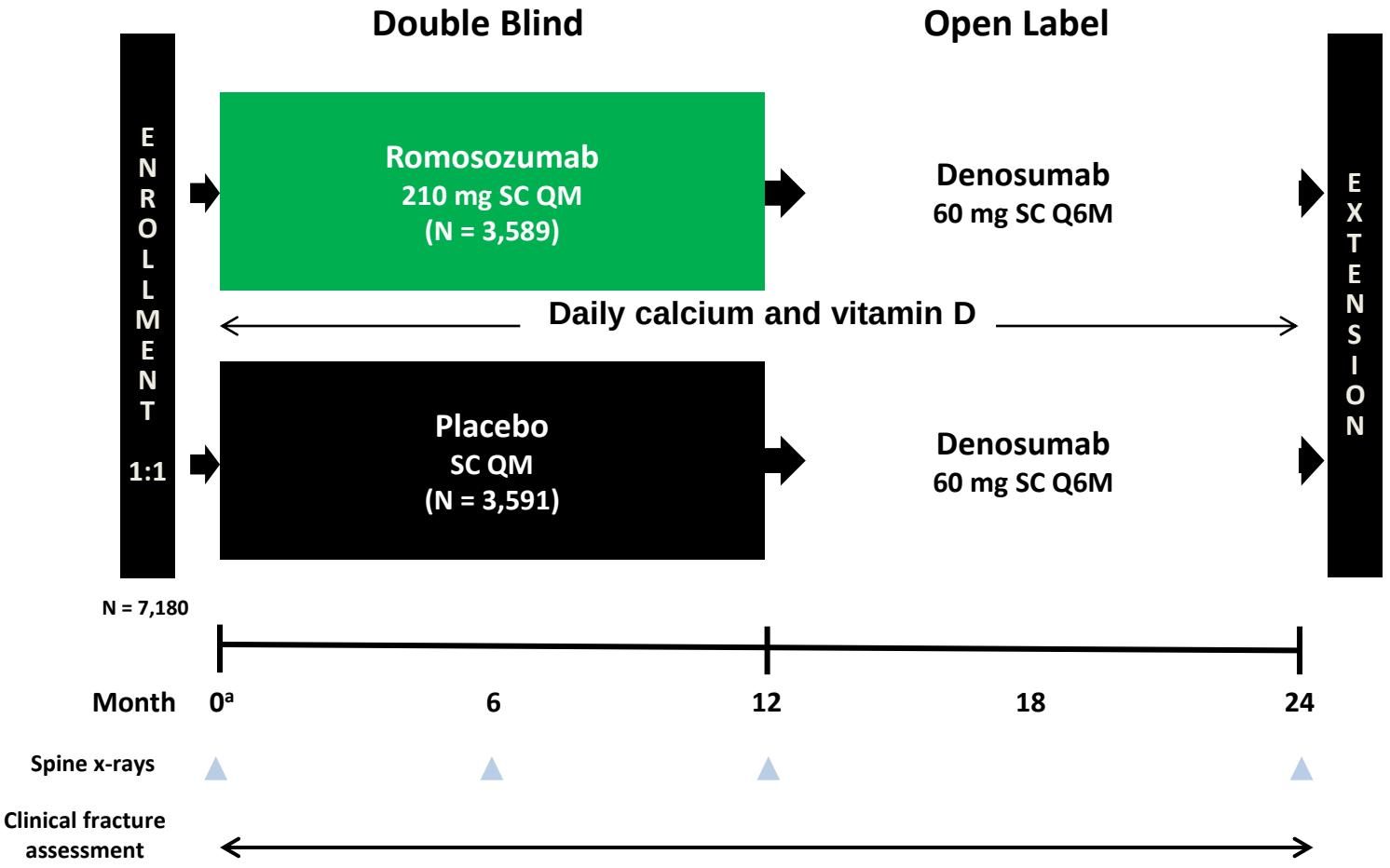
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Romosozumab Treatment in Postmenopausal Women with Osteoporosis

F. Cosman, D.B. Crittenden, J.D. Adachi, N. Binkley, E. Czerwinski, S. Ferrari, L.C. Hofbauer, E. Lau, E.M. Lewiecki, A. Miyauchi, C.A.F. Zerbini, C.E. Milmont, L. Chen, J. Maddox, P.D. Meisner, C. Libanati, and A. Grauer

Romosozumab FRAME Study Design

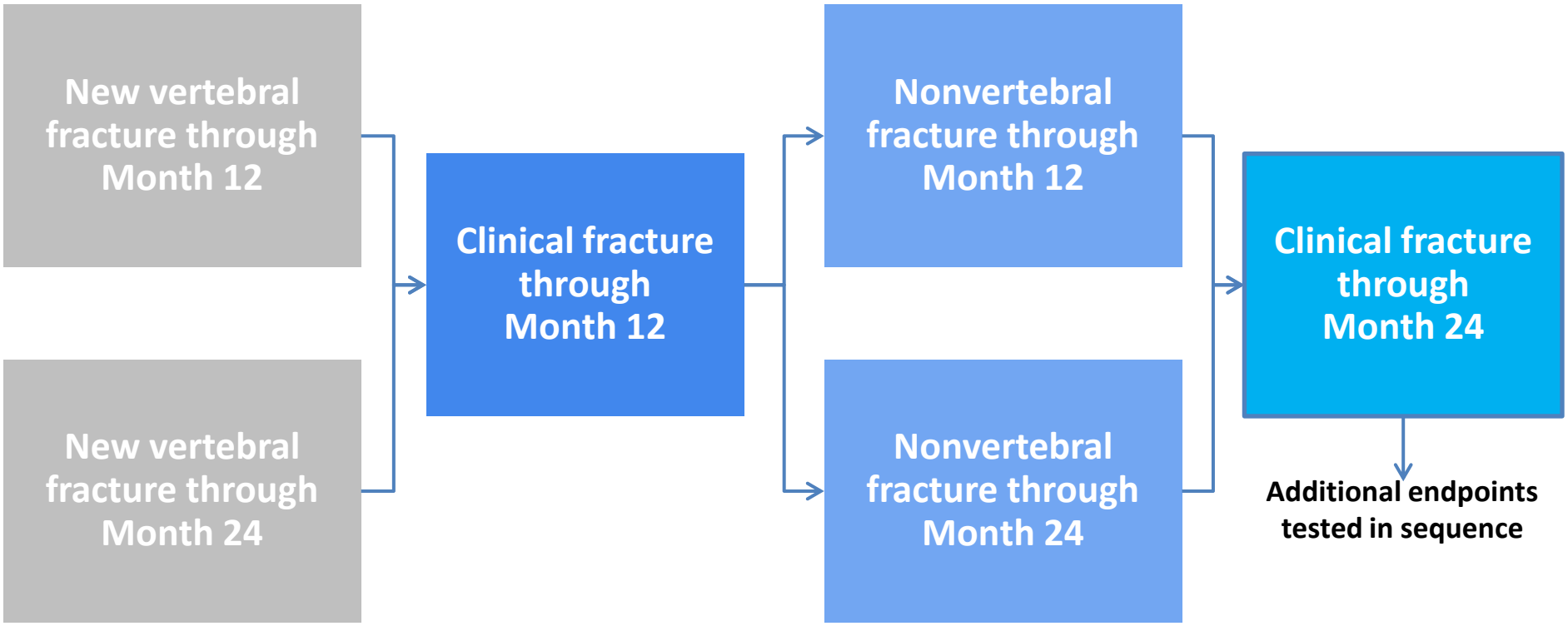


[a]Loading dose of 50,000–60,000 IU vitamin D

Key Eligibility Criteria and Endpoints

Inclusion Criteria	• Postmenopausal women age 55–90 years • BMD T-score ≤ –2.5 at the total hip or femoral neck
Exclusion Criteria	• BMD T-score ≤ –3.5 at the total hip or femoral neck • History of hip fracture or any severe or more than two moderate vertebral fractures • Recent osteoporosis therapy
Co-Primary Endpoints	• Subject incidence of new vertebral fracture through 12 and 24 months
Secondary Fracture Endpoints	• Subject incidence of clinical fracture, nonvertebral fracture, and other fracture categories through 12 and 24 months

Statistical Testing Sequence



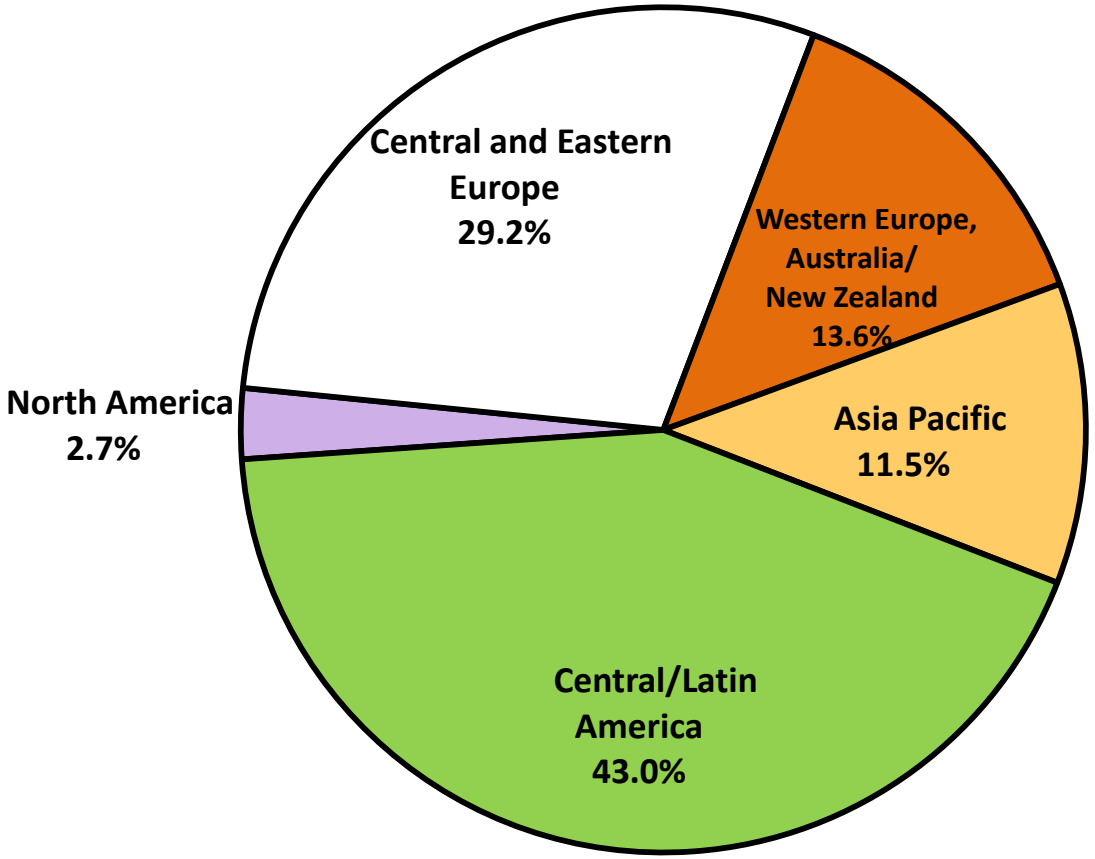
Co-Primary:
Need statistical significance (≤ 0.05) on both to proceed

Secondary:
Test at α = 0.05

Secondary:
Controlled by Hochberg[a] procedure;
if both *p*-values ≤ 0.05,
claim statistical significance on both;
if larger *p*-value > 0.05,
test smaller one at α = 0.025

[a]Hochberg Y. *Biometrika.* 1988;75:800-802.

Study Enrollment Geographic Region (Total N = 7,180)

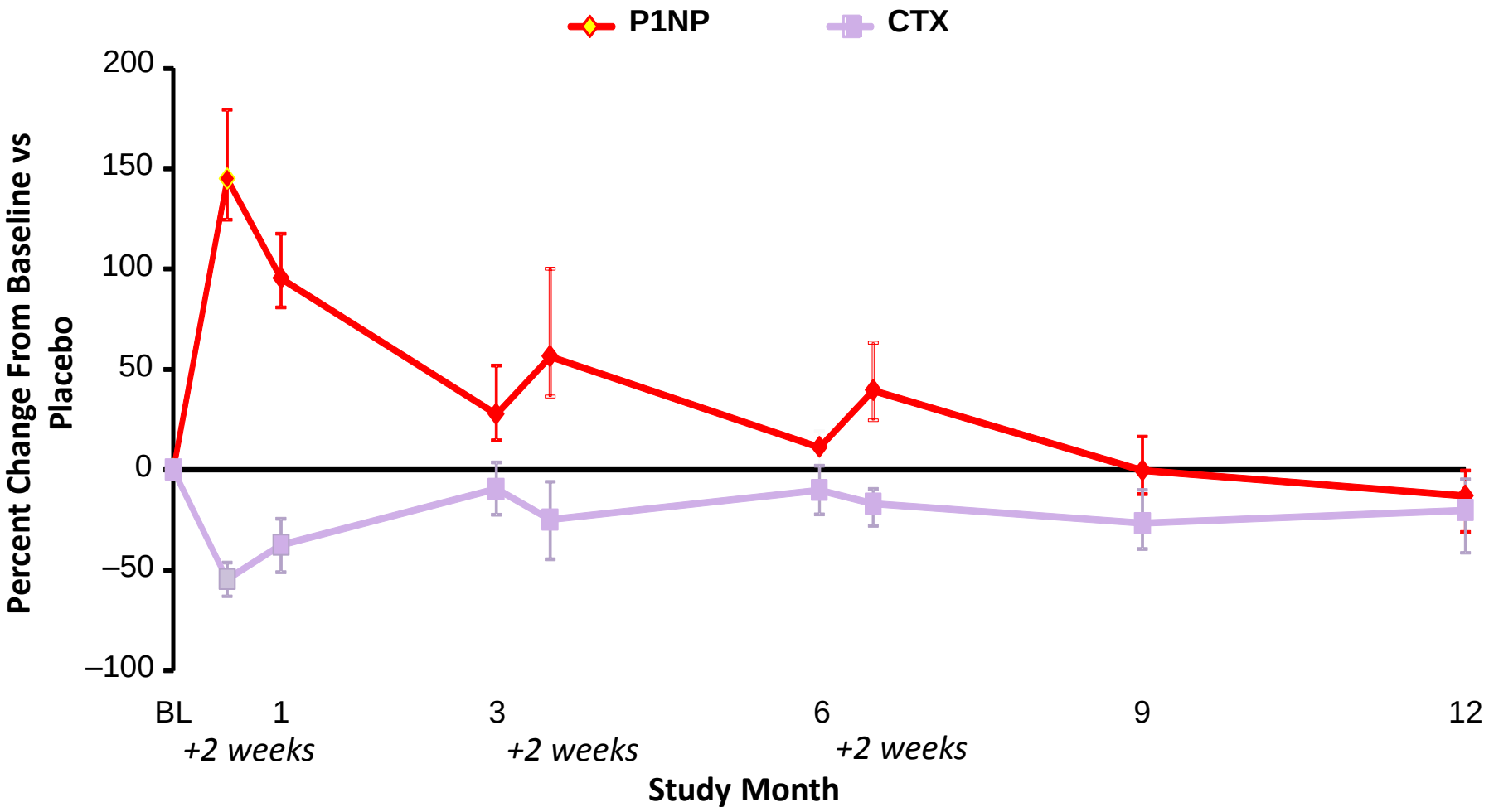


Baseline Characteristics and Subject Disposition

	Placebo (N = 3,591)	Romosozumab (N = 3,589)
Age, mean (SD), years	70.8 (6.9)	70.9 (7.0)
BMD T-score, mean (SD)		
Lumbar spine	–2.7 (1.0)	–2.7 (1.0)
Total hip	–2.5 (0.5)	–2.5 (0.5)
Prevalent vertebral fracture, %	18.0%	18.7%
Number of prevalent vertebral fractures, %		
1	13.8%	14.1%
≥ 2	4.1%	4.6%
Most severe vertebral fracture grade, %		
Mild	10.5%	10.5%
Moderate	7.3%	8.2%
Prior nonvertebral fracture on or after age 45, %	21.8%	21.7%
Completed 12-month double-blind period, %	**89%**	**89%**
Completed 24-month study period, %	84%	83%

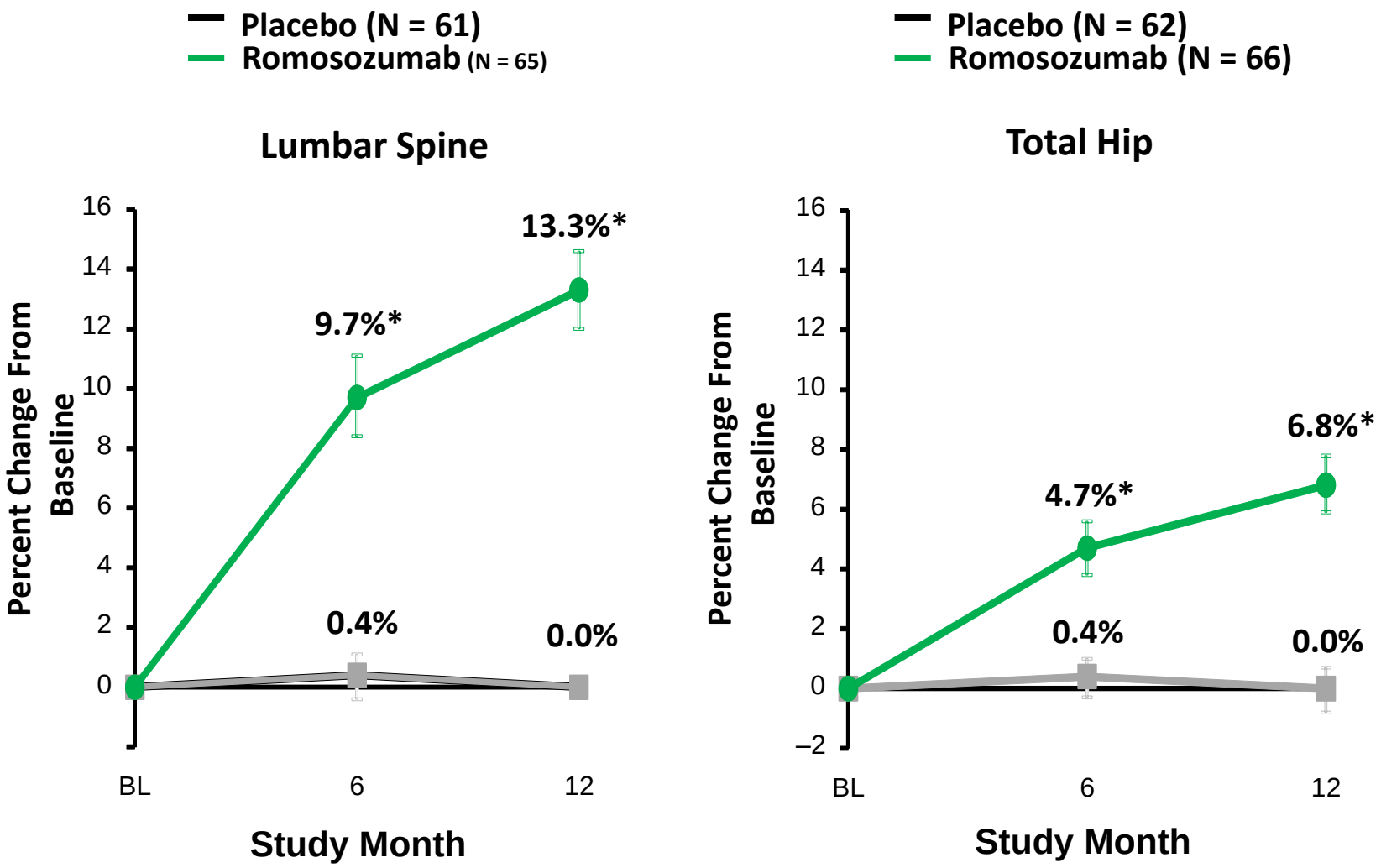
N = Number of subjects randomized. Percentages based on number of subjects randomized. Vertebral fracture grade based on Genant semiquantitative scale

Percent Change in Serum P1NP and CTX with Romosozumab Relative to Placebo Through Month 12



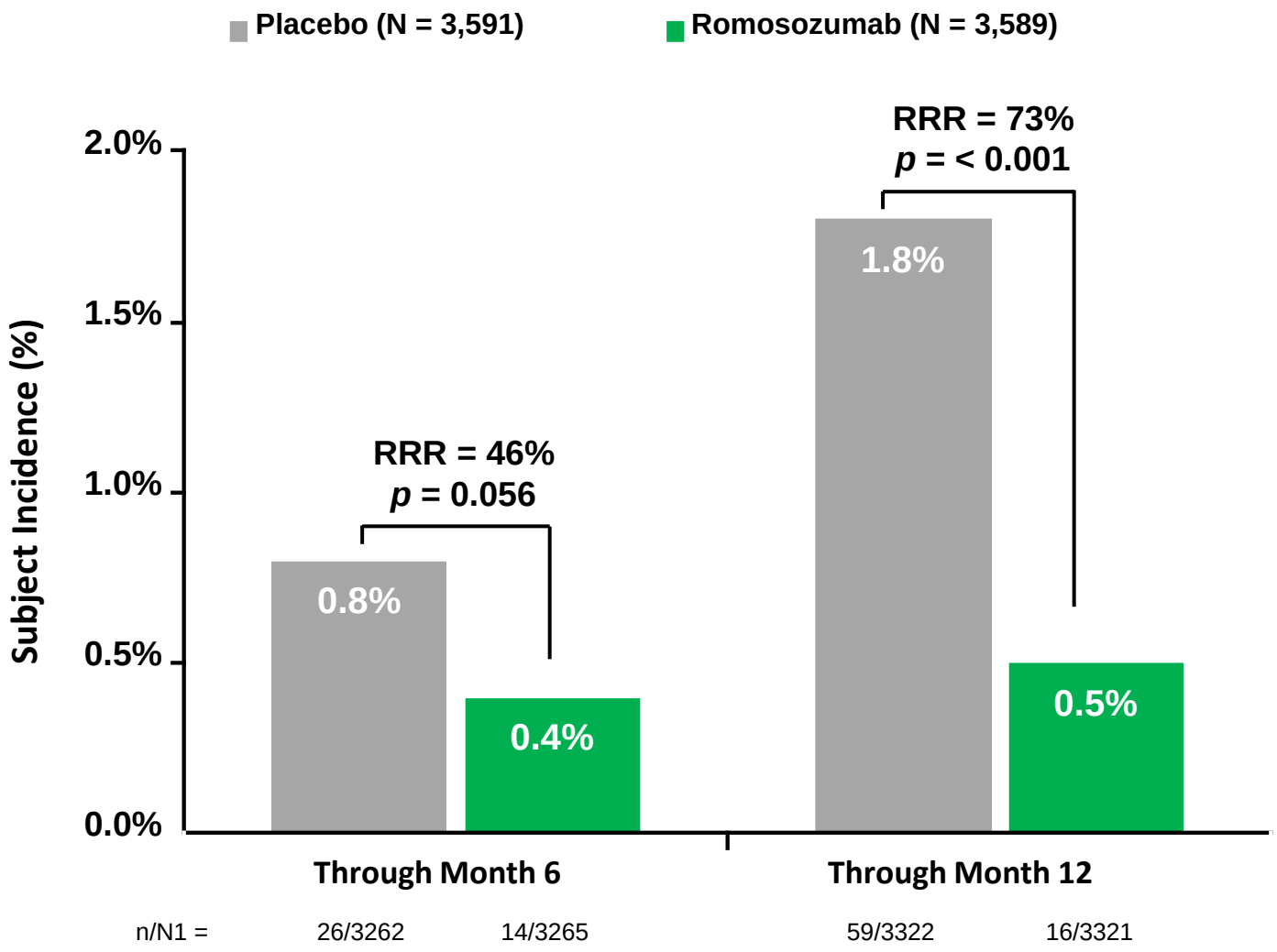
P1NP, romosozumab n = 62, placebo n = 62; CTX, romosozumab n = 61, placebo n = 62. Data presented as bootstrapped median treatment difference and 95% CI

Lumbar Spine and Total Hip BMD Through Month 12



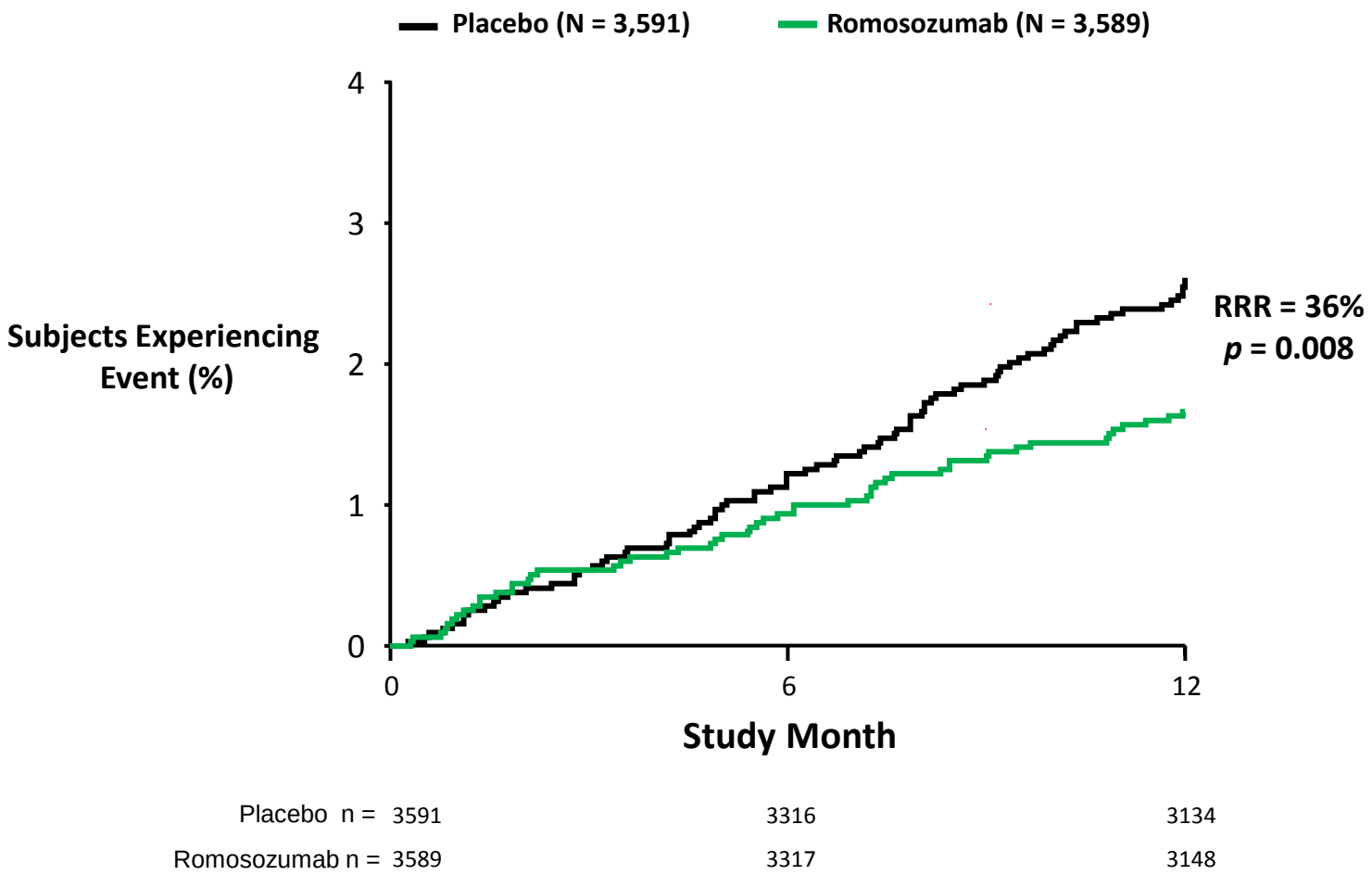
*$p < 0.001$ compared with placebo. Data are least square means (95% CI) adjusted for relevant baseline covariates

New Vertebral Fracture Incidence Through Month 12 (Co-Primary Endpoint)



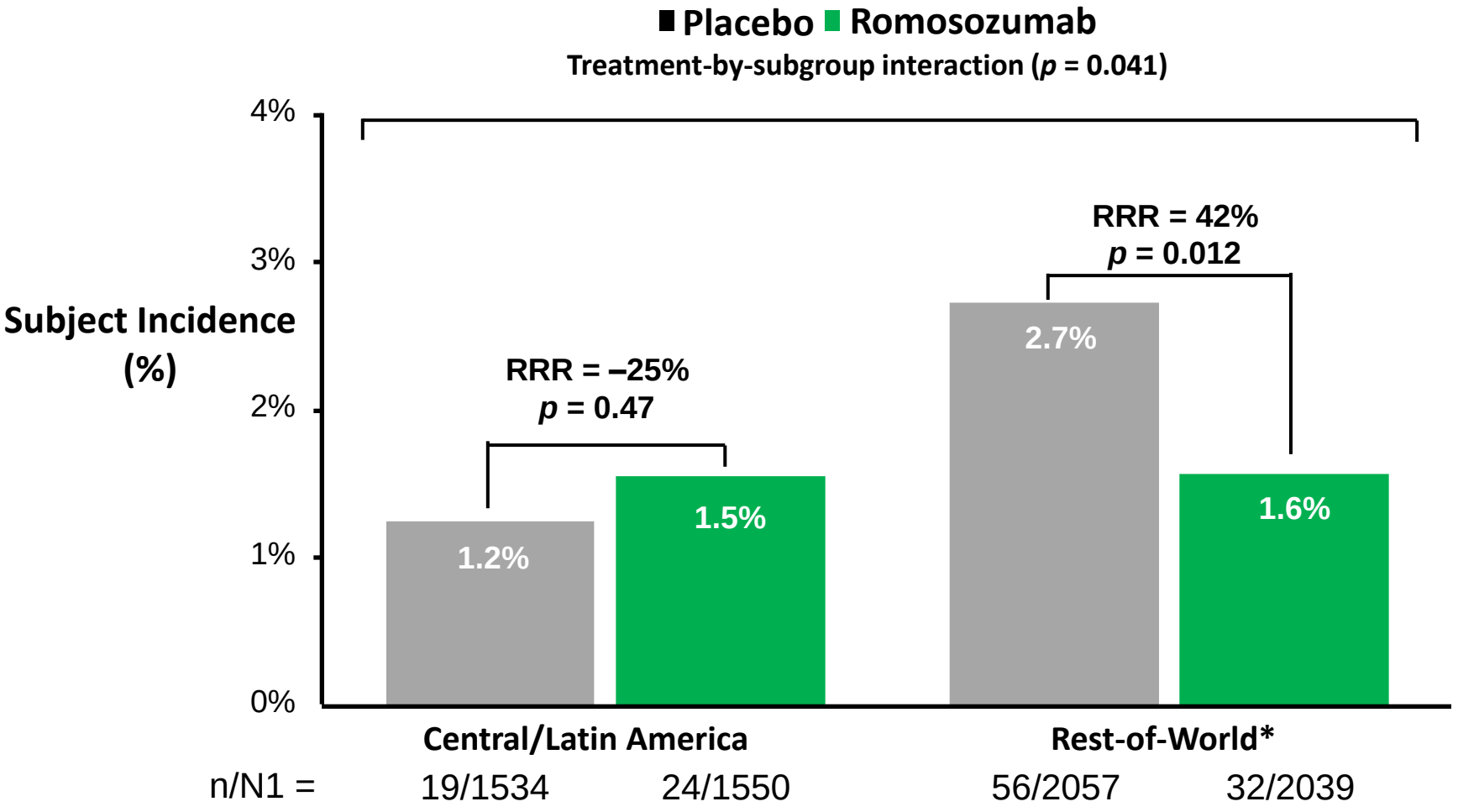
n/N1 = number of subjects with fractures/number of subjects in the primary analysis set for vertebral fractures
p-value based on logistic regression model adjusted for age (< 75, ≥ 75) and prevalent vertebral fracture

Time to First Clinical Fracture Through Month 12



Nonvertebral and symptomatic vertebral fracture. Nonvertebral fractures comprised the majority (more than 85%) of clinical fractures
Kaplan Meier curve based on data through month 24. n = number of subjects at risk for event at time point of interest. *P*-value based on RRR

Nonvertebral Fracture Incidence Through Month 12 in Central/Latin America vs Rest-of-World



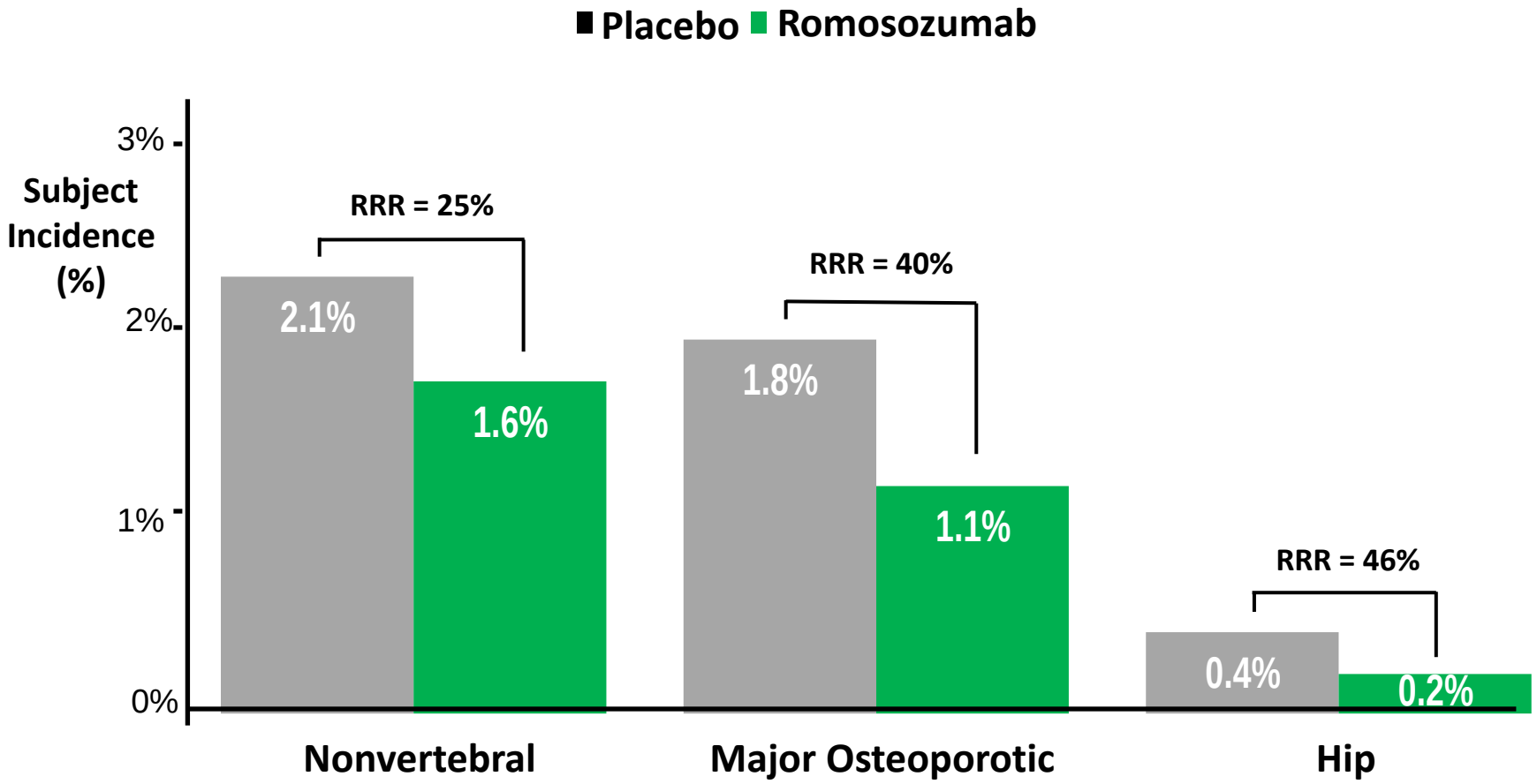
Latin America: 1.2% (placebo) vs 1.5% (RR 1.25, 95% CI 0.68-2.27), FRAX 8.7%

Non-Latin America: 2.7% (placebo) vs 1.6% (RR 0.58, 95% CI 0.37 -0.89, p =0.04), FRAX 17%

*Regions excluding Central/Latin America grouped post hoc

n/N1 = number of subjects with fractures/number of subjects in the full analysis set

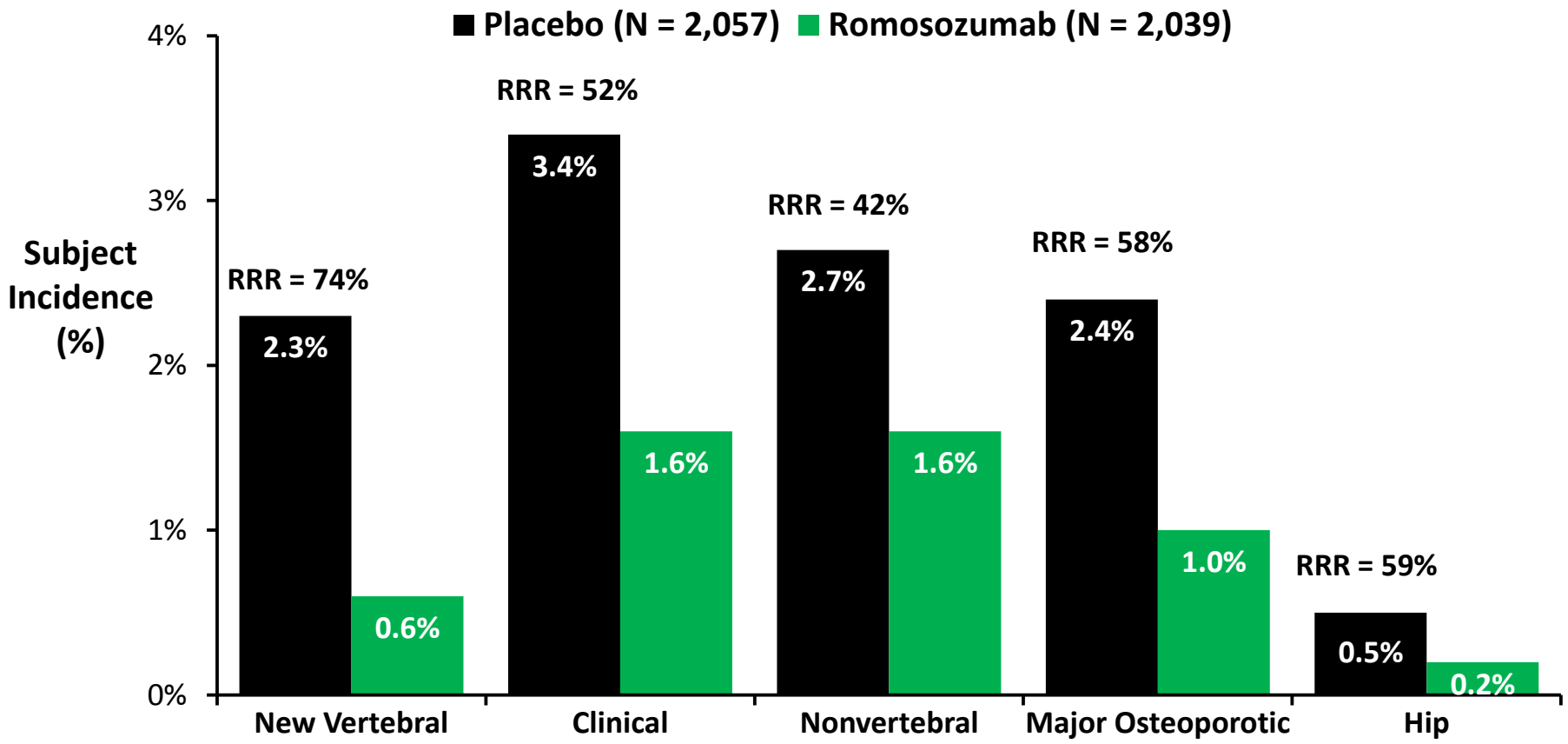
Other Key Exploratory Fracture Endpoints Through Month 12



	Nonvertebral	Major Osteoporotic	Hip
Placebo n =	**75**	**63**	**13**
Romosozumab n =	**56**	**38**	**7**
p (nominal)	0.096	0.012	0.18
p (adjusted)	0.096	NA[a]	0.18

Nonvertebral fractures excludes fractures of the skull, facial bones, metacarpals, fingers, and toes, pathologic fractures and fractures associated with high trauma
Major osteoporotic fractures: clinical vertebral, hip, forearm, and humerus, excluding pathologic fractures
[a]Osteoporotic fracture *p*-value not adjusted as not part of the testing sequence. n = number of subjects with fractures

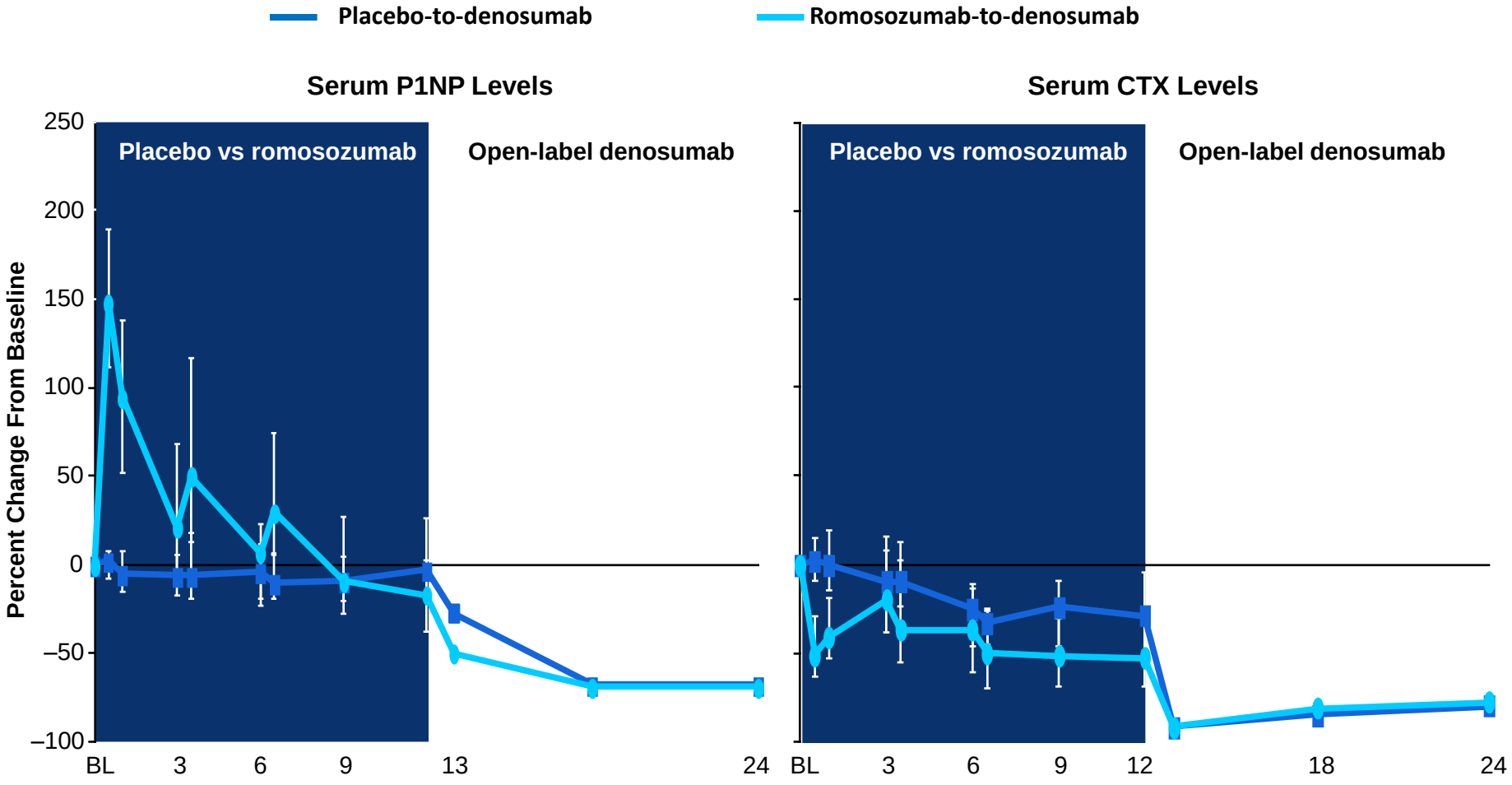
Key Fracture Endpoints Through Month 12 Excluding Central/Latin America



Placebo n/N1 =	43/1892	69/2057	56/2057	50/2057	10/2057
Romosozumab n/N1 =	11/1857	33/2039	32/2039	21/2039	4/2039
p	< 0.001	< 0.001	0.012	< 0.001	0.12

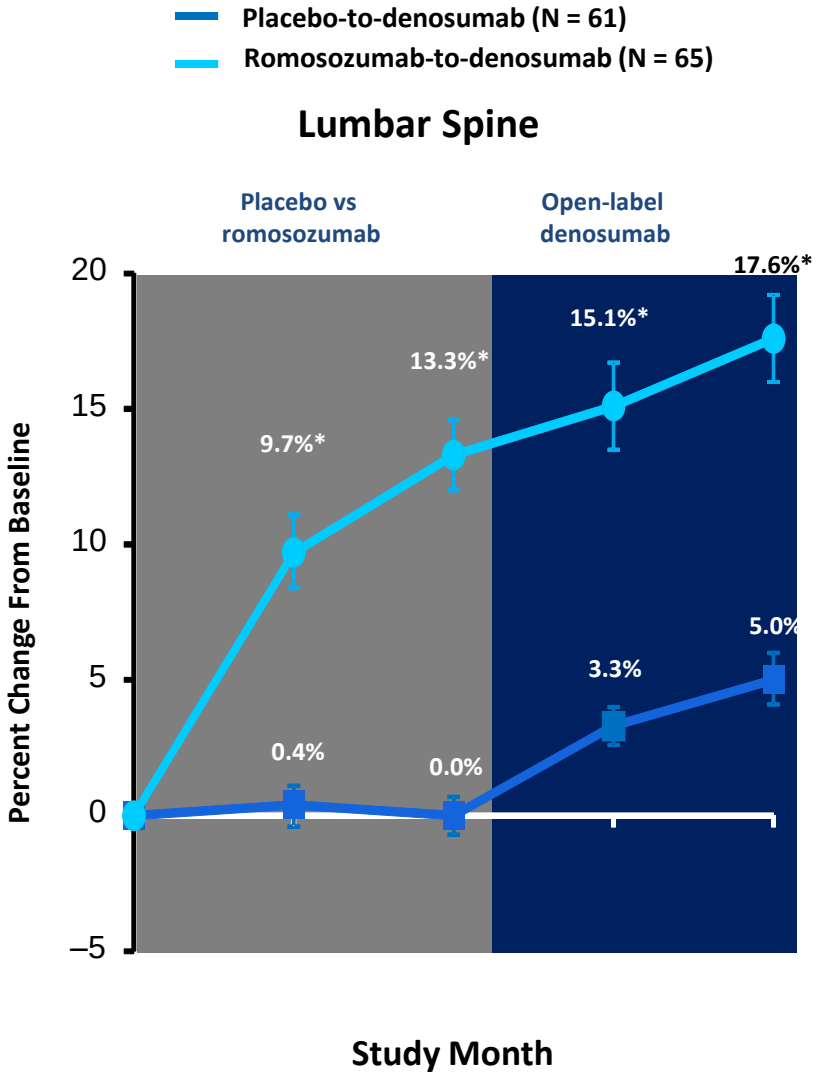
n/N1 = Number of subjects with fractures/number of subjects in the primary set in Rest-of-World population excluding Central/Latin American region Analyses were post hoc

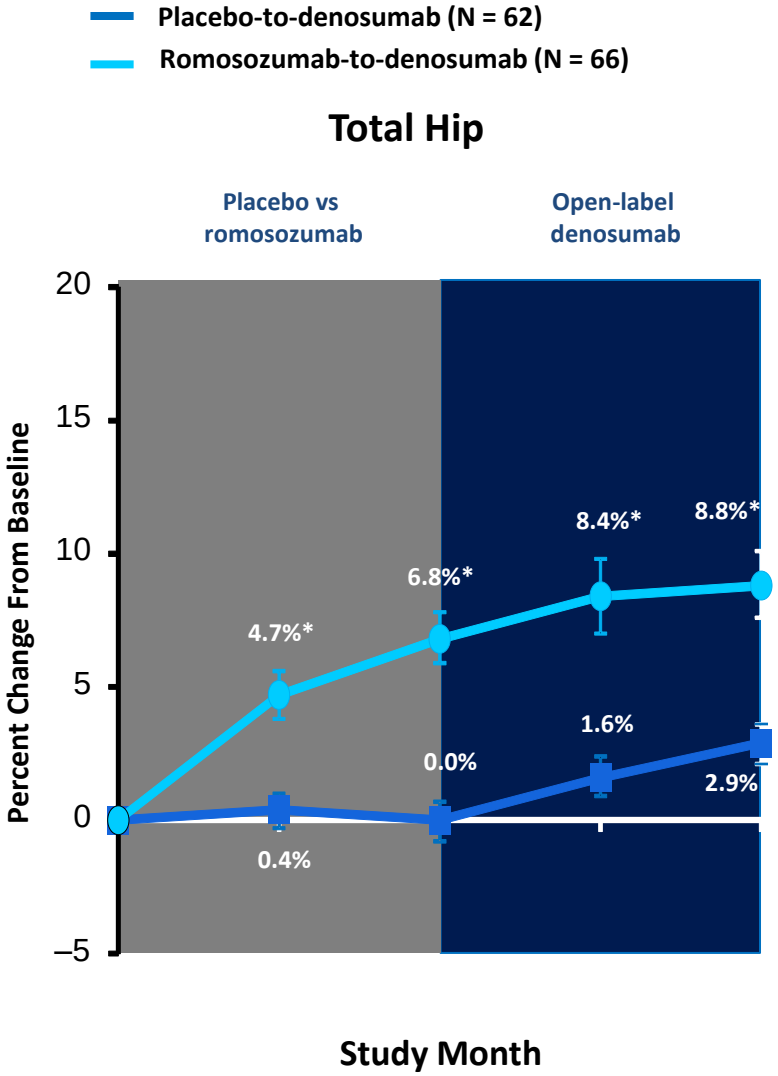
Serum P1NP and CTX Levels Through Month 24



Data are median and interquartile range. Placebo-to-denosumab n = 62; romosozumab-to-denosumab n = 62 (P1NP), n = 61 (CTX)

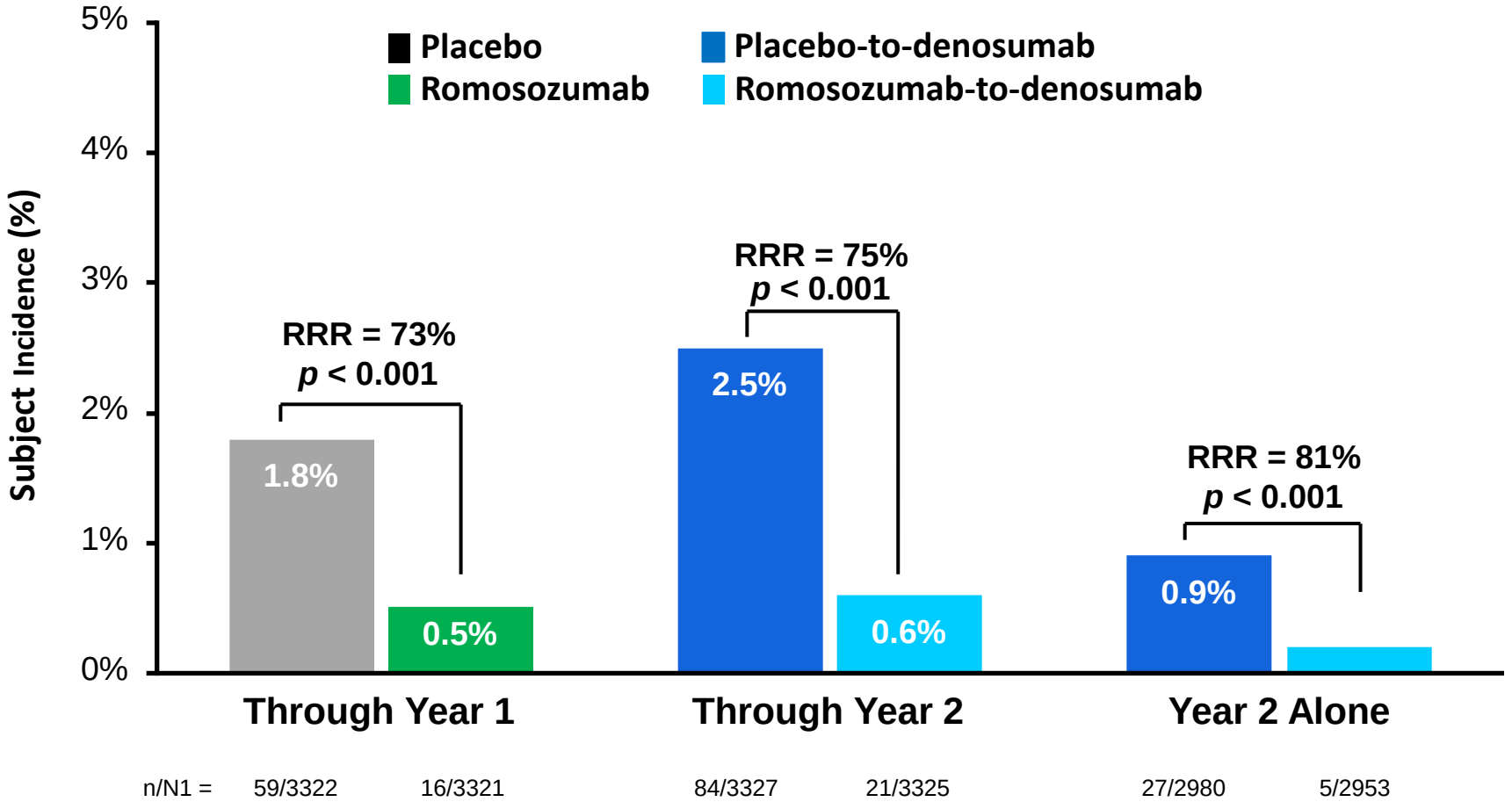
Lumbar Spine and Total Hip BMD Through Month 24





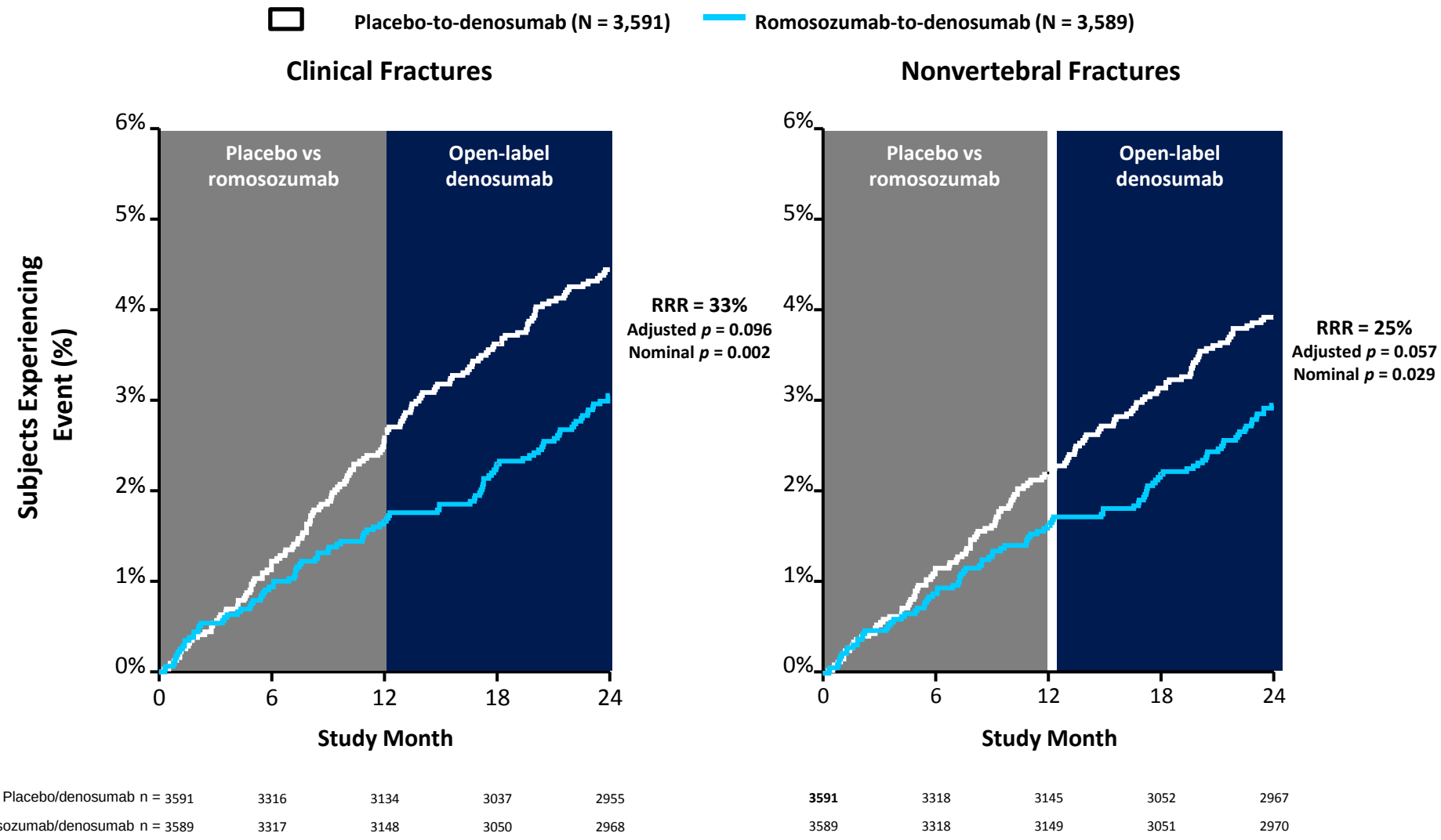
*$p < 0.001$ compared with placebo. Data are least square mean (95% CI) adjusted for relevant baseline covariates

Subject Incidence of New Vertebral Fracture Through Month 24 (Co-Primary Endpoint)



n/N1 = Number of subjects with fractures/number of subjects in the primary analysis set for vertebral fractures
***p*-value based on logistic regression model adjusted for age (< 75, ≥ 75) and prevalent vertebral fracture**

Time to First Clinical and Nonvertebral Fracture Through Month 24



Nonvertebral fractures comprised the majority (more than 85%) of clinical fractures. n = number of subjects at risk for event at time point of interest. *P*-value based on RRR

Romosozumab Safety Overview

Double-Blind Period	Placebo (N = 3,576) n (%)	Romosozumab (N = 3,581) n (%)
Subject Incidence of All Adverse Events[a]	2850 (79.7)	2806 (78.4)
Serious Adverse Events	312 (8.7)	344 (9.6)
Adjudicated cardiovascular events[b]	41 (1.1)	44 (1.2)
Deaths	23 (0.6)	29 (0.8)
Adjudicated cardiovascular deaths[b]	15 (0.4)	17 (0.5)
Events Leading to Study Discontinuation	50 (1.4)	44 (1.2)
Events of Interest[c]		
Hypocalcemia	0 (0.0)	1 (< 0.1)
Hypersensitivity[d]	245 (6.9)	242 (6.8)
Injection-site reactions	104 (2.9)	187 (5.2)
Atypical femoral fracture[b]	0 (0.0)	1 (< 0.1)
Osteonecrosis of the jaw[b,e]	0 (0.0)	1 (< 0.1)
Subject Incidence of Anti-romosozumab Antibody Formation[f]		
Binding antibodies	NA	646 (18.0)
Neutralizing antibodies	NA	25 (0.7)

N = number of subjects who received ≥ 1 dose of investigational product. [a]Occurring in ≥ 10% of subjects in either group: arthralgia (placebo, 12.0%; romosozumab, 13.0%), nasopharyngitis (placebo, 12.2%; romosozumab, 12.8%), back pain (placebo, 10.6%; romosozumab, 10.5%). [b]Includes adverse events adjudicated positive by an independent adjudication committee. For cardiovascular deaths, includes fatal events adjudicated as cardiovascular-related or undetermined (presumed cardiac-related)
[c]Event of Interest identified by pre-specified MedDRA search strategy. 7 serious adverse events in romosozumab group vs none in placebo. [e]One event also occurred in the open-label period after receipt of denosumab. [f]Antibody positive postbaseline through month 15 with a negative or no result at baseline. NA = only assessed in romosozumab subjects

Summary

- Romosozumab for 12 months compared with placebo (RRR):
  - New vertebral fracture: 73% ($p < 0.001$)
  - Clinical fracture: 36% ($p = 0.008$)
  - Nonvertebral fracture: 25% ($p = 0.096$)
    - Among subjects outside of Central/Latin America (post hoc): 42% ($p = 0.012$)

- Over 24 months, romosozumab-to-denosumab compared with placebo-to-denosumab (RRR):
  - New vertebral fracture: 75% ($p < 0.001$)
  - Clinical fracture: 33% (nominal $p = 0.002$; adjusted $p = 0.096$)
  - Nonvertebral fracture: 25% (nominal $p = 0.029$; adjusted $p = 0.057$)

Conclusion

- One year of romosozumab was well-tolerated and reduced vertebral and clinical fracture risk rapidly
- The sequence of romosozumab followed by denosumab appears to be a promising regimen for the treatment of osteoporosis

Healthy Aging
Sarcopenia, Frailty, Osteoarthritis

The effects of diet and exercise

The Microbiome and Musculoskeletal Conditions of Aging: A Review of Evidence for Impact and Potential Therapeutics

Claire J Steves, Sarah Bird,
Frances MK Williams, and Tim D Spector

JBMR, Vol. 31, No. 2, February 2016, pp 261–269

Microbiome

- Gut microbiome describes the genetic material of microorganisms within an animal intestine.
- A wide range of diverse diseases and conditions lying outside the gut have been demonstrated to be associated with an abnormal or dysfunctional microbiome

Alteration of the Microbiome

- Can be altered by antibiotics
- Energy restriction, high meat/fat diet, and changes in fiber modulate the microbiome
- May be altered by probiotics/prebiotics

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Why are they important?

- May cause alterations in the gut flora
  - influencing metabolites produced,
  - releasing short-chain fatty acids,
  - modulating the immune system,
  - increased solubility and absorption of minerals,
  - enhanced barrier function

JBMR, Vol. 31, No. 2, February 2016, pp 261–269

Frailty and sarcopenia

Effects of the Microbiome

- Frailty has been associated with alterations in the microbiome, in particular core butyrate producing commensals.
- A mouse model of sarcopenia appears to be impacted by specific Lactobacillus strains

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Osteoporosis

Effects of the Microbiome

- Osteoporosis has a substantial inflammatory component that may be affected by changes in the microbiome.
- Probiotics and prebiotics have been linked to improvements in bone density in human and animal studies, indicating that the microbiome may be an important therapeutic target in osteoporosis.

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Osteoporosis

Effects of the Microbiome

- Prebiotics increase calcium absorption in adolescents and women, and one demonstrated accompanying increased bone mineralization
- Adolescents given mixed short- and long-chain inulin-type fructans had significantly increased whole body BMC and BMD, compared to placebo
- Most likely because of changes in calcium absorption; however, changes in gut microbiota composition and the immune response may have been responsible

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Osteoporosis

Effects of the Microbiome

- Galacto-oligosaccharides (GOS) effect on calcium absorption and fecal microbiota examined
- Levels of beneficial fecal bifidobacteria were increased in a dose-dependent manner
- Calcium absorption also increased, but this was independent of dose.
- Microbiota changes accompanied increased calcium absorption in a low calcium diet in adolescent children of both sexes taking a soluble maize fiber compared with control but no changes in markers of bone turnover

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Osteoarthritis

Effects of the Microbiome

- Literature considering the microbiome and the use of pro/prebiotics in OA is sparse
- Lactobacillus casei alone or alongside type II collagen (CII) and glucosamine (GS) was given to arthritic rats
- L. Casei appeared to have synergistic action with CII and GS, effectively reducing pain, cartilage destruction, and lymphocyte infiltration more than the treatment with GS and CII together or separately.
- Co-administration led to reduced expression of numerous pro-inflammatory cytokines and matrix metalloproteinases and upregulation of anti-inflammatory cytokines IL-10 and IL-4.

JBMR, Vol. 31, No. 2, February 2016, pp 261–269

Conclusion

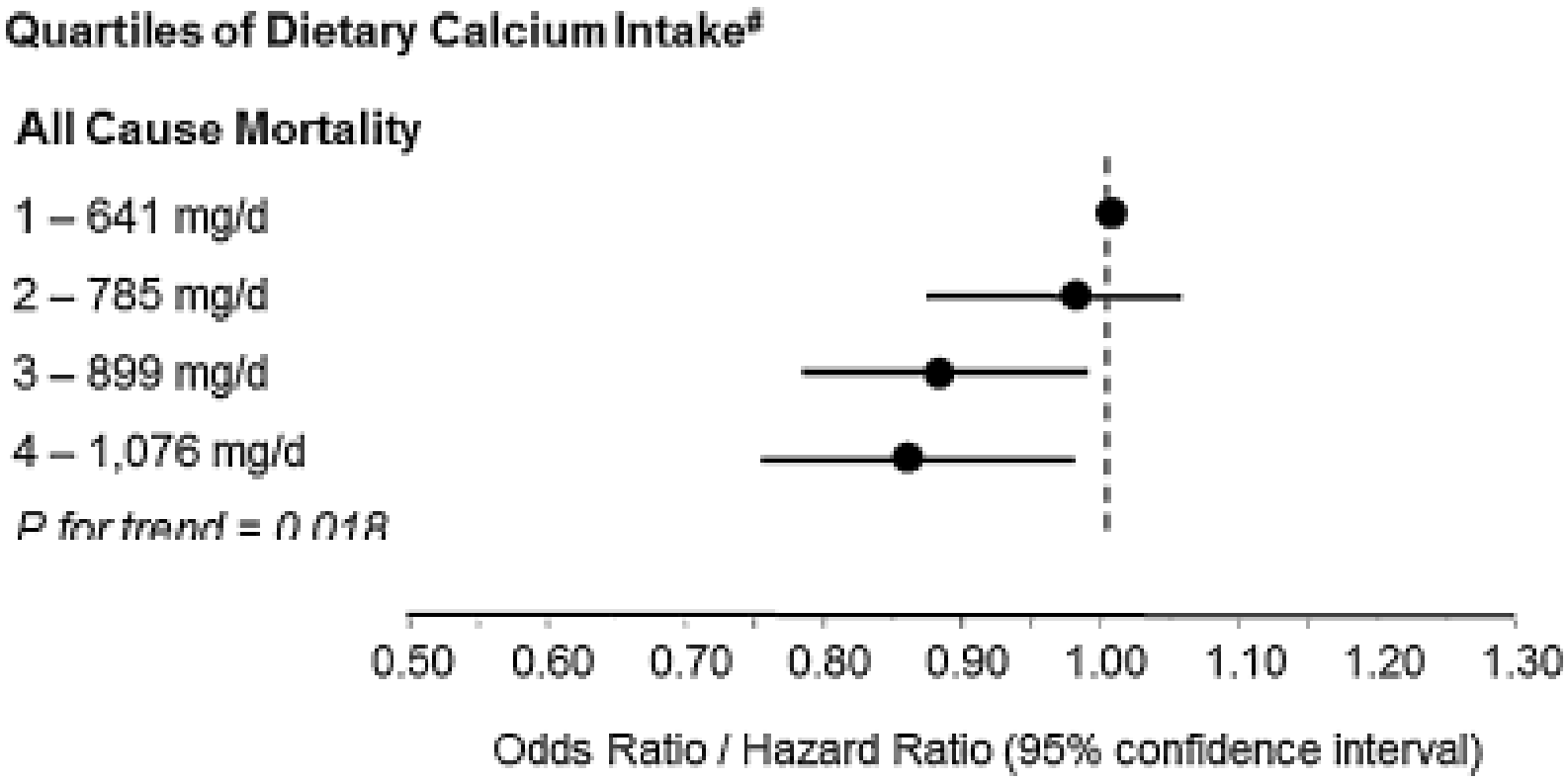
- The microbiome is a highly plausible target for modulation of diseases of aging owing to its close relationship with the innate and adaptive immune systems.
- It should not be considered in isolation because of the recognized influence of host genetics,geography, diet, and other factors.

Higher Dietary Calcium Intakes Are Associated With Reduced Risks of Fractures, Cardiovascular Events, and Mortality: A Prospective Cohort Study of Older Men and Women

Belal Khan, Caryl A Nowson, Robin M Daly, Dallas R English, Allison M Hodge, Graham G Giles and Peter R Ebeling

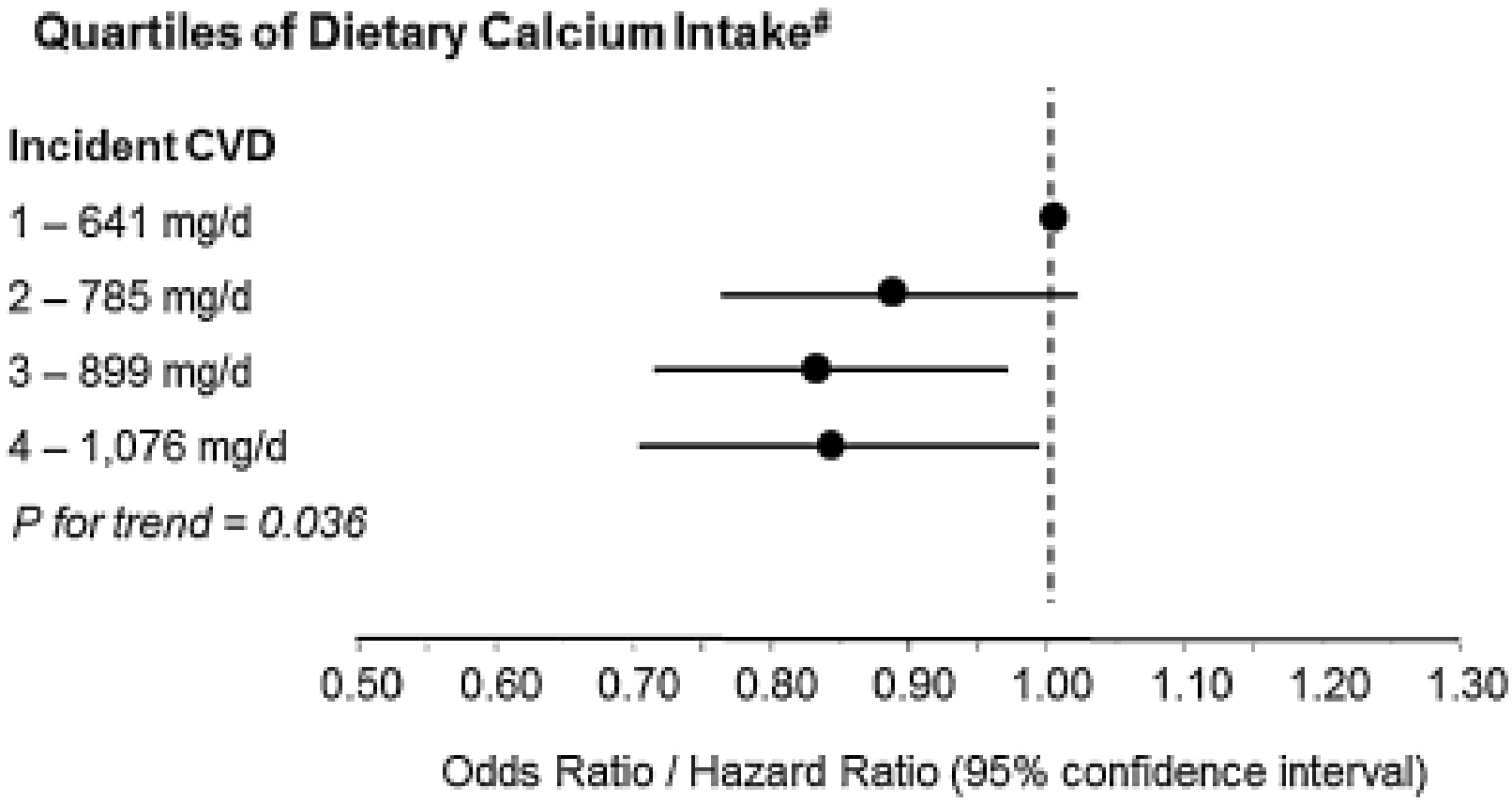
Khan et al. JBMR 2015;30:1758–1766

All Cause Mortality



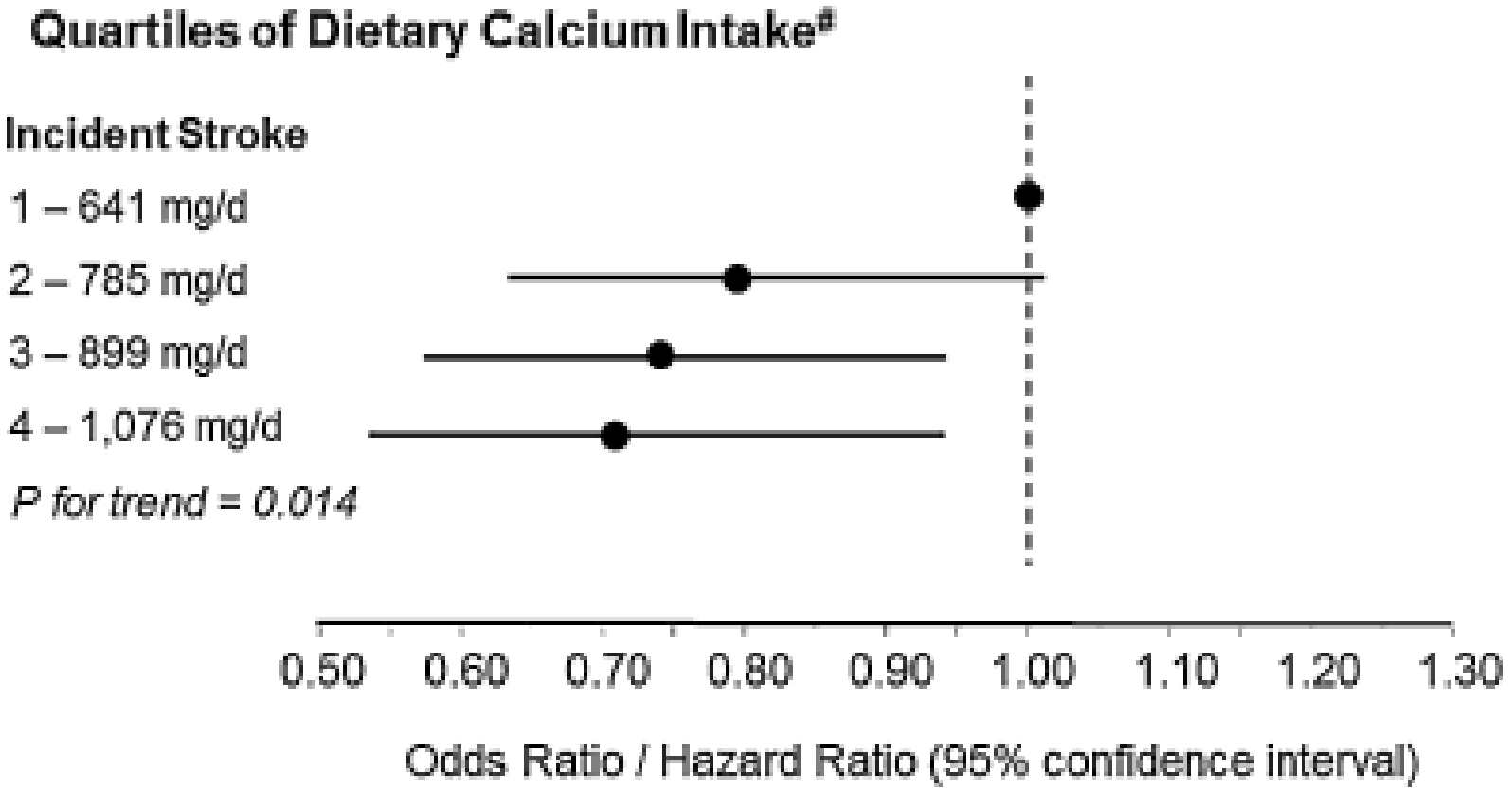
Khan et al. JBMR 2015;30:1758–1766

CVD Disease



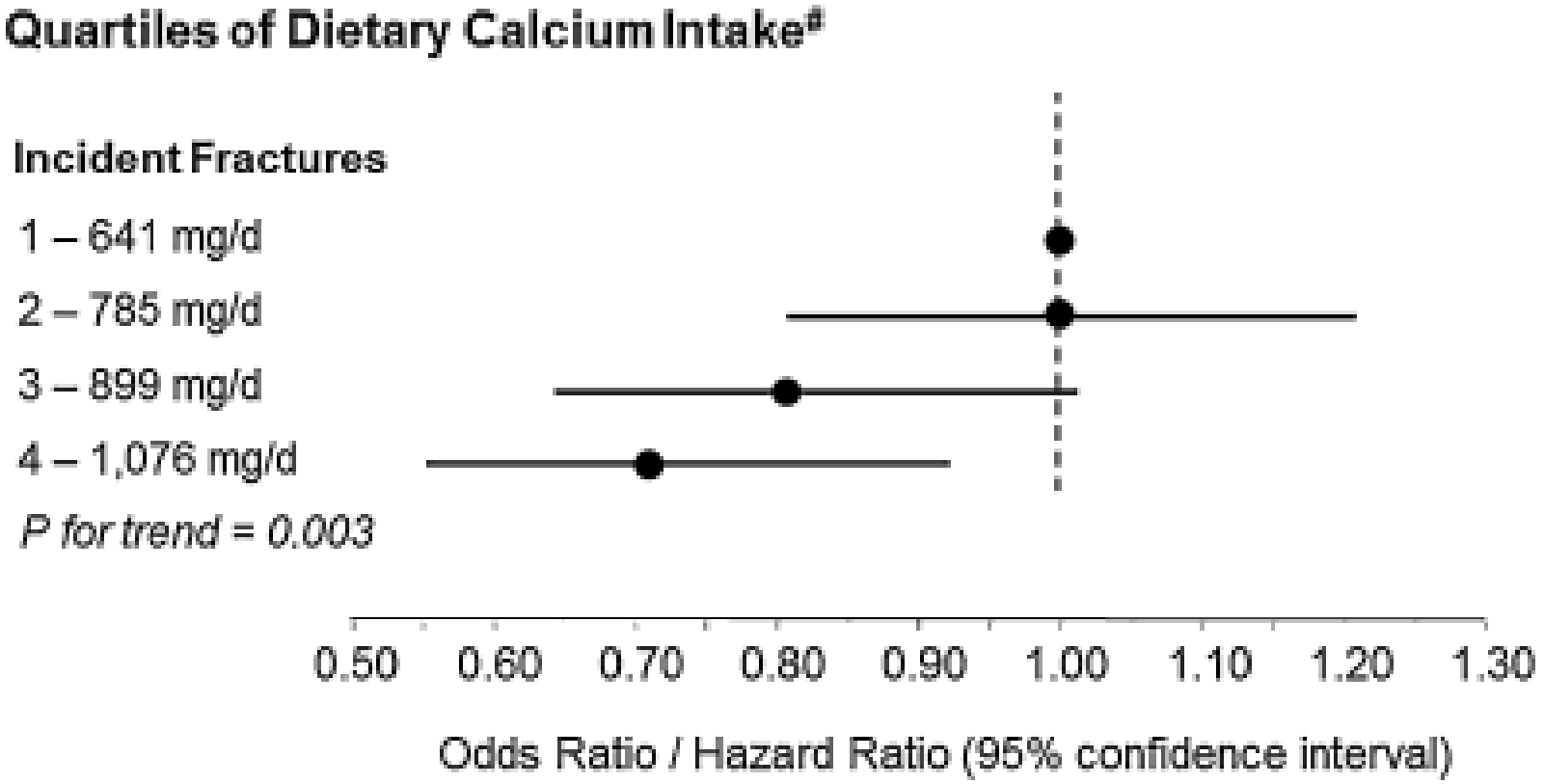
Khan et al. JBMR 2015;30:1758–1766

Incident Stroke



Khan et al. JBMR 2015;30:1758–1766

Incident Fractures

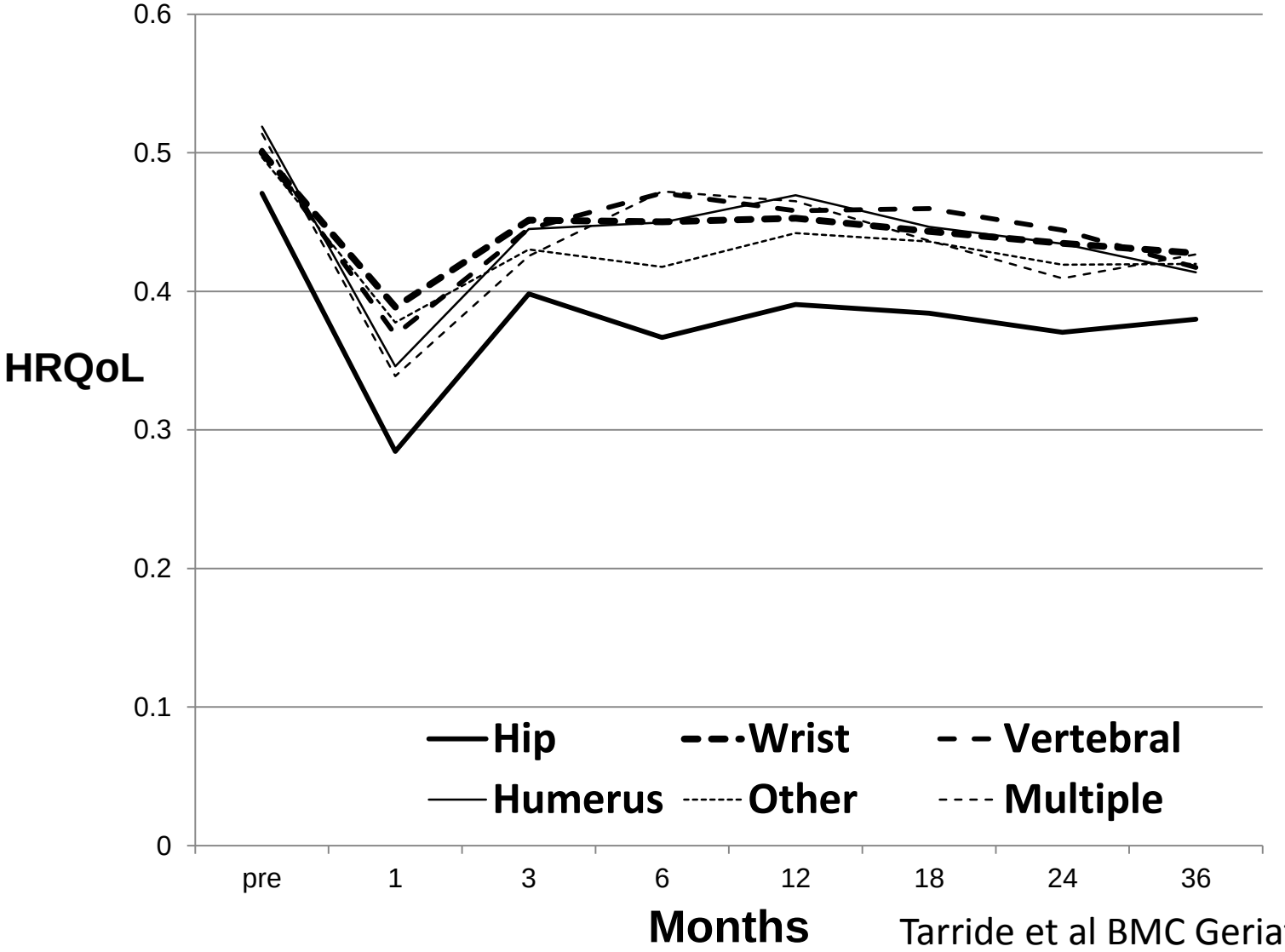


Khan et al. JBMR 2015;30:1758–1766

Higher dietary calcium intake within the current recommendation is safe and likely to be beneficial to health and to be associated with a decreased risk of all-cause mortality, cardiovascular disease, stroke and fractures

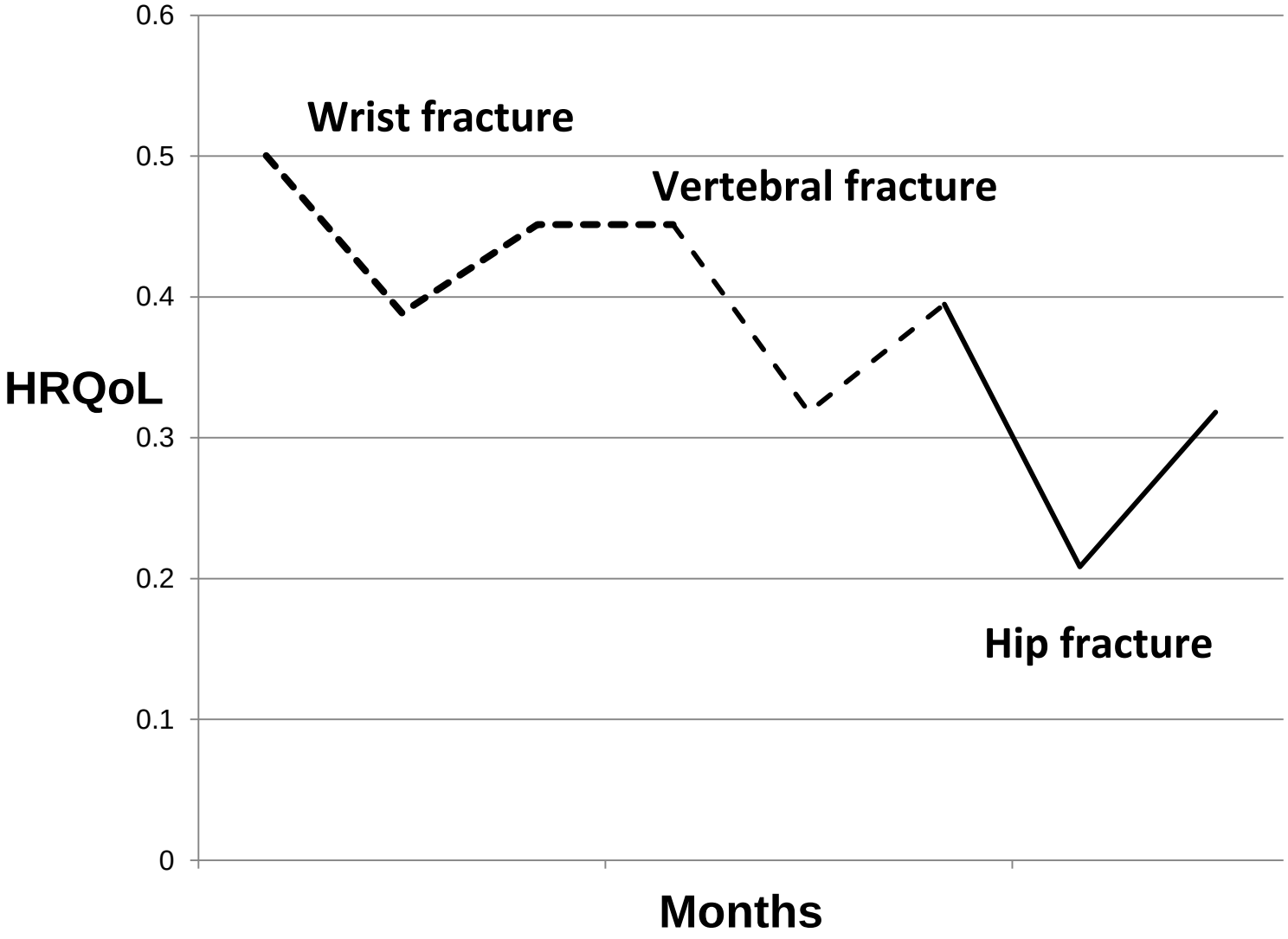
Osteoporosis, Quality of Life and Frailty

The Effect of Fractures on HRQoL from pre-fracture to 36 months post-fracture (Home care and LTC cohorts combined)



Tarride et al BMC Geriatrics 2016

The cumulative effects of serial fractures on HRQoL



Frailty increases after a Major Osteoporotic Fracture

Factors	Year 1 post-baseline			Year 2 post-baseline		
	With MOF (n=60)	Without MOF (n=3699)	P-value	With MOF (n=48)	Without MOF (n=3457)	P-value
Before MOF[1]						
Age: mean (SD)	71.9 (9.53)	69.2 (8.74)	0.019	70.3 (8.80)	69.8 (8.59)	0.65
FI: mean (SD)	0.28 (0.15)	0.24 (0.14)	0.008	0.34 (0.18)	0.28 (0.16)	0.003
After MOF[2]						
Age: mean (SD)	74.0 (9.50)	70.9 (8.84)	0.017	72.4 (8.78)	71.8 (8.58)	0.63
FI: mean (SD)	0.37 (0.19)	0.30 (0.17)	0.004	0.42 (0.21)	0.33 (0.18)	<0.001
Change before and after the onset of MOF[3]						
FI: mean (SD)	0.085 (0.086)	0.067 (0.077)	0.036	0.080 (0.11)	0.052 (0.097)	0.042

SD = standard deviation; FI = frailty index; MOF = major osteoporotic fracture.

[1] For Year 1, information before MOF was collected from baseline; for Year 2, information before MOF was collected from Year 1.

[2] For Year 1, information after MOF was collected from Year 2; for Year 2, information after MOF was collected from Year 3.

[3] The change of FI for Year 1 denoted as $FI_{(Year2-basline)}$; the change of FI for Year 2 denoted as $FI_{(Year3-Year1)}$.

Li et al J Bone Miner Res 2016

Frailty Predicts Major Osteoporotic Fracture

Factors	Year 2 post-baseline (n=48)		Year 3 post-baseline (n=41)	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Changed values[1]				
Age	1.29 (0.49-3.42)	0.60	1.23 (0.81-1.86)	0.33
FI	1.38 (0.96 - 1.94)	0.08	1.32 (0.94-1.85)	0.10
Absolute measures from previous year[2]				
Age	0.99 (0.96-1.03)	0.75	1.04 (1.01-1.08)	0.026
FI	1.33 (1.12-1.58)	0.001	1.25 (1.05-1.50)	0.017

MOF = major osteoporotic fracture; HR = hazard ratio; CI= confidence interval; FI = frailty index

[1] For Year 2, changed values were from Year 1 minus baseline, denoted as $FI_{(Year1\text{-}basline)}$; for Year 3, changed values were from Year 2 minus Year 1, denoted as $FI_{(Year2\text{-}Year1)}$.

[2] For Year 2, information was from Year 1; for Year 3, information was from Year 2.

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Frailty Predicts Falls and Mortality

Outcomes	Year 2 post-baseline		Year 3 post-baseline	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Changed values[2]				
Falls				
Age	1.05 (0.75-1.46)	0.79	1.02 (0.87-1.19)	0.82
FI	1.10 (0.97-1.25)	0.15	1.72 (0.96-3.06)	0.34
Death				
Age	1.23 (0.98-1.56)	0.081	0.74 (0.33-1.64)	0.45
FI	1.84 (1.34-2.53)	<0.001	1.33 (0.87-2.03)	0.20
Absolute measures from previous year[3]				
Falls				
Age	1.00 (0.99-1.02)	0.85	1.01 (1.00-1.03)	0.13
FI	1.18 (1.10-1.27)	<0.001	1.12 (1.02-1.22)	0.018
Death				
Age	1.06 (1.03-1.10)	<0.001	1.05 (1.02-1.09)	0.004
FI	1.58 (1.33-1.89)	<0.001	1.24 (1.07-1.46)	0.006

Li et al J Bone Miner Res 2016

Summary

- Fractures increase frailty
- Frailty is a predictor of major osteoporotic fractures, falls and mortality

Osteoarthritis

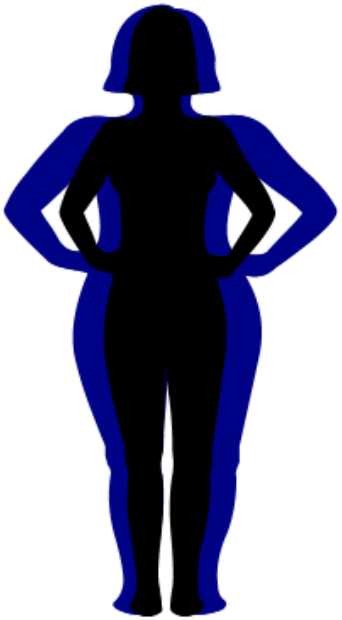
Body Weight!

Obesity – caused by unhealthy diets and physical inactivity - is the **strongest preventable risk factor** for the occurrence, progression and effect of large joint OA

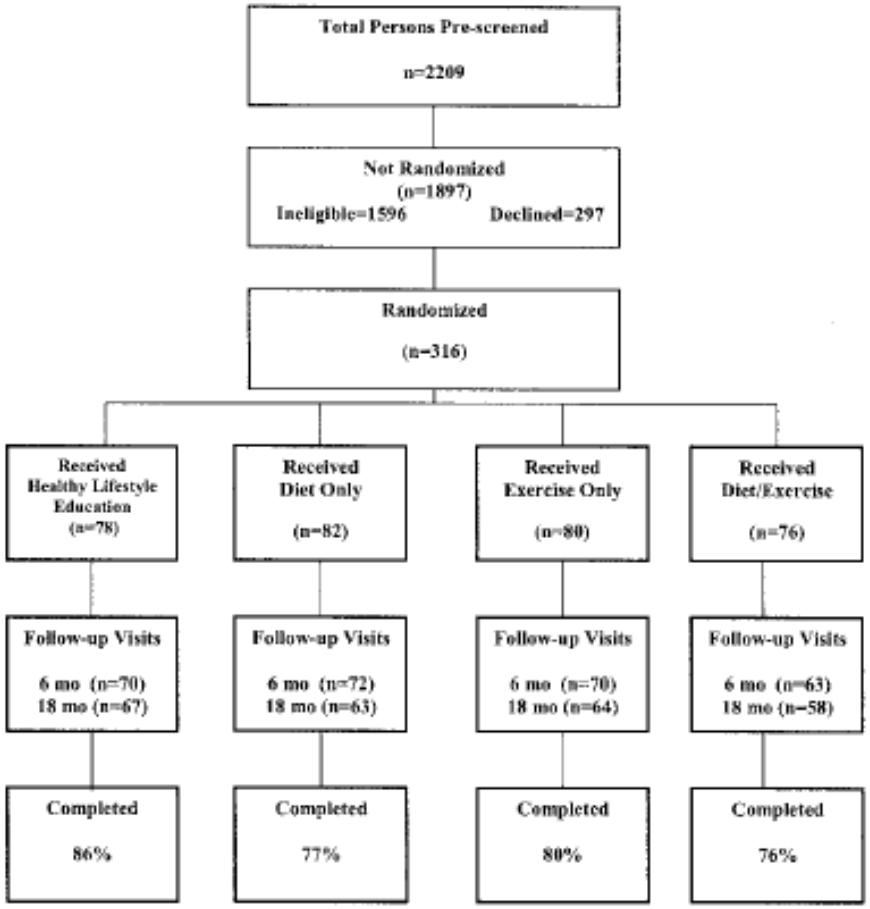
What can be done?

The **OBVIOUS** answer – **LOSE WEIGHT**

and **EXERCISE**!



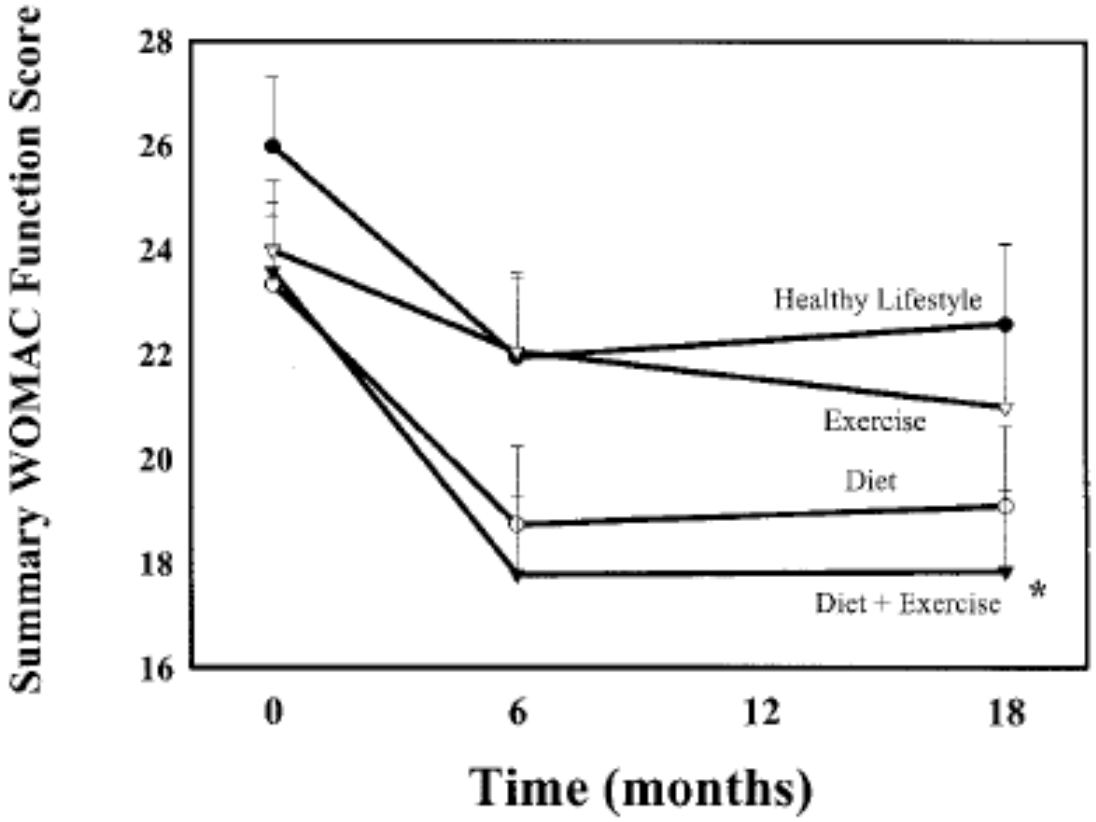
ADAPT Participant Progress



Progress of participants through the Arthritis, Diet, and Activity Promotion Trial (ADAPT).

Messier et al. Arthritis Rheum. 2004 ; 50 (5): 1501 – 1510

WOMAC Physical Function Summary Score



Mean SEM unadjusted Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) physical function summary scores across the 18-month intervention period. *P* 0.05, diet plus exercise group versus healthy lifestyle group.

Messier et al. Arthritis Rheum. 2004 ; 50 (5): 1501 – 1510

Six Minute Walk Distance

Study group	6-minute walk distance, meters			
	Baseline	6 months	18 months	Change from baseline at 18 months (95% confidence interval)
Healthy lifestyle	434.61 ± 10.96	428.56 ± 12.88	429.89 ± 12.77	−4.72 (−29.75, 20.31)
Diet only	425.98 ± 10.89	433.68 ± 11.94	435.63 ± 12.88	9.65 (−15.79, 35.09)
Exercise only	424.15 ± 11.42	465.04 ± 12.13	472.73 ± 13.12†	48.58 (22.87, 74.29)
Diet plus exercise	416.15 ± 11.34	482.37 ± 12.65	477.76 ± 13.12†	61.61 (35.90, 87.32)

* Values are the mean ± SEM.
† $P < 0.05$ versus healthy lifestyle.

Six-minute walk distance at baseline, 6 months, and 18 months and absolute change from baseline*

Messier et al. Arthritis Rheum. 2004 ; 50 (5): 1501 – 1510

Stair-Climb Time

Study group	Stair-climb time, seconds			
	Baseline	6 months	18 months	Change from baseline at 18 months (95% confidence interval)
Healthy lifestyle	9.59 ± 0.64	9.97 ± 0.75	9.37 ± 0.76	−0.22 (−1.71, 1.27)
Diet only	9.74 ± 0.65	9.88 ± 0.70	8.43 ± 0.78	−1.31 (−2.84, 0.22)
Exercise only	10.52 ± 0.66	8.87 ± 0.73	8.89 ± 0.78	−1.63 (−3.16, −0.10)
Diet plus exercise	10.99 ± 0.67	8.83 ± 0.78	8.45 ± 0.81†	−2.54 (−4.13, −0.95)

* Values are the mean ± SEM.
† $P < 0.05$ versus healthy lifestyle.

Stair-climb time at baseline, 6 months, and 18 months and absolute change from baseline*

Messier et al. Arthritis Rheum. 2004 ; 50 (5): 1501 – 1510

Self Reported Pain

Study group	WOMAC pain score			
	Baseline	6 months	18 months	Change from baseline at 18 months (95% confidence interval)
Healthy lifestyle	7.25 ± 0.39	6.19 ± 0.46	6.02 ± 0.45	−1.23 (−2.11, −0.35)
Diet only	6.58 ± 0.40	5.10 ± 0.43	5.51 ± 0.45	−1.07 (−1.95, −0.19)
Exercise only	6.64 ± 0.39	6.22 ± 0.45	6.24 ± 0.47	−0.40 (−1.32, 0.52)
Diet plus exercise	7.27 ± 0.41	5.47 ± 0.47	5.07 ± 0.47†	−2.20 (−3.12, −1.28)

* Values are the mean ± SEM scores (range 0–20, with higher scores indicating greater dysfunction). WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
† $P = 0.05$ versus healthy lifestyle.

Self-reported pain at baseline, 6 months, and 18 months and absolute change from baseline*

Messier et al. Arthritis Rheum. 2004 ; 50 (5): 1501 – 1510

Key Results of “ADAPT”

- Exercise + diet group had significant improvements in pain, 6-minute walk and stair climb time vs. control
- Exercise only group had significant improvements in walking distance than healthy lifestyle
- Exercise + diet group had 24% physical function improvement, 18% improvement in diet group
- Exercise + diet group had 30.3% pain improvement at 6 months with benefits maintained after 18 months

Messier et al. Arthritis Rheum. 2004 ; 50 (5): 1501 – 1510

Conclusion

Exercise and a healthy diet are the mainstays of healthy aging