Studies showing effect of vitamin K2 MK-7, and combinations on bone health

	Publication	Participants	Population	Duration	Results
1	Ronn et al. 2016	148	Women with osteopenia	1 year	MK-7 preserves bone microstructure compared to placebo
2	Knapen et al. 2013	744	Healthy postmenopausal women	3 years	Significant improvement of BMD and BMC Significant reduction of ucOC Significant increase of cOC
3	Fujita et al. 2012	1662	Healthy elderly men	Habitual intak	Habitual intake of natto was significantly associated with higher BMD and low ucOC
4	Genius and Bouchard 2012	77	Postmenopausal women with comprised bone health	1 year	Significant increase of BMD
5	Kanellakis et al. 2012	173	Healthy postmenopausal women	1 year	Significant increase of BMD
6	Michalek et al. 2011	176	Healthy	6 months	Significant increase of BMD
7	Forli et al. 2010	94	Patients post heart or lung transplantation	1 year	Significant increase of BMD
8	Emaus et al. 2010	334	Healthy postmenopausal women	1 year	No significant increase of BMD Significant increase of cOC Significant reduction of ucOC
9	Ikeda et al. 2006	944	Healthy women	3 years	Significant association between natto intake and MD in femoral neck
10	Katsuyama et al. 2004	73	Healthy postmenopausal women	1 year	No significant changes in stiffness index Significantly lower ucOC
11	Katsuyama et al. 2002	117	Healthy young women	Habitual intake	Bone stiffness positively associated with natto intake
12	Kaneki et al. 2001	105	Healthy women	Habitual intake	Significant inverse association between natto intake and hip fractures

Vitamin D and K potential role in immune health based on the covid-19 pandemic

	Author	Title	Journal
1	Janssen, R., Visser, M. P., Dofferhoff, A. S., Vermeer, C., Janssens, W., & Walk, J. (2020).	Vitamin K metabolism as the potential missing link between lung damage and thromboembolism in Coronavirus disease 2019.	British Journal of Nutrition, 1-8.
2	Dofferhoff, A. S., Piscaer, I., Schurgers, L. J., Visser, M. P., van den Ouweland, J. M., de Jong, P. A., Janssen, R. (2020).	Reduced Vitamin K Status as a Potentially Modifiable Risk Factor of Severe Coronavirus Disease 2019.	Clinical Infectious Diseases.
3	Linneberg, A., Kampmann, F. B., Israelsen, S. B., Andersen, L. R., Jørgensen, H. L., Sandholt, H., ... & Benfield, T. (2021).	The Association of Low Vitamin K Status with Mortality in a Cohort of 138 Hospitalized Patients with COVID-19.	Nutrients, 13(6), 1985.
4	Walk, J., Dofferhoff, A. S., van den Ouweland, J. M., van Daal, H., & Janssen, R. (2020).	Vitamin D-contrary to vitamin K-does not associate with clinical outcome in hospitalized COVID-19 patients.	medRxiv.
5	Janssen, R., & Walk, J. (2020).	Vitamin K epoxide reductase complex subunit 1 (VKORC1) gene polymorphism as determinant of differences in Covid-19-related disease severity.	Medical hypotheses, 144, 110218.
6	Dofferhoff, A., Walk, J., Visser, M. (2021).	The KOVIT trial: double-blind, randomized, placebo-controlled clinical trial [ongoing]	https://www.clinicaltrials.gov/ct2/show/NCT04770740
7	Berenjian, A., & Sarabadani, Z. (2020).	How menaquinone-7 deficiency influences mortality and morbidity among COVID-19 patients.	Biocatalysis and Agricultural Biotechnology, 29, 101792.
8	Goddek, S. (2020).	Vitamin D3 and K2 and their potential contribution to reducing the COVID-19 mortality rate.	International Journal of Infectious Diseases, 99, 286-290.
9	van Ballegooijen, A. J., Beulens, J. W., Kieneker, L. M., de Borst, M. H., Gansevoort, R. T., Kema, I. P., ... & Bakker, S. J. (2020).	Combined low vitamin D and K status amplifies mortality risk: a prospective study.	European journal of nutrition, 60(3), 1645-1654.
10	Popa, D. S., Bigman, G., & Rusu, M. E. (2021). T	he Role of Vitamin K in Humans: Implication in Aging and Age-Associated Diseases.	Antioxidants, 10(4), 566.

Studies showing effect of vitamin K2 MK-7, and combinations on cardiovascular health

	Author	Title	Journal
1	Koshihara, Y., & Hoshi, K. (1997).	Vitamin K2 enhances osteocalcin accumulation in the extracellular matrix of human osteoblasts in vitro. Journal of Bone and Mineral Research, 12(3), 431-438.	Journal of Bone and Mineral Research, 12(3), 431-438.
2	Fu, X., Wang, X. D., Mernitz, H., Wallin, R., Shea, M. K., & Booth, S. L. (2008)	9-Cis Retinoic Acid Reduces 1 α, 25-Dihydroxychole- calciferol-Induced Renal Calcification by Altering Vitamin K-Dependent γ-Carboxylation of Matrix γ-Carboxyglutamic Acid Protein in A/J Male Mice.	The Journal of nutrition, 138(12), 2337-2341.
3	Ushiroyama, T., Ikeda, A., & Ueki, M. (2002). Maturitas, 41(3), 211-221.	Effect of continuous combined therapy with vitamin K2 and vitamin D3 on bone mineral density and coagulofibrinolysis function in postmenopausal women.	Maturitas, 41(3), 211-221.
4	Iwamoto, J., Takeda, T., & Ichimura, S. (2000).	Effect of combined administration of vitamin D3 and vitamin K2 on bone mineral density of the lumbar spine in postmenopausal women with osteoporosis	Journal of orthopaedic science, 5(6), 546-551.
5	Rønn, Langdahl et al (2016)	Vitamin K2 (menaquinone-7) prevents age-related deterioration of trabecular bone microarchitecture at the tibia in postmenopausal women	Eur J Endocrinol, 175(6), 541-549.
6	Jackson, Bonds et al (2006).	Calcium plus vitamin D supplementation and the risk of fractures.	New England Journal of Medicine, 354(7), 669-683.
7	World Health Organization. (2014)	Global status report on noncommunicable diseases 2014 (No. WHO/NMH/NVI/15.1)	World Health Organization.
8	J.M. Geleijnse, et al.	Dietary Intake of Menaquinone is Associated with a Reduced Risk of Coronary Heart Disease: The Rotterdam Study,	J. Nutr. 134, 3100–3105 (2004).
9	G.C. Gast, et al.	A High Menaquinone Intake Reduces the Incidence of Coronary Heart Disease	Nutr. Metab. Cardiovasc. Dis. 19, 504–510 (2009).
10	M.H. Knapen, et al.	Menaquinone-7 Supplementation Improves Arterial Stiffness in Healthy Postmenopausal Women: Double- Blind Randomised Clinical Trial	Thrombosis and Haemostasis 113(5), 1135–1144 (2015).
11	Price Williamson et al (2000).	Warfarin-induced artery calcification is accelerated by growth and vitamin D. Arteriosclerosis, thrombosis, and vascular biology, 20(2), 317-327.	Arteriosclerosis, thrombosis, and vascular biology, 20(2), 317-327.
12	Wang L, Song Y, Manson JE, Pilz S, Mar	Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease: a meta-analysis of prospective stud- ies. Circ Cardiovasc Qual Outcomes. 2012;5:819–829. doi: 10.1161/ CIRCOUTCOMES.112.967604.	Circ Cardiovasc Qual Outcomes. 2012;5:819–829. doi: 10.1161/ CIRCOUTCOMES.112.967604.
13	Gast GC et al	A high menaquinone intake reduces the incidence of coronary heart dis- ease.	Nutr Metab Cardiovasc Dis. 2009;19:504–510. doi: 10.1016/j. numecd.2008.10.004.
14	Van Ballegooijen, Tomaschitz,et al (2017).	The synergistic interplay between vitamins D and K for bone and cardiovascular health: a narrative review. International journal of endocrinology, 2017.	International journal of endocrinology, 2017.
15	Mayer Jr, O. & Jardon et al (2017)	Synergistic effect of low K and D vitamin status on arterial stiffness in a general population	The Journal of nutritional biochemistry, 46, 83-89.

Science-based evidence of d3+k2 synergy, and Ca combination with Mg, and trace minerals

	Author / year	Participants	Intervention	Duration	Results
1	Iwamoto et al. 2000	Osteoporotic women ≥ 5y after menopause, N=92, mean age 64 years	1. Calcium lactate, 2 g/d 2. Vitamin D3, 0.75 µg/d 3. Vitamin K2 (MK-4), 45 mg/d 4. Vitamin K2 + D3	2 years	Combined D and K2 increased the BMD
2	Ushiroyama et al. 2002	Postmenopausal women with osteopenia and osteoporosis, N=126, mean age 53 years	1. Diet 2. Vitamin D, 1 µg/d 3. Vitamin K2 (MK-4), 45 mg/d 4. Vitamin K2 + D	2 years	Combined D and K2 increased the BMD
3	Yonemura et al. 2004	Patients with glomerulonephritis, N=60, mean age 32 years	1. Control 2. Vitamin D, 0.5 mg 3. Vitamin K2 (MK-4), 45 mg/d 4. Vitamin K2 + D	8 weeks	The preventive effects in groups D, K2 and D + K2 were similar
4	Binkley et al. 2009	Postmenopausal women, N=381, mean age 62 years	1. Calcium 315 mg/d + Vit D3 200 IU/d 2. Vitamin K1 1 mg/d, Ca, Vit D3 3. Vitamin K2 (MK-4) 45 mg/d, Ca, Vit D3	1 year	Similar effects in all groups
5	Je et al. 2011	Postmenopausal women, N=78, mean age 68 years	1. Calcium 630 mg/d, Vitamin D 400 IU/d 2. Ca + Vit D + Vitamin K2 (MK-4) 45 mg/d	6 months	BMD increased significantly in the Vitamin D + K2 group
6	Rønn et al. 2016	Postmenopausal women with osteopenia, N=148, mean age 67y	1. Calcium 800 mg/d + Vitamin D 38 µg/d 2. Ca + Vit D + Vitamin K2 (MK-7) 375 µg/d	1 year	Vitamin K2 + D + Ca group preserves trabecular structures
7	Strause, Linda, et al 1994	Postmenopausal women Mean age=66, N=59	1. Calcium only 2. Calciume plus trace element	2 years double-blind, placebo-controlled	Only subjects prescribed both a calcium and trace mineral supplement showed a reversal in bone mineral density loss
8	Orchard, Larson et al. 2014	Postmenopausal women Mean age=67, N=4778	Registered at clinicaltrials.gov as NCT00000611.		Lower magnesium intake is associated with lower BMD of the hip and whole body