



OPEN ACCESS

EDITED BY

Jean Maurice Delabar,
Centre National de la Recherche Scientifique
(CNRS), France

REVIEWED BY

Cathy W. Levenson,
Florida State University, United States
Adriana Ximenes-da-Silva,
Federal University of Alagoas, Brazil

*CORRESPONDENCE

Stefanos Roumeliotis
✉ st_roumeliotis@hotmail.com

†These authors have contributed equally to
this work and share first authorship

RECEIVED 13 November 2024

ACCEPTED 27 December 2024

PUBLISHED 15 January 2025

CITATION

Roumeliotis S, Kontogiorgos I, de Vries F,
Maresz K, Jeanne J-F, Leivaditis K and
Schurgers LJ (2025) The role of vitamin K2 in
cognitive impairment: linking vascular health
to brain health.

Front. Aging Neurosci. 16:1527535.

doi: 10.3389/fnagi.2024.1527535

COPYRIGHT

© 2025 Roumeliotis, Kontogiorgos, de Vries,
Maresz, Jeanne, Leivaditis and Schurgers. This
is an open-access article distributed under the
terms of the [Creative Commons Attribution
License \(CC BY\)](#). The use, distribution or
reproduction in other forums is permitted,
provided the original author(s) and the
copyright owner(s) are credited and that the
original publication in this journal is cited, in
accordance with accepted academic practice.
No use, distribution or reproduction is
permitted which does not comply with these
terms.

The role of vitamin K2 in cognitive impairment: linking vascular health to brain health

Stefanos Roumeliotis^{1*†}, Ioannis Kontogiorgos^{1†},
Femke de Vries², Katarzyna Maresz³, Jean-François Jeanne⁴,
Konstantinos Leivaditis¹ and Leon J. Schurgers²

¹Second Department of Nephrology, School of Medicine, AHEPA Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece, ²Department of Biochemistry, Cardiovascular Research Institute Maastricht, Maastricht, Netherlands, ³International Science & Health Foundation, Krakow, Poland, ⁴Gnosis by Lesaffre, Lesaffre International, R&D Department, Marcq-En-Baroeul, France

Cognitive impairment, marked by a decline in essential mental aspects such as attention, memory, and problem-solving, is significantly correlated with advancing age. This condition presents a major challenge for the elderly, adversely affecting quality of life, diminishing independence, and imposing substantial burdens on healthcare systems. Recent research indicates that vitamin K2 may be vital for preserving brain health and cognitive function. Traditionally recognized primarily for its role in blood coagulation, vitamin K has emerged in recent years as a nutrient with diverse biological effects essential for healthy aging. A growing body of evidence from both observational and interventional studies underscores the pivotal role of vitamin K2 in mitigating arterial calcification. This mechanism may link vascular health to cognitive function, suggesting that vitamin K2 could play a critical role in the prevention of cognitive impairment in aging populations.

KEYWORDS

vitamin K2, menaquinone-7, arterial calcification, arterial stiffness, dementia, cognitive function

Introduction

By 2050, the World Health Organization (WHO) projects that the global population of individuals aged 80 and older will triple, leading to a significantly aged population worldwide ([Ageing and Health, 2024](#)). Since aging is usually accompanied by heavy mortality and comorbidity which burdens the economic healthcare systems, recently, healthy aging has been in the center of scientific research. Cognitive impairment, termed as decline in mental status and abilities including attention, memory, and problem-solving, is a condition tightly and bidirectionally associated with advanced age. Decline in cognitive function is a major concern for the elderly, because it might affect quality of life and lead to loss of independence and burden health care systems. Therefore, it soon became evident that early detection of modifiable risk factors for cognitive decline is of utmost importance. Among these factors, during recent years, accumulating evidence suggest that dietary components, like nutritional vitamin K might play pivotal role in brain function and cognitive function.

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide ([Mensah et al., 2019](#)). Previous research has established a link between vascular remodeling, atherosclerosis and brain function, and it is now widely recognized that CVD

is negatively correlated with cognitive health (Alosco and Hayes, 2015; Dolan et al., 2010; Rusanen et al., 2014). Arterial stiffness, in particular, appears to be a critical factor in the functional and structural brain changes associated with aging (Vlachopoulos et al., 2010). Previous studies have demonstrated that arterial stiffness contribute to cognitive decline through impaired cerebral perfusion. Given these, arterial stiffness has emerged as a potential therapeutic target to mitigate cognitive decline, highlighting the importance of early vascular interventions in preserving cognitive health.

In this article, we review the association between vitamin K and cerebral function, discussing novel developments regarding its therapeutic role in arterial stiffness and cognitive health.

The link between arterial stiffness and cognitive status

As arterial stiffness increases with age, the pulsatile load transmitted to peripheral arteries becomes abnormal, resulting in end-organ damage. The brain, with its high-flow, low-resistance vascular system, is particularly vulnerable to this damage (Thorin-Trescases and Thorin, 2016). Arterial stiffness has been associated with age-related cerebral changes, such as atrophy and small vessel disease (Townsend et al., 2015; Laurent and Boutouyrie, 2020). Among the non-invasive measures of vascular stiffness, pulse wave velocity (PWV) is considered the gold standard. PWV measures arterial stiffness along the entire aortic pathway, providing a reliable, feasible, and accurate assessment of vascular health (Laurent et al., 2006; Boutouyrie et al., 2014). Increased arterial stiffness leads to impaired cerebral blood flow and white matter hypoperfusion, contributing to white matter (WM) structural abnormalities and white matter hyperintensities (WMH) (Jefferson et al., 2018; Promjunyakul et al., 2016). Moreover, recent studies have demonstrated that arterial stiffness, as measured by PWV, is negatively associated with total brain volume, brain atrophy, and cognitive function (Palta et al., 2019; Haidegger et al., 2023; Tomoto et al., 2023; Coffin et al., 2022).

In the Atherosclerosis Risk in Communities–Neurocognitive Study, the authors measured cognition status and performed brain magnetic resonance imaging to identify cerebral microbleeding, lacunar infarcts, white matter hyperintensities' volumes, and the signature pathognomonic region for Alzheimer's disease in a big cohort of older adults, aged 67–90 years (Palta et al., 2019). When patients were stratified according to their cfPWV and central pulse pressure values, the authors found that those with impaired central arterial hemodynamics presented with increased white matter hyperintensities, reduced total brain volumes and significantly poorer scores for general cognition, processing speed and executive function (Palta et al., 2019). This tight association between central arterial stiffness and brain structure impairment (assessed by reduced total brain volume, increased brain white matter hyperintensity volume and brain atrophy), is independent of gender and age (Tomoto et al., 2023) and of BP values and variability (Haidegger et al., 2023). Even in a diverse population of 460 people with a mean age of 70 ± 8 years with normal cognitive ability, mild impairment or dementia, surrogate markers

of arterial stiffness were strongly associated with brain macro- and micro-structure impairment and both executive and global cognitive function decline. Specifically, cfPWV was an independent predictor of both high brain white matter volumes and diffusion based free water volumes (Coffin et al., 2022).

Several studies have proposed a causal relationship between arterial stiffness and cognitive impairment (Beulens et al., 2010; Rahimi Sakak et al., 2021; Tarkesh et al., 2020), with the most robust evidence emerging from meta-analyses. Pase et al. conducted a meta-analysis of six longitudinal studies involving 3,947 participants, finding that PWV is predictive of cognitive decline, as measured by the Mini-Mental State Examination (MMSE; $\beta = -0.03$, 95% CI: -0.06 to 0.01) (Pase et al., 2012). Van Sloten et al. performed a systematic review and meta-analysis to explore the association between arterial stiffness, microvascular cerebral disease (assessed by brain MRI), and cognitive function (van Sloten et al., 2015). While this study demonstrated a positive association between arterial stiffness and microvascular cerebral disease (OR: 1.39, 95% CI: 1.21–1.60), it could not definitively establish a correlation between PWV and cognitive impairment due to significant heterogeneity among the included studies (van Sloten et al., 2015). The primary limitations of these meta-analyses are the variability and quality of the studies involved.

To address these limitations, more recent meta-analyses have provided a comprehensive examination of the association between arterial stiffness and cognitive function over a long period. Alvarez-Bueno et al. conducted a meta-analysis of 38 studies (29 cross-sectional and nine longitudinal), including 43,115 participants, and assessed the relationship between arterial stiffness and specific cognitive indices, such as global cognition, executive function, and memory (Alvarez-Bueno et al., 2020). The results indicated that PWV was inversely correlated with global cognition (adjusted pooled ES = -0.21 , 95% CI: -0.30 to -0.11), executive function (adjusted pooled ES = -0.08 , 95% CI: -0.14 to -0.03), and memory (adjusted pooled ES = -0.13 , 95% CI: -0.20 to -0.05) (Alvarez-Bueno et al., 2020). For the first time, this meta-analysis provided pooled estimates of the tight relationship between arterial stiffness and various cognitive functions. Another meta-analysis, spanning studies from January 1986 to March 2020, conducted separate qualitative and quantitative assessments of both cross-sectional and longitudinal studies (Liu et al., 2021). The cross-sectional analysis revealed a strong, negative association between memory, processing speed, and aortic PWV, while the longitudinal analysis found that participants in the high PWV category had a 44% higher risk of cognitive decline compared to those in the low category (OR: 1.44; 95% CI: 1.24–1.85) (Liu et al., 2021). Moreover, for every 1 m/s increase in aortic PWV, there was a 3.9% increase in the risk of cognitive impairment (OR: 1.039; 95% CI: 1.005–1.073) (Liu et al., 2021). The meta-regression analysis further indicated that the association between arterial stiffness and cognitive impairment intensified with age (Liu et al., 2021).

Traditionally, it has been proposed that intimal arterial calcification leads to obstruction of the artery and plaque rupture, whereas, calcification of the media might lead to arterial stiffness, systolic hypertension and high PWV, which in turn trigger diastolic dysfunction and eventually heart failure. Arterial calcification is a major determinant of stiffening the arteries, which is considered

the hallmark of vascular aging and an independent predictor of cardiovascular diseases. The pathogenetic mechanisms responsible for vascular stiffness recently shifted from collagen and elastin to the differentiation of vascular smooth muscle cells to osteoblastic phenotype, which is triggered by oxidative stress and inflammation, membrane mechanotransduction, lipid metabolism, genetic factors and epigenetics (Lacolley et al., 2020).

Cognitive dysfunction, which is prevalent in aging populations, may be partially explained by increased arterial stiffness and calcification.

Vitamin k

Vitamin K is a family of fat-soluble compounds, including vitamin K1 (phylloquinone) and vitamin K2 (menaquinones), which are structurally similar. While traditionally recognized for its role in blood clotting, recent studies have expanded the clinical relevance and understanding of vitamin K and now include bone and vascular health. Vitamin K-dependent proteins (VKDPs) rely on vitamin K to undergo γ -glutamylcarboxylation, a modification essential for their biological activity. This family of proteins includes hepatic VKDPs such as prothrombin, FVII, FIX, and FX, protein S and protein C as well as extrahepatic VKDPs such as matrix Gla-protein (MGP), which is involved in inhibiting vascular calcification, and osteocalcin, which plays a role in bone mineralization.

Vitamin K1, predominantly found in plant-based foods like leafy green vegetables, is the primary dietary form of vitamin K. Vitamin K2, however, is mainly produced by bacteria and is present in animal-derived foods and fermented products such as natto (fermented soy) and cheese. The structural differences between K1 and K2 influence their bioavailability, absorption, bioactivity, and distribution within tissues (Halder et al., 2019). Compared to vitamin K1, the K2 subtype menaquinone-7 (MK-7) has a significantly longer half-life, accumulates more effectively in blood, and exhibits greater biological activity, particularly in facilitating the carboxylation of extrahepatic VKDPs (Schurgers et al., 2007b). Currently, the daily recommended intake (DRI) for vitamin K is based solely on its role in blood coagulation and focuses primarily on preventing hemorrhaging. However, there is no established consensus on the optimal intake of vitamin K2, particularly with respect to its broader roles in bone, vascular, and cognitive health (Akbulut et al., 2020; Neofytou et al., 2024).

Recent research suggests that adequate vitamin K intake is necessary for activating extrahepatic VKDPs, which are critical for long-term health and cognitive function (Popescu and German, 2021). Circulating dephosphorylated, uncarboxylated Matrix Gla protein (dp-ucMGP), a marker of extrahepatic vitamin K deficiency, could represent a novel therapeutic target for mitigating both arterial stiffness and cognitive decline. MK-7 supplementation has been shown to be safe and well-tolerated, with no serious adverse events, and has demonstrated efficacy in improving vitamin K status in the elderly. Furthermore, evidence from clinical trials suggests that MK-7 may delay or even reverse vascular calcification (Knape et al., 2015; Mansour et al., 2017; Eelderink et al., 2023; Naiyarakseree et al., 2023; Kurnatowska et al., 2015; Lees et al., 2019; Li et al., 2023).

TABLE 1 VKDPs connected with the brain function.

VKD	Involved in	References
Gas6	Cell survival and growth, chemotaxis, mitogenesis, and myelination	Binder et al., 2011; Varnum et al., 1995; Gilchrist et al., 2020
Protein S	Antithrombotic and signaling-mediated neuroprotective actions	Zhu et al., 2010
	Modulation of the blood-brain barrier	
Protein C	Antithrombotic, anti-inflammatory, anti-apoptotic, and cell-signaling activities	Griffin et al., 2016
Osteocalcin	Brain development	Oury et al., 2013
	Production of several neurotransmitters that favor learning and memory formation	Obri et al., 2018
MGP	Inhibition of vascular calcification	Schurgers et al., 2008; Santa-Maria et al., 2010

Evaluation of vitamin K

Assessing vitamin K intake and status in both population and clinical studies presents several challenges, as a range of methods are employed, each with limitations (Akbulut et al., 2020). The food frequency questionnaire (FFQ) is commonly used but is often inadequate for evaluating vitamin K2 intake due to incomplete food composition databases. Biomarkers that reflect vitamin K intake, absorption, and metabolism provide a more comprehensive assessment than dietary questionnaires. However, there is no single gold-standard test for vitamin K status. Various VKDPs, such as uncarboxylated prothrombin (PIVKA-II), the ratio of uncarboxylated to carboxylated osteocalcin (ucOC/cOC), and desphosphorylated-uncarboxylated MGP (dp-ucMGP), serve as markers of vitamin K status and are linked to diverse health outcomes. Recent studies have also linked these biomarkers to cognitive decline. Given the distinct functions of these biomarkers, employing multiple markers or combining them with dietary intake data could enhance the precision of vitamin K status evaluation (Shea and Booth, 2016).

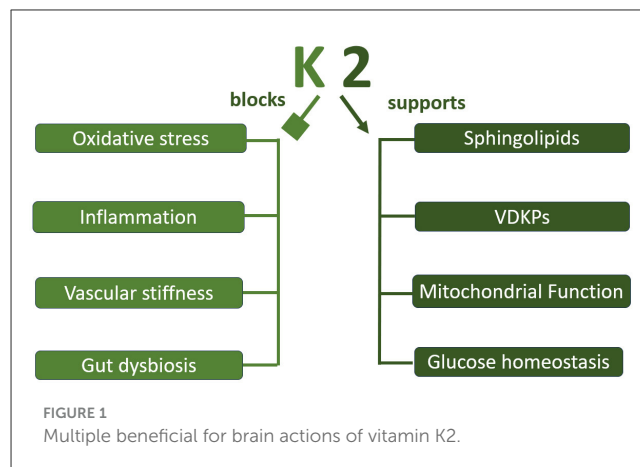
The role of vitamin K in brain function

Beyond its well-established role in haemostasis, emerging evidence suggests that vitamin K plays a critical role in brain function. Vitamin K affects cognitive and neural processes through various mechanisms, including the activity of several VKDPs (Table 1). Notably, growth arrest-specific 6 (Gas6) regulates cell survival and myelination (Binder et al., 2011; Varnum et al., 1995; Gilchrist et al., 2020), protein S mediates neuroprotective and antithrombotic effects by modulating the blood-brain barrier (Zhu et al., 2010) and MGP, a potent inhibitor of vascular calcification, has been linked to cognitive performance (Shea et al., 2022).

In addition to influencing VKDPs, vitamin K exerts antioxidant effects by reducing levels of reactive oxygen species (ROS), with

MK-7 being particularly effective in this regard (Mukai et al., 1993; Muszyńska et al., 2020; Shandilya et al., 2021). Given the link between oxidative stress, inflammation, and cognitive decline in the elderly (Baierle et al., 2015), the anti-inflammatory and antioxidant properties of vitamin K offer a promising prevention strategy (Huang et al., 2021; Yu et al., 2016). It is well established that vitamin K exerts beneficial effects on glucose homeostasis. Although the majority of studies focused on phylloquinone, MK-7 has also shown promising results in experimental studies and clinical trials. The large community-dwelling, prospective Dutch study in 38,094 participants showed that only dietary menaquinones were strongly and inversely associated with the risk for developing incident type 2 diabetes, during a long follow-up of 10 years; the association with dietary vitamin K1 was marginally lost (Beulens et al., 2010). Moreover, an RCT showed that daily 360 µg of MK-7 for 12 weeks in insulin-dependent patients with diabetes improved significantly fasting glucose levels, glycated hemoglobin, insulin concentrations and homeostatic model assessment for insulin resistance (HOMA-IR). Moreover, compared to the placebo, the MK-7 group had significantly higher number of patients that achieved optimum glycemic control (assessed by HbA1c and plasma glucose levels within target values) (Rahimi Sakak et al., 2021). Similar results were reported by another RCT in polycystic ovary syndrome patients; even low dose of MK-7 (90 µg daily for 8 weeks) significantly reduced serum fasting insulin, homeostatic model assessment for insulin resistance and β-cell function index, increased insulin sensitivity check index, improved lipid profile parameters and decreased waist circumference and body fat mass (Tarkesh et al., 2020). Taken together, these data highlight the beneficial effects of vitamin K (especially MK-7) on glycemic homeostasis, lipid metabolism and fat mass distribution. Maintaining optimum glucose metabolism is of utmost importance of brain cell function and viability and on the other hand, impaired glucose homeostasis occurs even at early stages of degenerative neurological conditions, including Parkinson's and Alzheimer's disease and contributes to the progression of these diseases (Camandola and Mattson, 2017; Putzu et al., 2018). This might be explained by the fact that glucose metabolism affects various factors that trigger brain aging, including glucose transport, nucleic acid repair, mitochondrial function and gut microbiome, which is the backbone of the gut-brain bidirectional axis (Wachsmuth et al., 2022). Therefore, MK-7, by regulating glucose metabolism might affect indirectly, brain structure and function.

Vitamin K also influences sphingolipid metabolism, which plays a critical role in neuronal function by regulating enzymes involved in sphingolipid biosynthesis (Alessenko and Albi, 2020; Denisova and Booth, 2005). Notably, certain functions of vitamin K2, such as its role as a mitochondrial electron carrier and transcriptional regulator via the steroid and xenobiotic receptor (SXR), are unique compared to vitamin K1 (Horie-Inoue and Inoue, 2008; Lin et al., 2021; Tang et al., 2022). While mitochondrial dysfunction is strongly associated with cognitive decline (Apajai et al., 2020), further research is needed to establish whether improved mitochondrial function correlates with cognitive enhancement in humans.



Experimental studies

Animal studies have demonstrated that vitamin K deficiency leads to decreased levels of menaquinone-4 and sphingolipids in the brain, which may impair cognition and behavior (Tamadon-Nejad et al., 2018). Given the detrimental impact of suboptimal vitamin K status on the nervous system, it has been hypothesized that vitamin K2 supplementation could benefit brain function and cognition. In aged rats, MK-7 treatment reversed age-related cognitive deficits, improved inflammatory markers and redox balance, inhibited cerebrovascular calcification, and increased Gas6 protein expression, which was accompanied by cognitive improvements (Elkattawy et al., 2022; Lee et al., 2022). Another potential mechanism linking vitamin K deficiency to cognitive decline involves gut microbiome alterations. Inadequate vitamin K intake has been associated with significant changes in gut microbial composition (Tooley, 2020; Ellis et al., 2021) and animal models have demonstrated that vitamin K2 supplementation can improve cognitive outcomes by modulating the gut-brain axis (Chatterjee et al., 2023). These findings suggest that vitamin K2 has a multifaceted potential to enhance cognitive function, as illustrated in Figure 1.

Clinical studies

The hypothesis that vitamin K depletion may adversely affect brain function is supported by clinical evidence, primarily derived from observational studies. A meta-analysis of eight studies involving 97,595 patients revealed that, compared to traditional long-term antithrombotic therapy with vitamin K antagonists (VKAs), which significantly reduce overall vitamin K status, the use of novel oral anticoagulants (NOACs) may reduce the risk of cognitive impairment (Zhang et al., 2018). Moreover, community-based studies have demonstrated that higher vitamin K intake is associated with reduced cognitive decline in the elderly (Chouet et al., 2015; Presse et al., 2008), and increased circulating vitamin K levels are linked to improved cognitive function (Presse et al., 2013), suggesting a potential preventive role against cognitive deterioration. Although multiple observational

studies have examined the relationship between cognitive status, vitamin K-dependent biomarkers, and vitamin K2 concentrations in the brain, the results have been inconsistent, highlighting inherent challenges in this research area (Shea et al., 2022; Kiely et al., 2020; Ross et al., 2022; van den Heuvel et al., 2015).

There is accumulating data suggesting that increased dietary vitamin K intake abrogates the progression of cognitive decline in older adults and increased plasma/serum markers of vitamin K status are correlated with improved cognitive function. Since vitamin K is mainly found in leafy vegetables, this association could be an epiphenomenon of healthy diet and lifestyle. Moreover, the data regarding the types and quantity of vitamin K in the brain and their clinical significance are scarce. To test the research hypothesis that brain vitamin K levels might be associated with cognitive impairment and dementia, Booth et al., quantified vitamin K levels in regions of the human brain and examined their possible association with ante-mortem tests of cognitive ability and post-mortem neuropathologic findings in 325 decedents that participated in the Rush Memory and Aging Project (MAP). Apolipoprotein E genotypes were determined and K1 and MK-4 levels were evaluated in 4 different brain regions. Compared to phyloquinone, vitamin K2 (specifically MK-4) was the predominant form of vitamin K in all brain regions. Increased brain MK-4 levels were linked to decreased odds of mild cognitive decline, dementia, Braak stage, Alzheimer's disease scores and less neurofibrillary tangle density (Booth et al., 2022). Moreover, higher pro-mortem vitamin K1 was related with better cognitive function test scores and delayed progression of cognitive decline (Booth et al., 2022). These findings support the hypothesis that vitamin K2 plays a significant role in brain health. Although preliminary, these insights into the connection between vitamin K2 and cognitive performance in human studies offer intriguing avenues for further investigation (Booth et al., 2022).

Vitamin k2 and cardiovascular health—evidence from interventional studies

Arterial stiffness is a dynamic process regulated by various proteins and molecules. Among these, matrix Gla protein (MGP) is the most potent tissue inhibitor of arterial stiffness and calcification. Experimental data suggest that vitamin K2, by activating MGP, may prevent vascular calcification and arterial stiffness, and support cardiovascular health (Spronk et al., 2003; Schurgers et al., 2007a; Scheiber et al., 2015). Based on these findings, a growing number of clinical studies have been conducted to investigate the effects of vitamin K2 in high-risk populations, such as patients with chronic kidney disease (CKD), end-stage kidney disease (ESKD), and diabetes. However, clinical research specifically evaluating the effects of vitamin K2 on arterial stiffness and cognitive performance remains limited (Figure 2). These emerging findings warrant further exploration, particularly through well-designed interventional studies, to fully elucidate the role of vitamin K2 in both cardiovascular and cognitive health.

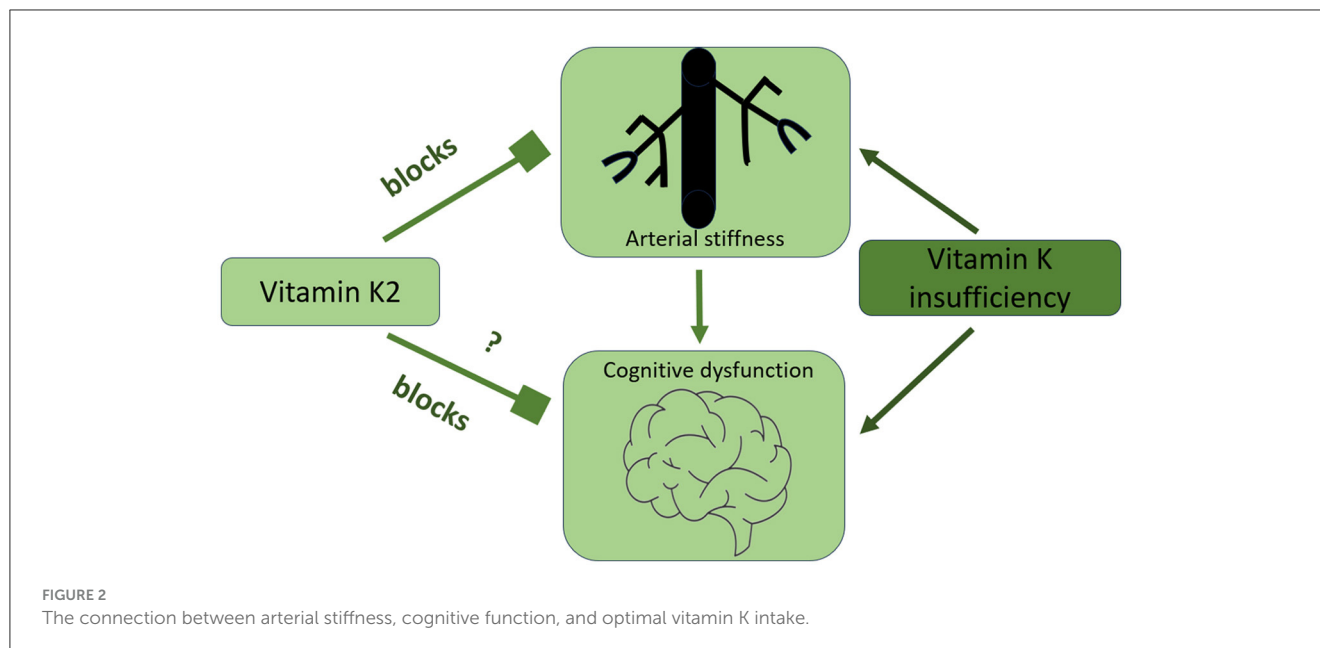
Accumulating evidence suggests that dp-ucMGP is associated with several surrogate markers of arterial calcification (Roumeliotis et al., 2019; Hariri et al., 2021). Additionally, clinical data from studies in patients with impaired kidney function suggest that elevated plasma dp-ucMGP levels serve as independent predictors of adverse clinical outcomes, including all-cause and cardiovascular mortality (Kaesler et al., 2021; Keyzer et al., 2015; Roumeliotis et al., 2020, 2022a). The Rotterdam study was among the first to investigate the association between dietary vitamin K intake and cardiovascular events and all-cause mortality in a large cohort of 4,807 subjects without pre-existing cardiovascular disease (CVD) at baseline (Geleijnse et al., 2004). This landmark study demonstrated that only vitamin K2 (menaquinones) was inversely associated with coronary heart disease incidence, aortic calcification and mortality whereas vitamin K1 failed to show association with any of the outcomes. Moreover, vitamin K2 intake was negatively correlated with all-cause mortality and severe aortic calcification, underscoring the pivotal role of vitamin K consumption in cardiovascular disease prevention (Geleijnse et al., 2004).

Following the recognition of dp-ucMGP as an independent predictor of vascular calcification (VC), several studies explored its association with cardiovascular morbidity and mortality. Findings indicate that elevated dp-ucMGP levels are linked to adverse cardiovascular outcomes and mortality in both the general population (van den Heuvel et al., 2014; Liu et al., 2015) and in specific patient groups, including individuals with diabetes (Dalmeijer et al., 2013; Liabeuf et al., 2014), chronic kidney disease (CKD) (Schurgers et al., 2010; Roumeliotis et al., 2017) and those with pre-existing cardiovascular conditions (Ueland et al., 2010; Capoulade et al., 2014; Mayer et al., 2016).

Given this scientific background, numerous randomized controlled trials (RCTs) have been conducted to investigate the potential effects of vitamin K2, specifically menaquinone-7 (MK-7), on the progression of vascular calcification and cardiovascular disease prevention. One of the earliest double-blind RCTs investigating MK-7 supplementation in 244 postmenopausal women found that long-term (3-year) MK-7 administration of 180 µg/day improved arterial stiffness, as measured by the stiffness index (SI β; MK-7 group: -0.67 ± 2.78 vs. placebo group: $+0.15 \pm 2.51$, $p = 0.018$) (Knapen et al., 2015). The beneficial effects were particularly pronounced in participants with increased baseline vascular stiffness (Knapen et al., 2015).

The KING trial (Vitamin K2 in Renal Graft), a single-center study involving 60 stable kidney transplant recipients, demonstrated that daily supplementation with MK-7 (360 µg/day) for 8 weeks resulted in a 14.2% reduction in carotid-femoral pulse wave velocity (cfPWV), a measure of arterial stiffness (pre-VK: 9.8 ± 2.2 m/s vs. post-VK: 8.4 ± 1.5 m/s, $p < 0.001$), reflecting a 40% improvement in subclinical vitamin K deficiency (Mansour et al., 2017). Similarly, another RCT in 40 kidney transplant recipients showed that 12 weeks of MK-7 supplementation (360 µg/day) led to a significant reduction in dp-ucMGP levels and arterial stiffness [MK-7 group: Δ dp-ucMGP -385 (-631 to -269) pmol/L vs. placebo group: $+39$ (-188 to $+183$) pmol/L, $p < 0.001$] (Eelderink et al., 2023).

A notable study conducted by Naiyarakseree et al. evaluated the effects of oral MK-7 (375 µg once daily) for 24 weeks



in 96 hemodialysis patients with pre-existing arterial stiffness, demonstrating that MK-7 reduced cfPWV in diabetic patients [−10.0% (95% CI: −15.9 to −0.8) vs. placebo: +3.8% (95% CI: −5.8 to +11.6), $p = 0.008$] (Naiyarakseree et al., 2023). A meta-analysis of 14 longitudinal studies, encompassing 10,726 patients and 13 RCTs involving 2,162 participants, found that vitamin K supplementation decreased arterial calcification by 9.1% (95% CI: −17.7 to −0.5, $p = 0.04$) through a 44.7% improvement in vitamin K status (95% CI: −65.1 to −24.3, $p < 0.0001$). Moreover, vitamin K-dependent proteins were strongly associated with reductions in cardiovascular disease and mortality (HR: 0.45, 95% CI: 0.07 to 0.83, $p = 0.02$) (Lees et al., 2019).

While MK-7 has proven to be the most bioactive and clinically relevant form of vitamin K, some studies have investigated the effects of vitamin K1 supplementation on vascular calcification and cardiovascular health. These studies suggest that vitamin K1 reduces vascular calcification (Brandenburg et al., 2017; Saritas et al., 2022). However, it is important to note that once vitamin K1 enters the body, it is partially converted to MK-4 in the intestines and other tissues, implying that the clinical effects of phyloquinone may be mediated via its transformation into MK-4.

However, when K1 enters the human body, it is converted to K2 in the intestine and other tissues and thus, the clinical effects of phyloquinone are exerted through transformation to K2.

Despite promising results, some RCTs, particularly in CKD patients, have yielded negative outcomes regarding the effects of vitamin K supplementation on arterial stiffness and cardiovascular risk. Trials such as the Trevasc-HDK study (Haroon et al., 2023), K4Kidneys study (Witham et al., 2020), ViKTORIES study (Lees et al., 2021), Valkyrie study (De Vriese et al., 2020), RenakVit trial (Levy-Schousboe et al., 2021) and the study by Oikonomaki et al. (2019), reported no significant improvement in cardiovascular outcomes. However, these studies suffered from various limitations, including small sample sizes, high dropout rates, and suboptimal vitamin K dosing (360 μg MK-7, 3 times/wk in the Trevasc-HDK,

400 $\mu\text{g}/\text{day}$ m-7 in the K4Kidneys, menadiol diphosphate 5 mg, thrice weekly in the ViKTORIES, vitamin K2 2000 μg thrice weekly in the Valkyrie, 360 μg MK-7 daily in the RenakVit, 200 μg MK-7 daily in the Greek study). For example, in the RenakVit trial, only 21 patients completed the study (Levy-Schousboe et al., 2021). The ViKTORIES study raised concerns about the methods used to assess vitamin K deficiency, specifically regarding the accuracy of dp-ucMGP assays (Te Velde-Keyzer and de Borst, 2022) and the Valkyrie study, included very old patients with increased Agatston score (where arteries are in an advanced calcification non-reversible state) (De Vriese et al., 2020). Moreover, dose-finding studies have indicated that even doses as high as 460 $\mu\text{g}/\text{day}$ of MK-7 are insufficient to fully correct vitamin K deficiency in hemodialysis patients, suggesting that higher doses (>500 $\mu\text{g}/\text{day}$) are necessary (Caluwé et al., 2014; Westenfeld et al., 2012).

To address these limitations, ongoing trials such as the UCASAL-VITK study (NCT04539418) and the VIKIPEDIA study (NCT04900610) are investigating the effects of higher MK-7 doses in hemodialysis (2,000 μg iv thrice weekly) and peritoneal dialysis (1,000 $\mu\text{g}/\text{day}$) patients, respectively (Roumeliotis et al., 2022b). The results of these trials are expected to provide crucial insights into the safety, tolerability, and efficacy of optimal MK-7 doses in uremic populations.

Conclusion

Vascular calcification and arterial stiffness may represent pathophysiological mechanisms underlying the onset and progression of cognitive decline. Vitamin K deficiency is a key determinant of arterial health and, by extension, may influence cognitive function in the elderly. To elucidate the potential therapeutic benefits of MK-7 supplementation on cognitive function, future RCTs are needed. These trials should focus on using optimal dosages (>500 $\mu\text{g}/\text{day}$), ensuring long follow-up

periods, and utilizing the most bioactive form of vitamin K (MK-7). Such studies are essential to establish whether vitamin K2 supplementation can play a role in preventing or mitigating cognitive decline in aging populations.

Author contributions

SR: Writing – original draft, Writing – review & editing. IK: Investigation, Methodology, Writing – original draft. FV: Validation, Writing – review & editing. KM: Methodology, Project administration, Writing – review & editing. J-FJ: Project administration, Visualization, Writing – review & editing. KL: Investigation, Writing – original draft. LS: Supervision, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This study was supported by Gnosis by Lesaffre (Lesaffre International).

Conflict of interest

FV and LS was an employee at the Cardiovascular Research Institute Maastricht-CARIM) and SR and KM have scientific

collaborations and received research fundings from Gnosis by Lesaffre, Lesaffre International. LS receives grants to institutions from Gnosis by Lesaffre and Bayer, and is a shareholder of Coagulation Profile. J-FJ was an employee of Gnosis by Lesaffre (Lesaffre International).

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Generative AI statement

The author(s) declare that no Gen AI was used in the creation of this manuscript.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

- Ageing and Health (2024). Available at: <https://www.who.int/news-room/factsheets/detail/ageing-and-health> (accessed February 25, 2024).
- Akbulut, A. C., Pavlic, A., Petsophonsakul, P., Halder, M., Maresz, K., Kramann, R., et al. (2020). Vitamin K2 needs an RDI separate from vitamin K1. *Nutrients* 12:1852. doi: 10.3390/nu12061852
- Alessenko, A. V., and Albi, E. (2020). Exploring sphingolipid implications in neurodegeneration. *Front. Neurol.* 11:437. doi: 10.3389/fneur.2020.00437
- Alosco, M. L., and Hayes, S. M. (2015). Structural brain alterations in heart failure: a review of the literature and implications for risk of Alzheimer's disease. *Heart Fail. Rev.* 20, 561–571. doi: 10.1007/s10741-015-9488-5
- Alvarez-Bueno, C., Cunha, P. G., Martinez-Vizcaino, V., Pozuelo-Carrascosa, D. P., Visier-Alfonso, M. E., Jimenez-Lopez, E., et al. (2020). Arterial stiffness and cognition among adults: a systematic review and meta-analysis of observational and longitudinal studies. *J. Am. Heart Assoc.* 9:e014621. doi: 10.1161/JAHA.119.014621
- Apaijai, N., Sriwichaiin, S., Phrommintikul, A., Jaiwongkam, T., Kerdphoo, S., Chansirikarnjana, S., et al. (2020). Cognitive impairment is associated with mitochondrial dysfunction in peripheral blood mononuclear cells of elderly population. *Sci. Rep.* 10:21400. doi: 10.1038/s41598-020-78551-4
- Baierle, M., Nascimento, S. N., Moro, A. M., Brucker, N., Freitas, F., Gauer, B., et al. (2015). Relationship between inflammation and oxidative stress and cognitive decline in the institutionalized elderly. *Oxid. Med. Cell. Longev.* 2015:804198. doi: 10.1155/2015/804198
- Beulens, J. W. J., van der A, D. L., Grobbee, D. E., Sluijs, I., Spijkerman, A. M. W., and van der Schouw, Y. T. (2010). Dietary phylloquinone and menaquinones intakes and risk of type 2 diabetes. *Diabetes Care* 33, 1699–1705. doi: 10.2337/dc09-2302
- Binder, M. D., Xiao, J., Kemper, D., Ma, G. Z. M., Murray, S. S., Kilpatrick, T. J., et al. (2011). Gas6 increases myelination by oligodendrocytes and its deficiency delays recovery following cuprizone-induced demyelination. *PLoS ONE* 6:e17727. doi: 10.1371/journal.pone.0017727
- Booth, S. L., Shea, M. K., Barger, K., Leurgans, S. E., James, B. D., Holland, T. M., et al. (2022). Association of vitamin K with cognitive decline and neuropathology in community-dwelling older persons. *Alzheimers. Dement.* 8:e12255. doi: 10.1002/trc2.12255
- Boutouyrie, P., Fliser, D., Goldsmith, D., Covic, A., Wiecek, A., Ortiz, A., et al. (2014). Assessment of arterial stiffness for clinical and epidemiological studies: methodological considerations for validation and entry into the European renal and cardiovascular medicine registry. *Nephrol. Dial. Transplant.* 29, 232–239. doi: 10.1093/ndt/gft309
- Brandenburg, V. M., Reinartz, S., Kaesler, N., Krüger, T., Dirrichs, T., Kramann, R., et al. (2017). Slower progress of aortic valve calcification with vitamin K supplementation: results from a prospective interventional proof-of-concept study. *Circulation* 135, 2081–2083. doi: 10.1161/CIRCULATIONAHA.116.027011
- Caluwé, R., Vandecasteele, S., Van Vlem, B., Vermeer, C., and De Vriese, A. S. (2014). Vitamin K2 supplementation in haemodialysis patients: a randomized dose-finding study. *Nephrol. Dial. Transplant.* 29, 1385–1390. doi: 10.1093/ndt/gft464
- Camandola, S., and Mattson, M. P. (2017). Brain metabolism in health, aging, and neurodegeneration. *EMBO J.* 36, 1474–1492. doi: 10.15252/embj.201695810
- Capoulade, R., Côté, N., Mathieu, P., Chan, K. L., Clavel, M.-A., Dumesnil, J. G., et al. (2014). Circulating levels of matrix Gla protein and progression of aortic stenosis: a substudy of the aortic stenosis progression observation: measuring effects of rosuvastatin (ASTRONOMER) trial. *Can. J. Cardiol.* 30, 1088–1095. doi: 10.1016/j.cjca.2014.03.025
- Chatterjee, K., Mazumder, P. M., Sarkar, S. R., Saha, R., Chatterjee, A., Sarkar, B., et al. (2023). Neuroprotective effect of vitamin K2 against gut dysbiosis associated cognitive decline. *Physiol. Behav.* 269:114252. doi: 10.1016/j.physbeh.2023.114252
- Chouet, J., Ferland, G., Féart, C., Rolland, Y., Presse, N., Boucher, K., et al. (2015). Dietary Vitamin K intake is associated with cognition and behaviour among geriatric patients: the CLIP study. *Nutrients* 7, 6739–6750. doi: 10.3390/nu7085306
- Coffin, C., Suerken, C. K., Bateman, J. R., Whitlow, C. T., Williams, B. J., Espeland, M. A., et al. (2022). Vascular and microstructural markers of cognitive pathology. *Alzheimers. Dement.* 14:e12332. doi: 10.1002/alz.065669
- Dalmeijer, G. W., van der Schouw, Y. T., Magdeleyns, E. J., Vermeer, C., Verschuren, W. M. M., Boer, J. M. A., et al. (2013). Matrix Gla protein species and risk of

- cardiovascular events in type 2 diabetic patients. *Diabetes Care* 36, 3766–3771. doi: 10.2337/dc13-0065
- De Vriese, A. S., Caluwé, R., Pyfferoen, L., De Bacquer, D., De Boeck, K., Delanote, J., et al. (2020). Trial of vitamin K antagonist replacement by rivaroxaban with or without vitamin K2 in hemodialysis patients with atrial fibrillation: the Valkyrie Study. *J. Am. Soc. Nephrol.* 31, 186–196. doi: 10.1681/ASN.2019060579
- Denisova, N. A., and Booth, S. L. (2005). Vitamin K and sphingolipid metabolism: evidence to date. *Nutr. Rev.* 63, 111–121. doi: 10.1111/j.1753-4887.2005.tb00129.x
- Dolan, H., Crain, B., Troncoso, J., Resnick, S. M., Zonderman, A. B., O'Brien, R. J., et al. (2010). Atherosclerosis, dementia, and Alzheimer disease in the Baltimore longitudinal study of aging cohort. *Ann. Neurol.* 68, 231–240. doi: 10.1002/ana.22055
- Eelderink, C., Kremer, D., Riphagen, I. J., Knobbe, T. J., Schurgers, L. J., Pasch, A., et al. (2023). Effect of vitamin K supplementation on serum calcification propensity and arterial stiffness in vitamin K-deficient kidney transplant recipients: a double-blind, randomized, placebo-controlled clinical trial. *Am. J. Transplant.* 23, 520–530. doi: 10.1016/j.ajt.2022.12.015
- Elkattawy, H. A., Ghoneim, F. M., Eladl, M. A., Said, E., Ebrahim, H. A., El-Shafey, M., et al. (2022). Vitamin K2 (menaquinone-7) reverses age-related structural and cognitive deterioration in naturally aging rats. *Antioxidants* 11:514. doi: 10.3390/antiox11030514
- Ellis, J. L., Karl, J. P., Oliverio, A. M., Fu, X., Soares, J. W., Wolfe, B. E., et al. (2021). Dietary vitamin K is remodeled by gut microbiota and influences community composition. *Gut Microbes* 13, 1–16. doi: 10.1080/19490976.2021.1887721
- Geleijnse, J. M., Vermeer, C., Grobbee, D. E., Schurgers, L. J., Knapen, M. H. J., van der Meer, I. M., et al. (2004). Dietary intake of menaquinone is associated with a reduced risk of coronary heart disease: the Rotterdam Study. *J. Nutr.* 134, 3100–3105. doi: 10.1093/jn/134.11.3100
- Gilchrist, S. E., Goudarzi, S., and Hafizi, S. (2020). Gas6 inhibits toll-like receptor-mediated inflammatory pathways in mouse microglia via Axl and Mer. *Front. Cell. Neurosci.* 14:576650. doi: 10.3389/fncel.2020.576650
- Griffin, J. H., Fernández, J. A., Lyden, P. D., and Zlokovic, B. V. (2016). Activated protein C promotes neuroprotection: mechanisms and translation to the clinic. *Thromb. Res.* 141(Suppl 2), S62–S64. doi: 10.1016/S0049-3848(16)30368-1
- Haidegger, M., Lindenbeck, S., Hofer, E., Rodler, C., Zweiker, R., Perl, S., et al. (2023). Arterial stiffness and its influence on cerebral morphology and cognitive function. *Ther. Adv. Neurol. Disord.* 16:17562864231180715. doi: 10.1177/17562864231180715
- Halder, M., Petsophonsakul, P., Akbulut, A. C., Pavlic, A., Bohan, F., Anderson, E., et al. (2019). Vitamin K: double bonds beyond coagulation insights into differences between vitamin K1 and K2 in health and disease. *Int. J. Mol. Sci.* 20:896. doi: 10.3390/ijms20040896
- Hariri, E., Kassis, N., Iskandar, J.-P., Schurgers, L. J., Saad, A., Abdelfattah, O., et al. (2021). Vitamin K2-a neglected player in cardiovascular health: a narrative review. *Open Heart* 8:e001715. doi: 10.1136/openhrt-2021-001715
- Haroon, S., Davenport, A., Ling, L.-H., Tai, B.-C., Teo, L.-L.-S., Schurgers, L., et al. (2023). Randomized controlled clinical trial of the effect of treatment with vitamin K2 on vascular calcification in hemodialysis patients (Trevasc-HDK). *Kidney Int. Rep.* 8, 1741–1751. doi: 10.1016/j.ekir.2023.06.011
- Horie-Inoue, K., and Inoue, S. (2008). Steroid and Xenobiotic receptor mediates a novel vitamin K2 signaling pathway in osteoblastic cells. *J. Bone Miner. Metab.* 26, 9–12. doi: 10.1007/s00774-007-0792-6
- Huang, S.-H., Fang, S.-T., and Chen, Y.-C. (2021). Molecular mechanism of vitamin K2 protection against amyloid- β -induced cytotoxicity. *Biomolecules* 11:423. doi: 10.3390/biom11030423
- Jefferson, A. L., Cambrono, F. E., Liu, D., Moore, E. E., Neal, J. E., Terry, J. G., et al. (2018). Higher aortic stiffness is related to lower cerebral blood flow and preserved cerebrovascular reactivity in older adults. *Circulation* 138, 1951–1962. doi: 10.1161/CIRCULATIONAHA.118.032410
- Kaesler, N., Schurgers, L. J., and Floege, J. (2021). Vitamin K and cardiovascular complications in chronic kidney disease patients. *Kidney Int.* 100, 1023–1036. doi: 10.1016/j.kint.2021.06.037
- Keyzer, C. A., Vermeer, C., Joosten, M. M., Knapen, M. H. J., Drummen, N. E. A., Navis, G., et al. (2015). Vitamin K status and mortality after kidney transplantation: a cohort study. *Am. J. Kidney Dis.* 65, 474–483. doi: 10.1053/j.ajkd.2014.09.014
- Kiely, A., Ferland, G., Ouliass, B., O'Toole, P. W., Purtil, H., O'Connor, E. M., et al. (2020). Vitamin K status and inflammation are associated with cognition in older Irish adults. *Nutr. Neurosci.* 23, 591–599. doi: 10.1080/1028415X.2018.1536411
- Knapen, M. H. J., Braam, L. A. J. L. M., Drummen, N. E., Bekers, O., Hoeks, A. P. G., Vermeer, C., et al. (2015). Menaquinone-7 supplementation improves arterial stiffness in healthy postmenopausal women. A double-blind randomised clinical trial. *Thromb. Haemost.* 113, 1135–1144. doi: 10.1160/TH14-08-0675
- Kurnatowska, I., Grzelak, P., Masajtis-Zagajewska, A., Kaczmarek, M., Stefańczyk, L., Vermeer, C., et al. (2015). Effect of vitamin K2 on progression of atherosclerosis and vascular calcification in nondialyzed patients with chronic kidney disease stages 3–5. *Pol. Arch. Med. Wewn.* 125, 631–640. doi: 10.20452/pamw.3041
- Lacolley, P., Regnault, V., and Laurent, S. (2020). Mechanisms of arterial stiffening: from mechanotransduction to epigenetics. *ATVB* 40, 1055–1062. doi: 10.1161/ATVBAHA.119.313129
- Laurent, S., and Boutouyrie, P. (2020). Arterial stiffness and hypertension in the elderly. *Front. Cardiovasc. Med.* 7:544302. doi: 10.3389/fcvm.2020.544302
- Laurent, S., Cockcroft, J., Van Bortel, L., Boutouyrie, P., Giannattasio, C., Hayoz, D., et al. (2006). Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur. Heart J.* 27, 2588–2605. doi: 10.1093/eurheartj/ehl254
- Lee, B., Choi, G.-M., Hong, J.-P., Cho, D.-E., Kim, Y., Yeom, M., et al. (2022). Menaquinone-7 ameliorates cerebrovascular calcification-associated memory decline in aged mice. *Life Sci.* 307:120912. doi: 10.1016/j.lfs.2022.120912
- Lees, J. S., Chapman, F. A., Witham, M. D., Jardine, A. G., and Mark, P. B. (2019). Vitamin K status, supplementation and vascular disease: a systematic review and meta-analysis. *Heart* 105, 938–945. doi: 10.1136/heartjnl-2018-313955
- Lees, J. S., Rankin, A. J., Gillis, K. A., Zhu, L. Y., Mangion, K., Rutherford, E., et al. (2021). The ViKTORIES trial: a randomized, double-blind, placebo-controlled trial of vitamin K supplementation to improve vascular health in kidney transplant recipients. *Am. J. Transplant.* 21, 3356–3368. doi: 10.1111/ajt.16556
- Levy-Schousboe, K., Frimodt-Møller, M., Hansen, D., Peters, C. D., Kjærgaard, K. D., Jensen, J. D., et al. (2021). Vitamin K supplementation and arterial calcification in dialysis: results of the double-blind, randomized, placebo-controlled RenaKvit trial. *Clin. Kidney J.* 14, 2114–2123. doi: 10.1093/ckj/sfab017
- Li, T., Wang, Y., and Tu, W.-P. (2023). Vitamin K supplementation and vascular calcification: a systematic review and meta-analysis of randomized controlled trials. *Front. Nutr.* 10:1115069. doi: 10.3389/fnut.2023.1115069
- Liabeuf, S., Bourron, O., Olivier, B., Vemeer, C., Theuwissen, E., Magdeleyns, E., et al. (2014). Vascular calcification in patients with type 2 diabetes: the involvement of matrix Gla protein. *Cardiovasc. Diabetol.* 13:85. doi: 10.1186/1475-2840-13-85
- Lin, X., Wen, X., Wei, Z., Guo, K., Shi, F., Huang, T., et al. (2021). Vitamin K2 protects against A β 42-induced neurotoxicity by activating autophagy and improving mitochondrial function in *Drosophila*. *Neuroreport* 32, 431–437. doi: 10.1097/WNR.0000000000001599
- Liu, Q., Fang, J., Cui, C., Dong, S., Gao, L., Bao, J., et al. (2021). Association of aortic stiffness and cognitive decline: a systematic review and meta-analysis. *Front. Aging Neurosci.* 13:680205. doi: 10.3389/fnagi.2021.680205
- Liu, Y.-P., Gu, Y.-M., Thijs, L., Knapen, M. H. J., Salvi, E., Citterio, L., et al. (2015). Inactive matrix Gla protein is causally related to adverse health outcomes: a mendelian randomization study in a Flemish population. *Hypertension* 65, 463–470. doi: 10.1161/HYPERTENSIONAHA.114.04494
- Mansour, A. G., Hariri, E., Daaboul, Y., Korjian, S., El Alam, A., Protogerou, A. D., et al. (2017). Vitamin K2 supplementation and arterial stiffness among renal transplant recipients—a single-arm, single-center clinical trial. *J. Am. Soc. Hypertens.* 11, 589–597. doi: 10.1016/j.jash.2017.07.001
- Mayer, O., Seidlerová, J., Vaněk, J., Karnosová, P., Bruthans, J., Filipovský, J., et al. (2016). Inactive matrix Gla protein is causally related to adverse health outcomes: an additional mortality risk in heart failure patients with vascular disease. *Int. J. Cardiol.* 203, 916–922. doi: 10.1016/j.ijcard.2015.10.226
- Mensah, G. A., Roth, G. A., and Fuster, V. (2019). The global burden of cardiovascular diseases and risk factors: 2020 and beyond. *J. Am. Coll. Cardiol.* 74, 2529–2532. doi: 10.1016/j.jacc.2019.10.009
- Mukai, K., Morimoto, H., Kikuchi, S., and Nagaoka, S. (1993). Kinetic study of free-radical-scavenging action of biological hydroquinones (reduced forms of ubiquinone, vitamin K and tocopherol quinone) in solution. *Biochim. Biophys. Acta* 1157, 313–317. doi: 10.1016/0304-4165(93)90115-O
- Muszyńska, M., Ambroźewicz, E., Gegotek, A., Gryniewicz, G., and Skrzydlewska, E. (2020). Protective effects of vitamin K compounds on the proteomic profile of osteoblasts under oxidative stress conditions. *Molecules* 25:1990. doi: 10.3390/molecules25081990
- Naiyarakseree, N., Phannajit, J., Naiyarakseree, W., Mahatanan, N., Asavapujanamane, P., Lekhyananda, S., et al. (2023). Effect of menaquinone-7 supplementation on arterial stiffness in chronic hemodialysis patients: a multicenter randomized controlled trial. *Nutrients* 15:2422. doi: 10.3390/nu15112422
- Neofytou, I. E., Stamou, A., Demopoulos, A., Roumeliotis, S., Zebekakis, P., Liakopoulos, V., et al. (2024). Vitamin K for vascular calcification in kidney patients: still alive and kicking, but still a lot to learn. *Nutrients* 16:1798. doi: 10.3390/nu16121798
- Obri, A., Khramian, L., Karsenty, G., and Oury, F. (2018). Osteocalcin in the brain: from embryonic development to age-related decline in cognition. *Nat. Rev. Endocrinol.* 14, 174–182. doi: 10.1038/nrendo.2017.181
- Oikonomaki, T., Papatirou, M., Ntrini, T., Kalogeropoulou, C., Zabakis, P., Kalavrizioti, D., et al. (2019). The effect of vitamin K2 supplementation on vascular calcification in haemodialysis patients: a 1-year follow-up randomized trial. *Int. Urol. Nephrol.* 51, 2037–2044. doi: 10.1007/s11255-019-02275-2
- Oury, F., Khramian, L., Denny, C. A., Gardin, A., Chamouni, A., Goeden, N., et al. (2013). Maternal and offspring pools of osteocalcin influence brain development and functions. *Cell* 155, 228–241. doi: 10.1016/j.cell.2013.08.042

- Palta, P., Sharrett, A. R., Wei, J., Meyer, M. L., Kucharska-Newton, A., Power, M. C., et al. (2019). Central arterial stiffness is associated with structural brain damage and poorer cognitive performance: the ARIC Study. *J. Am. Heart Assoc.* 8:e011045. doi: 10.1161/JAHA.118.011045
- Pase, M. P., Herbert, A., Grima, N. A., Pipingas, A., and O'Rourke, M. F. (2012). Arterial stiffness as a cause of cognitive decline and dementia: a systematic review and meta-analysis. *Intern. Med. J.* 42, 808–815. doi: 10.1111/j.1445-5994.2011.02645.x
- Popescu, A., and German, M. (2021). Vitamin K2 holds promise for Alzheimer's prevention and treatment. *Nutrients* 13:2206. doi: 10.3390/nu13072206
- Presse, N., Belleville, S., Gaudreau, P., Greenwood, C. E., Kergoat, M.-J., Morais, J. A., et al. (2013). Vitamin K status and cognitive function in healthy older adults. *Neurobiol. Aging* 34, 2777–2783. doi: 10.1016/j.neurobiolaging.2013.05.031
- Presse, N., Shatenstein, B., Kergoat, M.-J., and Ferland, G. (2008). Low vitamin K intakes in community-dwelling elders at an early stage of Alzheimer's disease. *J. Am. Diet. Assoc.* 108, 2095–2099. doi: 10.1016/j.jada.2008.09.013
- Promjunyakul, N.-O., Lahna, D. L., Kaye, J. A., Dodge, H. H., Erten-Lyons, D., Rooney, W. D., et al. (2016). Comparison of cerebral blood flow and structural penumbras in relation to white matter hyperintensities: a multi-modal magnetic resonance imaging study. *J. Cereb. Blood Flow. Metab.* 36, 1528–1536. doi: 10.1177/0271678X16651268
- Putzu, A., Valtorta, S., Di Grigoli, G., Haenggi, M., Belloli, S., Malgaroli, A., et al. (2018). Cerebral glucose metabolism after cardiac arrest and resuscitation in rats using [18F]FDG positron emission tomography and autoradiography. *Neurocrit. Care* 28, 370–378. doi: 10.1007/s12028-017-0445-0
- Rahimi Sakak, F., Moslehi, N., Niroomand, M., and Mirmiran, P. (2021). Glycemic control improvement in individuals with type 2 diabetes with vitamin K2 supplementation: a randomized controlled trial. *Eur. J. Nutr.* 60, 2495–2506. doi: 10.1007/s00394-020-02419-6
- Ross, R. D., Olali, A. Z., Shi, Q., Hoover, D. R., Sharma, A., Weber, K. M., et al. (2022). Brief report: undercarboxylated osteocalcin is associated with cognition in women with and without HIV. *J. Acquir. Immune Defic. Syndr.* 91, 162–167. doi: 10.1097/QAI.00000000000003043
- Roumeliotis, S., Dounousi, E., Eleftheriadis, T., and Liakopoulos, V. (2019). Association of the inactive circulating matrix Gla protein with vitamin K intake, calcification, mortality, and cardiovascular disease: a review. *Int. J. Mol. Sci.* 20, 628. doi: 10.3390/ijms20030628
- Roumeliotis, S., Duni, A., Vaios, V., Kitsos, A., Liakopoulos, V., Dounousi, E., et al. (2022a). Vitamin K supplementation for prevention of vascular calcification in chronic kidney disease patients: are we there yet? *Nutrients* 14:925. doi: 10.3390/nu14050925
- Roumeliotis, S., Roumeliotis, A., Georgianos, P. I., Thodis, E., Schurgers, L. J., Maresz, K., et al. (2022b). Vitamin K In PERitoneal DIAlysis (VIKIPEDIA): rationale and study protocol for a randomized controlled trial. *PLoS ONE* 17:e0273102. doi: 10.1371/journal.pone.0273102
- Roumeliotis, S., Roumeliotis, A., Panagoutsos, S., Giannakopoulou, E., Papanas, N., Manolopoulos, V. G., et al. (2017). Matrix Gla protein T-138C polymorphism is associated with carotid intima media thickness and predicts mortality in patients with diabetic nephropathy. *J. Diabetes Complicat.* 31, 1527–1532. doi: 10.1016/j.jdiacomp.2017.06.012
- Roumeliotis, S., Roumeliotis, A., Stamou, A., Leivaditis, K., Kantartzis, K., Panagoutsos, S., et al. (2020). The association of Dp-ucMGP with cardiovascular morbidity and decreased renal function in diabetic chronic kidney disease. *Int. J. Mol. Sci.* 21:6035. doi: 10.3390/ijms21176035
- Rusanen, M., Kivipelto, M., Levalahti, E., Laatikainen, T., Tuomilehto, J., Soininen, H., et al. (2014). Heart diseases and long-term risk of dementia and Alzheimer's disease: a population-based CAIDE Study. *J. Alzheimers. Dis.* 42, 183–191. doi: 10.3233/JAD-132363
- Santa-Maria, I., Avila, J., and Rabano, A. (2010). Differential gene expression analysis of human entorhinal cortex support a possible role of some extracellular matrix proteins in the onset of Alzheimer disease. *Neurosci. Lett.* 468, 225–228. doi: 10.1016/j.neulet.2009.11.002
- Saritas, T., Reinartz, S., Krüger, T., Ketteler, M., Liangos, O., Labriola, L., et al. (2022). Vitamin K1 and progression of cardiovascular calcifications in hemodialysis patients: the VitaVasK randomized controlled trial. *Clin. Kidney J.* 15, 2300–2311. doi: 10.1093/ckj/sfac184
- Scheiber, D., Veulemans, V., Horn, P., Chatrou, M. L., Potthoff, S. A., Kelm, M., et al. (2015). High-dose menaquinone-7 supplementation reduces cardiovascular calcification in a murine model of extrasosseous calcification. *Nutrients* 7, 6991–7011. doi: 10.3390/nu7085318
- Schurgers, L. J., Barreto, D. V., Barreto, F. C., Liabeuf, S., Renard, C., Magdeleyns, E. J., et al. (2010). The circulating inactive form of matrix Gla protein is a surrogate marker for vascular calcification in chronic kidney disease: a preliminary report. *Clin. J. Am. Soc. Nephrol.* 5, 568–575. doi: 10.2215/CJN.07081009
- Schurgers, L. J., Cranenburg, E. C. M., and Vermeer, C. (2008). Matrix Gla-protein: the calcification inhibitor in need of vitamin K. *Thromb. Haemost.* 100, 593–603. doi: 10.1160/TH08-02-0087
- Schurgers, L. J., Spronk, H. M. H., Soute, B. A. M., Schiffrers, P. M., DeMey, J. G. R., Vermeer, C., et al. (2007a). Regression of warfarin-induced medial elastocalcinosis by high intake of vitamin K in rats. *Blood* 109, 2823–2831. doi: 10.1182/blood-2006-07-035345
- Schurgers, L. J., Teunissen, K. J. F., Hamulyák, K., Knapen, M. H. J., Vik, H., Vermeer, C., et al. (2007b). Vitamin K-containing dietary supplements: comparison of synthetic vitamin K1 and natto-derived menaquinone-7. *Blood* 109, 3279–3283. doi: 10.1182/blood-2006-08-040709
- Shandilya, S., Kesari, K. K., and Ruokolainen, J. (2021). Vitamin K2 modulates organelle damage and tauopathy induced by streptozotocin and menadione in SH-SY5Y cells. *Antioxidants* 10:983. doi: 10.3390/antiox10060983
- Shea, M. K., and Booth, S. L. (2016). Concepts and controversies in evaluating vitamin K status in population-based studies. *Nutrients* 8:8. doi: 10.3390/nu8010008
- Shea, M. K., Wang, J., Barger, K., Weiner, D. E., Booth, S. L., Seliger, S. L., et al. (2022). Vitamin K status and cognitive function in adults with chronic kidney disease: the chronic renal insufficiency cohort. *Curr. Dev. Nutr.* 6:nzac111. doi: 10.1093/cdn/nzac111
- Spronk, H. M. H., Soute, B. M., Schurgers, L. J., Thijssen, H. H. W., De Mey, J. G. R., and Vermeer, C. (2003). Tissue-specific utilization of menaquinone-4 results in the prevention of arterial calcification in warfarin-treated rats. *J. Vasc. Res.* 40, 531–537. doi: 10.1159/000075344
- Tamadon-Nejad, S., Ouliass, B., Rochford, J., and Ferland, G. (2018). Vitamin K deficiency induced by warfarin is associated with cognitive and behavioral perturbations, and alterations in brain sphingolipids in rats. *Front. Aging Neurosci.* 10:213. doi: 10.3389/fnagi.2018.00213
- Tang, H., Zheng, Z., Wang, H., Wang, L., Zhao, G., Wang, P., et al. (2022). Vitamin K2 modulates mitochondrial dysfunction induced by 6-hydroxydopamine in SH-SY5Y cells via mitochondrial quality-control loop. *Nutrients* 14:1504. doi: 10.3390/nu14071504
- Tarkesh, F., Namavar Jahromi, B., Hejazi, N., and Tabatabaee, H. (2020). Beneficial health effects of menaquinone-7 on body composition, glycemic indices, lipid profile, and endocrine markers in polycystic ovary syndrome patients. *Food Sci. Nutr.* 8, 5612–5621. doi: 10.1002/fsn3.1837
- Te Velde-Keyzer, C. A., de Borst, M. H. (2022). Vitamin K supplementation and vascular health after kidney transplantation. *Am. J. Transplant.* 22, 318–319. doi: 10.1111/ajt.16741
- Thorin-Trescases, N., and Thorin, E. (2016). Lifelong cyclic mechanical strain promotes large elastic artery stiffening: increased pulse pressure and old age-related organ failure. *Can. J. Cardiol.* 32, 624–633. doi: 10.1016/j.cjca.2015.12.022
- Tomoto, T., Tarumi, T., and Zhang, R. (2023). Central arterial stiffness, brain white matter hyperintensity and total brain volume across the adult lifespan. *J. Hypertens.* 41, 819–829. doi: 10.1097/HJH.00000000000003404
- Tooley, K. L. (2020). Effects of the human gut microbiota on cognitive performance, brain structure and function: a narrative review. *Nutrients* 12:3009. doi: 10.3390/nu12103009
- Townsend, R. R., Wilkinson, I. B., Schiffrin, E. L., Avolio, A. P., Chirinos, J. A., Cockcroft, J. R., et al. (2015). Recommendations for improving and standardizing vascular research on arterial stiffness: a scientific statement from the American Heart Association. *Hypertension* 66, 698–722. doi: 10.1161/HYP.0000000000000033
- Ueland, T., Gullestad, L., Dahl, C. P., Aukrust, P., Aakhus, S., Solberg, O. G., et al. (2010). Undercarboxylated matrix Gla protein is associated with indices of heart failure and mortality in symptomatic aortic stenosis. *J. Intern. Med.* 268, 483–492. doi: 10.1111/j.1365-2796.2010.02264.x
- van den Heuvel, E. G. H. M., van Schoor, N. M., Lips, P., Magdeleyns, E. J. P., Deeg, D. J. H., Vermeer, C., et al. (2014). Gla protein, a marker of vitamin K status, as a risk factor of cardiovascular disease. *Maturitas* 77, 137–141. doi: 10.1016/j.maturitas.2013.10.008
- van den Heuvel, E. G. H. M., van Schoor, N. M., Vermeer, C., Zwijsen, R. M. L., den Heijer, M., and Comijs, H. C. (2015). Vitamin K status is not associated with cognitive decline in middle aged adults. *J. Nutr. Health Aging* 19, 908–912. doi: 10.1007/s12603-015-0579-8
- van Sloten, T. T., Protogerou, A. D., Henry, R. M. A., Schram, M. T., Launer, L. J., Stehouwer, C. D. A., et al. (2015). Association between arterial stiffness, cerebral small vessel disease and cognitive impairment: a systematic review and meta-analysis. *Neurosci. Biobehav. Rev.* 53, 121–130. doi: 10.1016/j.neubiorev.2015.03.011
- Varnum, B. C., Young, C., Elliott, G., Garcia, A., Bartley, T. D., Fridell, Y. W., et al. (1995). Axl receptor tyrosine kinase stimulated by the vitamin K-dependent protein encoded by growth-arrest-specific gene 6. *Nature* 373, 623–626. doi: 10.1038/373623a0
- Vlachopoulos, C., Aznaouridis, K., and Stefanadis, C. (2010). Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J. Am. Coll. Cardiol.* 55, 1318–1327. doi: 10.1016/j.jacc.2009.10.061

- Wachsmuth, H. R., Weninger, S. N., and Duca, F. A. (2022). Role of the gut–brain axis in energy and glucose metabolism. *Exp. Mol. Med.* 54, 377–392. doi: 10.1038/s12276-021-00677-w
- Westenfeld, R., Krueger, T., Schlieper, G., Cranenburg, E. C. M., Magdeleyns, E. J., Heidenreich, S., et al. (2012). Effect of vitamin K2 supplementation on functional vitamin K deficiency in hemodialysis patients: a randomized trial. *Am. J. Kidney Dis.* 59, 186–195. doi: 10.1053/j.ajkd.2011.10.041
- Witham, M. D., Lees, J. S., White, M., Band, M., Bell, S., Chantler, D. J., et al. (2020). Vitamin K supplementation to improve vascular stiffness in CKD: the K4kidneys randomized controlled trial. *J. Am. Soc. Nephrol.* 31, 2434–2445. doi: 10.1681/ASN.2020020225
- Yu, Y.-X., Li, Y.-P., Gao, F., Hu, Q.-S., Zhang, Y., Chen, D., et al. (2016). Vitamin K2 suppresses rotenone-induced microglial activation *in vitro*. *Acta Pharmacol. Sin.* 37, 1178–1189. doi: 10.1038/aps.2016.68
- Zhang, C., Gu, Z.-C., Shen, L., Pan, M.-M., Yan, Y.-D., Pu, J., et al. (2018). Non-vitamin K antagonist oral anticoagulants and cognitive impairment in atrial fibrillation: insights from the meta-analysis of over 90,000 patients of randomized controlled trials and real-world studies. *Front. Aging Neurosci.* 10:258. doi: 10.3389/fnagi.2018.00258
- Zhu, D., Wang, Y., Singh, I., Bell, R. D., Deane, R., Zhong, Z., et al. (2010). Protein S controls hypoxic/ischemic blood-brain barrier disruption through the TAM receptor tyro3 and sphingosine 1-phosphate receptor. *Blood* 115, 4963–4972. doi: 10.1182/blood-2010-01-262386