REVIEW PAPER

DOI: https://doi.org/10.20883/medical.402

Effect of vitamin K supplementation on anthropometric parameters and adipokine levels – a systematic review

Małgorzata Jamka[a], Harald Walach[b], Magdalena Hołubiec[c], Maria Wasiewicz[d], Jarosław Walkowiak[e,*]

Department of Pediatric Gastroenterology and Metabolic Diseases, Poznan University of Medical Sciences, Poland

* *Corresponding Autor:* Jarosław Walkowiak, MD, PhD; Department of Paediatric Gastroenterology and Metabolic Diseases, Poznan University of Medical Sciences, 27/33 Szpitalna Street, 60-572 Poznan, Poland; phone: +48618491432; fax: +48618472685; email: jarwalk@ump.edu.pl

[a] https://orcid.org/0000-0002-0257-6180
[b] https://orcid.org/0000-0003-4603-7717
[c] https://orcid.org/0000-0001-7627-9157
[d] https://orcid.org/0000-0002-7084-663X
[e] https://orcid.org/0000-0001-5813-5707

ABSTRACT

Aim. The aim of this systematic review was to assess the effect of vitamin K supplementation on anthropometric parameters and adipokine levels in adults.
Material and Methods. Four databases (PubMed, Web of Sciences, Scopus and the Cochrane Library) were searched to select studies in which the effect of vitamin K supplementation on body weight, body mass index (BMI), fat mass, leptin and adiponectin levels were assessed.
Results. We identified nine studies that included a total of 542 subjects. Vitamin K supplementation did not influence body weight, BMI and percentage of fat mass. In addition, the effect of vitamin K supplementation on adipokines levels was equivocal.
Conclusions. Vitamin K supplementation did not affect anthropometric parameters and adipokines levels. Nevertheless, further studies are needed to clarify the effect of vitamin K supplementation on these parameters in adults.

Keywords: vitamin K, dietary supplements, body weight, leptin, adiponectin.

Introduction

Vitamin K is a fat-soluble vitamin that occurs in two forms: phylloquinone (vitamin K_1) and menaquinone (MK; vitamin K_2). Phylloquinone is synthesised by green vegetables such as spinach, broccoli, cabbage and brussels sprouts, whereas MK is produced by bacteria and occurs mainly in fermented food products like cheese and curd, as well as in animal products such as meat and eggs [1, 2].

Historically interest in vitamin K has focused on its role in haemostasis [3] and bone health [4]. Recently, much more attention was paid to the role of vitamin K in cardio-metabolic disorders [5, 6]. Several epidemiological studies have shown that higher vitamin K intake was associated with improved glycaemic status and insulin homeo-

stasis [7, 8]. However, these findings are in contrast to the results of randomised controlled trials (RCT) [9, 10]. On the other hand, a significant association between high vitamin K intake and a reduction in coronary heart disease was found [11, 12]. Limited evidence from human studies also suggests that vitamin K might improve blood lipid profile [13, 14]. Indeed, Braam et al. [13] observed that higher phylloquinone intake was associated with lower serum triglyceride (TG) concentrations. Moreover, Koitaya et al. [15] showed that MK-4 supplementation significantly decreased high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) levels. Additionally, the Framingham study observed that high serum vitamin K concentrations were associated with lower levels of inflammatory markers, which suggest a potential role of vitamin K in suppression of chronic inflammation [16], which is associated with the development of many metabolic disturbances, such as type 2 diabetes mellitus (T2DM) and cardiovascular diseases (CVD) [17, 18].

Recently, some evidence for a link between vitamin K, body mass and adipokine levels were found [19, 20]. Studies on an animal model showed that long-term supplementation of vitamin K_1 and MK-4 might reduce fat accumulation [19]. In humans, Knapen et al. [20] suggested a beneficial effect of vitamin K on fat metabolism. On the other hand, Shea et al. [21] did not find an association between vitamin K supplementation and changes in body weight and body composition.

Therefore, the aim of this systematic review was to assess the effect of vitamin K supplementation on anthropometric parameters and adipokine levels in adults.

Methods

Search strategy

PubMed, Web of Sciences, Scopus and the Cochrane Library databases were searched between October and November 2019 using the following medical subject headings terms (Mesh) and equivalent: *"vitamin K OR vitamin K_1 OR vitamin K_2 OR vitamin K_3" AND "dietary supplements" NOT "animals"*. No time limitations were applied in searching the databases. In addition, reference lists of retrieved articles were scanned for searching any missed studies that met the inclusion criteria. Before starting the review process, the systematic review protocol was prepared and registered with PROSPERO under the registration number: CRD42017079368 [22].

Study selection

Experimental studies: RTCs, non-randomized controlled trials and uncontrolled trials (UCT) in English and analysing the effects of vitamin K supplementation (as a single supplement) on anthropometric parameters and adipokine levels at least for 3 weeks in adults were included in this study. Eligible studies must have reported at least one of the following outcomes: body weight, body mass index (BMI), serum leptin and adiponectin concentrations. Any vitamin K or vitamin K analogue intervention was eligible because we were looking for a class effect. Co-administration with other dietary supplements was not allowed. We included studies that were conducted on healthy adults worldwide, as well as subjects with a history of cardio-metabolic diseases (e.g., hypertension, hyperlipidaemia, prediabetes, T2DM or previously diagnosed CVD (defined as documented myocardial infarction, coronary revascularisation, previous confirmed ischaemic stroke, or peripheral vascular disease defined as claudication symptoms with angiographically proven arterial stenosis or ankle-brachial pressure index of < 0.7)). There were no restrictions based on gender, body weight, the ethnicity of study participants, location of study or sample size.

Quality assessment

Two investigators (JW & MJ) evaluated each article independently in three main stages of the extraction process (**Figure 1**). First, the reviewers screened article titles, then abstracts and finally full texts for eligibility for inclusion in the systematic review. Disagreements were resolved by discussion between the reviewers until a consensus was reached. All reviewers agreed on the final decision of the studies to be included. Primary authors of relevant articles were contacted directly if the data sought were unavailable or published only in abstract form. For a quality assessment of included publications, the checklist derived from the *"Standard quality assessment criteria for evaluating primary research papers from a variety of field"* described by Kmet et al. [23] was used.

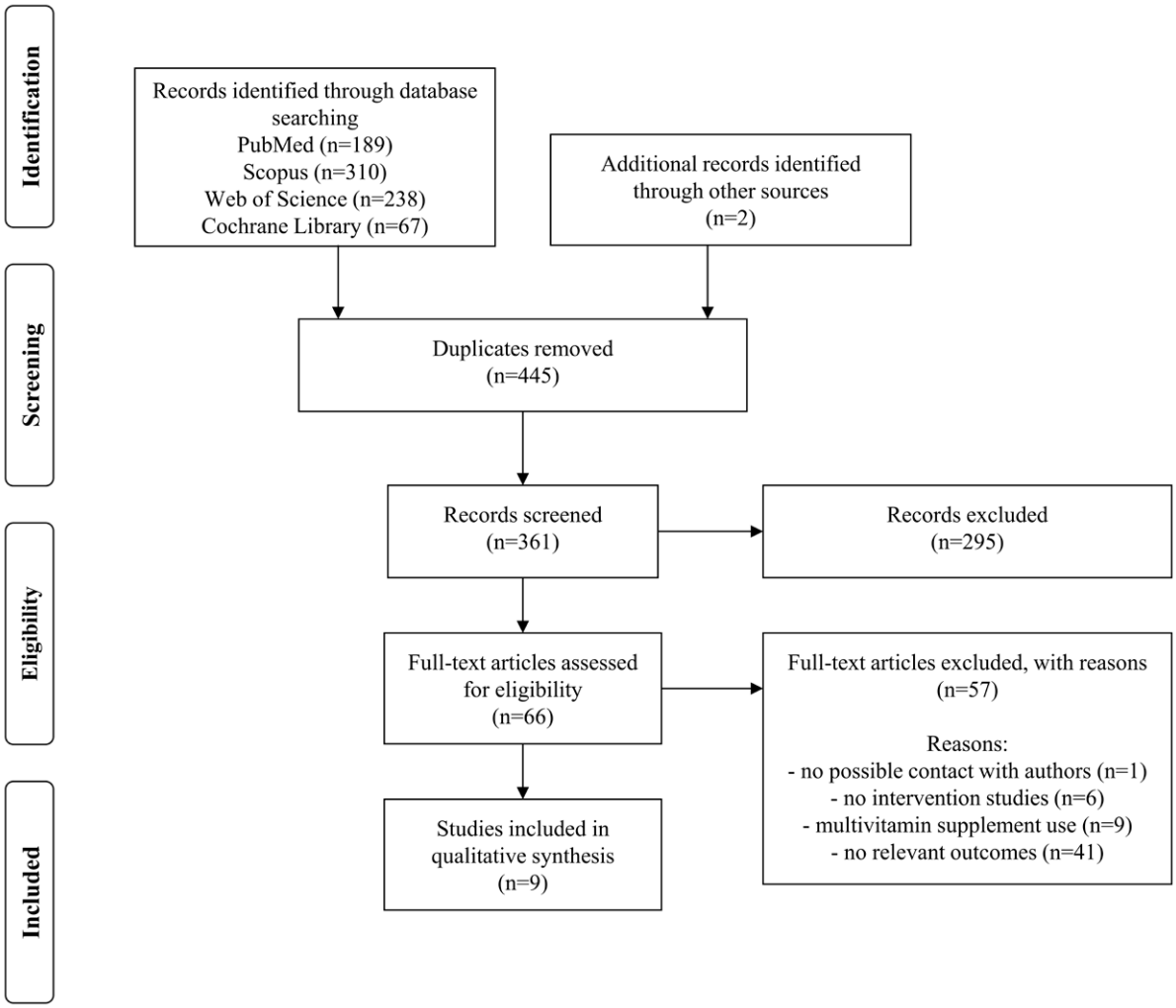

Figure 1. Process of the search

Data extraction

Eligible studies were reviewed and the following data were abstracted: 1) first author's name; 2) year of publication; 3) country; 4) study design and method of blinding; 5) type of intervention (form and dose of vitamin K, route of administration and duration of intervention); 6) number of participants; 6) characteristic of study participants (age, sex, origin and vitamin K intake); 7) baseline and post-intervention serum concentrations of vitamin K_1, menaquinone-4 (MK-4), menaquinone-7 (MK-7), uncarboxylated osteocalcin (ucOC); 8) outcomes: baseline and post-intervention body weight, BMI, serum leptin and adiponectin concentrations.

Statistical analysis

Data were presented as means ± standard deviations (SD). A p value less than 0.05 was considered to be statistically significant. Because of the high heterogeneity of the included studies, the synthesis in the form of meta-analysis was not performed. Results from individual studies were dealt with descriptively.

Results

Study selection

The search results are presented in Figure 1. We retrieved 189 records from the PubMed, 310 from the Scopus, 238 from the Web of Sciences and 67 from the Cochrane Library databases. Two additional references were identified from searching reference lists of the included papers. We identified and removed 445 duplications, leaving a total of 361 records. Initial screening of the title and abstract resulted in the exclusion of 295 references

leaving 66 articles to source in full text. After further inspection, we excluded 57 papers. The full text was not available for one study and contact with authors was not possible. Six papers were excluded because they were not intervention studies. Nine studies did not meet the inclusion criteria as they used a multivitamin supplement. The remaining 41 papers were excluded as they did not report relevant outcomes. Eventually, nine articles met the inclusion criteria and were further analysed [14, 15, 20, 24–29], one of which two references were related to the same population and the same intervention but reported on different outcomes [25, 26].

Study characteristics

The characteristics of the included studies are presented in **Table 1**. All papers were published between 2008 [29] and 2016 [24]. Eight studies were designed as RCTs [14, 15, 20, 24–26, 28, 29] and one paper was designed as UCT [27]. Five studies were conducted in Asia [14, 15, 25–27], three studies were performed in Europe [20, 24, 28] and one study was conducted in North America [29]. MK-4 supplementation was used in four studies [14, 15, 20, 27]. Doses of MK-4 ranged from 300 µg/d [27] to 45000 µg/d [20]. MK-7 was supplemented in three studies [20, 24, 28]. The dose of MK-7 ranged from 10 µg/d [20] to 360 µg/d [20, 28]. Vitamin K_1 was supplemented in two studies in dose from 600 µg/d [29] to 1000 µg/d [25, 26]. The time of intervention period in all included studies ranged from 4 weeks [25, 26] to 26 weeks [29].

Population characteristics

The baseline characteristics of the study populations are presented in **Table 2**. In all, 542 subjects were included in nine studies [14, 15, 20, 24–29]. The study size varied from 15 [27] to 164 [20] participants. The mean age of the study participants ranged between 25 years [27] and 76 years [24] in the intervention groups and varied from 37 years [29] to 77 years [24] in the control groups. The majority of the studies included only female participants [14, 15, 25, 26, 29], while one research was performed only in men [27]. Five papers included only Asian participants [14, 15, 25–27], while four studies were conducted in Caucasian subjects [20, 24, 28, 29]. At baseline, vitamin K intake was reported in seven papers [14, 15, 25–29]. In most studies [14, 15, 28, 29], vitamin K intake was higher than the recommended daily intake (RDI) in the adult population [30]. In the intervention groups, vitamin K intake ranged from 40.18 µg/d [25] to 243.20 µg/d [29], while similar values were observed in the control groups.

The effects of vitamin K supplementation on vitamin K status

The effect of vitamin K supplementation on vitamin K_1 levels was analysed in three studies [14, 15, 27]. One study reported that MK-4 supplementation significantly increased serum concentrations of vitamin K_1, however, there were no differences between the intervention group and the control group [15]. On the other hand, Nakamura et al. [27] observed a statistically signifi-

Table 1. Characteristics of included studies

Main author	Year	Country	Study design	Subjects (n)[a]	Intervention	Dose of vit. K (µg/d)	Time of intervention (week)
Fulton et al. [24]	2016	Scotland	RCT[b]	77	MK-7	100	26
Rasekhi et al. [25, 26]	2015	Iran	RCT[b]	82	Vit. K_1	1000	4
Koitaya et al. [14]	2014	Japan	RCT[b]	48	MK-4	1500	52
Nakamura et al. [27]	2014	Japan	UCT[c]	15	MK-4	0–1500[d]	5
Dalmeijer et al. [28]	2012	The Netherlands	RCT[b]	60	MK-7	180 or 360[e]	12
Knapen et al. [20]	2012	The Netherlands	RCT[b]	42	MK-7	0–360[f]	12
				164	MK-4	45000	156
Koitaya et al. [15]	2009	Japan	RCT[b]	40	MK-4	1500	4
Volpe et al. [29]	2008	USA	RCT[b]	14	Vit. K_1	600	26

[a] – Number of subjects who completed the study
[b] – Randomized Controlled Trial
[c] – Uncontrolled Trial
[d] – Subjects received MK-4 daily for 5 weeks at 0, 300, 600, 900 and 1500 µg/d in weeks 1, 2, 3, 4, and 5, respectively
[e] – Subjects received 180 µg/d or 360 µg/d MK-7 or placebo
[f] – All participants were randomised into seven groups of six subjects each. Each group received a daily supplement containing either 0, 10, 20, 45, 90, 180 or 360 µg/d MK-7 for 12 weeks

Table 2. Characteristics of subjects (n = 528)

Study	Group	Subjects (n)[a]	Age (years)		Sex (% of women)	Race / Ethnicity (%)	Vitamin K intake at baseline (μg/d). Mean ± SD
			Mean ± SD	Range			
Fulton et al. [24]	Intervention group[b] Control group	38 39	76 ± 4 77 ± 5	≥ 70	47% 42%	Caucasian — 100%	N/A
Rasekhi et al. [25, 26]	Intervention group[b] Control group	39 43	40 ± 5	22–45	100%	Asian — 100%	62.69 ± 15.45[25] 60.94 ± 14.13[26] 57.16 ± 19.03[25] 55.55 ± 17.73[26]
Koitaya et al. [14]	Intervention group[b] Control group	24 24	58 ± 4	50–65	100%	Asian — 100%	166.00 ± 81.00 182.00 ± 88.00
Nakamura et al. [27]	Intervention group[b]	15	25[c]	20–29	0%	Asian — 100%	40.18 (0.00–540.27)[c]
Dalmeijer et al. [28]	Intervention group[bd] Intervention group[be] Control group	22[d] 18[e] 20	59 ± 3[d] 60 ± 3[e] 59 ± 3	40–65	54%[d] 67%[e] 60%	Caucasian — 100%	179.00 ± 136.00[f] 24.70 ± 16.50[g] 191.00 ± 167.00[f] 23.50 ± 22.70[g] 203.00 ± 159.00[f] 26.00 ± 18.70[g]
Knapen et al. [20]	Intervention group[bh] Intervention group[bi] Intervention group[bj] Intervention group[bk] Intervention group[bd] Intervention group[be] Control group	6[h] 6[i] 6[j] 6[k] 6[d] 6[e] 6	28 ± 7[lm] 27 ± 7[no]	25–45	52%	Caucasian — 100%	N/A
	Intervention group[bp] Control group	89[n] 75	66 ± 6[p] 65 ± 6	55–75	100%		
Koitaya et al. [15]	Intervention group[b] Control group	20 20	60 ± 3 59 ± 4	53–65	100%	Asian — 100%	233.00 ± 114.00 285.00 ± 223.00
Volpe et al. [29]	Intervention group[b] Control group	8 6	35 ± 8 37 ± 10	25–50	100	Caucasian — 100%	243.20 ± 174.60 380.50 ± 200.20

[a] — Number of subjects who completed the study
[b] — Group receiving vit. K supplementation
[c] — Median (range)
[d] — Group received 180 μg/d MK-7
[e] — Group received 360 μg/d MK-7
[f] — Vit. K_1
[g] — Vit. K_2
[h] — Group received 10 μg/d MK-7
[i] — Group received 20 μg/d MK-7
[j] — Group received 45 μg/d MK-7
[k] — Group received 90 μg/d MK-7
[l] — Men
[m] — n = 20
[n] — Women
[o] — n = 22
[p] — Group received MK-4
N/A — not available

cant decrease of vitamin K_1 levels, and one other study showed no effect of MK-4 supplementation on serum vitamin K_1 concentrations [14].

Three studies analysed the effect of MK-4 supplementation on MK-4 levels. All studies noted that MK-4 supplementation increased MK-4 levels [14, 15, 27].

The effect of MK-4 supplementation on MK-7 levels was assessed in two studies, in which a non-significant decrease in serum MK-7 concentrations was found [14, 27].

Five studies analysed the effect of vitamin K supplementation on ucOC levels [14, 15, 20, 25, 27]. Rasekhi et al. [25] reported that vitamin K_1 supplementation significantly decreased ucOC concentrations, while no effect was observed in the control group. Similarly, a decrease in ucOC levels was shown after MK-4 supplementation [14, 15, 20, 27]. The same effect was noted by Knapen et al. [20] when MK-7 supplementation in dose from 90 μg/d to 360 μg/d was used (**Table 3**).

Table 3. Changes in serum concentrations of vit. K_1, MK-4, MK-7 and ucOC (ng/ml) during the intervention period in the intervention and the controls in selected studies

Study	Intervention (dose of vit. K (µg/d))	Group	n[a]	Vitamin K_1 (ng/ml) Mean ± SD		MK-4 (ng/ml) Mean ± SD		MK-7 (ng/ml) Mean ± SD		ucOC (ng/ml) Mean ± SD	
				Pre-intervention	Post-intervention	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention
Rasekhi et al. [25]	Vit. K_1 (1000)	Intervention[b] Control	39 43	N/A		N/A		N/A		5.57 ± 2.34 4.77 ± 2.49	2.47 ± 1.91[#*] 4.79 ± 2.43
Koitaya et al. [14]	MK-4 (1500)	Intervention[b]	24	0.58 ± 0.54	0.35 ± 0.15[c] 0.40 ± 0.30[d]	0.10 ± 0.00	0.47 ± 1.03[c] 0.29 ± 0.18[d*]	4.08 ± 7.53	1.47 ± 2.02[c] 2.39 ± 2.71[d]	6.40 ± 2.70	2.80 ± 1.00[c*#] 3.60 ± 1.50[d*#]
		Control	24	0.45 ± 0.33	0.36 ± 0.29[c#] 0.39 ± 0.26[d]	0.10 ± 0.00	0.10 ± 0.00[c] 0.10 ± 0.00[d]	4.11 ± 5.05	3.87 ± 5.43[c] 3.24 ± 3.39[d]	5.70 ± 3.00	4.20 ± 2.10[c#] 4.90 ± 2.30[d#]
Nakamura et al. [27]	MK-4 (0–1500)	Intervention[b]	15	0.35 (0.22–0.85)[e]	0.20 (0.08–0.49)[e#]	0.14 (0.10–0.17)[e]	0.58 (0.33–1.78)[e#]	0.43 (0.10–7.92)[e]	0.25 (0.13–0.93)[e]	5.03 (2.20–23.03)[e]	6.77 (1.89–14.52)[ef] 4.82 (1.84–8.73)[eg#] 2.98 (1.27–6.90)[eh#] 3.92 (1.88–7.52)[ei#]
Dalmeijer et al. [28]	MK-7 (180) MK-7 (360)	Intervention[b] Intervention[b] Control	22 18 20	N/A		N/A		N/A		2.40 ± 1.83 2.63 ± 1.64 2.67 ± 1.40	N/A
Knapen et al. [20]	MK-7 (10) MK-7 (20) MK-7 (45) MK-7 (90) MK-7 (180) MK-7 (360)	Intervention[b] Intervention[b] Intervention[b] Intervention[b] Intervention[b] Intervention[b] Control	6 6 6 6 6 6 6	N/A		N/A		N/A		2.20[j] 5.10[j] 3.70[j] 4.60[j] 6.30[j] 2.40[j] 4.00[j]	3.40[j] 5.20[j] 3.80[j] 3.10[j#] 3.40[j#] 1.00[j#] 4.60[j]
	MK-4 (45000)	Intervention[b] Control	89 75	N/A		N/A		N/A		3.20 ± 1.90 3.00 ± 1.60	-2.40 ± 1.60[k*] -0.04 ± 0.10[k]
Koitaya et al. [15]	MK-4 (1500)	Intervention[b]	20	0.60[j]	0.78[jl#] 0.70[jm]	0.10[j]	2.00[jl#] 1.10[jm*]	N/A		3.50[j]	2.20[jl*#] 2.20[jm*#]
		Control	20	0.70[j]	0.68[jl] 0.60[jm]	0.10[j]	0.10[jl] 0.10[jm]			5.10[j]	6.00[jl] 5.80[jm]

[a] – Number of subjects who completed the study; [b] – receiving vit. K supplementation; [c] – Data after 6 months of intervention; [d] – Data after 12 months of intervention; [e] – Median (range); [f] – Data after 15 days of intervention (0–7 days – 0 µg/d MK-4, 8–14 days – 300 µg/d MK-4); [g] – Data after 22 days of intervention (0–7 days – 0 µg/d MK-4, 8–14 days – 300 µg/d MK-4, 14–21 days – 600 µg/d MK-4); [h] – Data after 29 days of intervention (0–7 days – 0 µg/d MK-4, 8–14 days – 300 µg/d MK-4, 14–21 days – 600 µg/d MK-4, 22–28 days – 900 µg/d MK-4); [i] – Data after 36 days of intervention (0–7 days – 0 µg/d MK-4, 8–14 days – 300 µg/d MK-4, 14–21 days – 600 µg/d MK-4, 22–28 days – 900 µg/d MK-4, 29–36 days – 1500 µg/d MK-4); [j] – Data from figure; [k] – Changes from baseline; [l] – Data after 2 weeks of intervention; [m] – Data after 4 weeks of intervention; [o] – Mean ± standard error; [*] – p value (difference between intervention vs. controls) < 0.05
[#] – p value (baseline vs. intervention) < 0.05
N/A – not available

The effects of vitamin K supplementation on anthropometric parameters

Changes in body weight [14, 15, 20, 25–27, 29] and BMI [14, 15, 20, 25–27] after vitamin K supplementation were analysed in seven studies, while changes in fat mass were assessed in three studies [25, 26, 29] included in this systematic review. Average baseline BMI values in the intervention groups ranged from 21.10 kg/m^2 [15] to 28.34 kg/m^2 [25, 26]. Similar values were observed in the control groups. Following the intervention period, mean body weight, BMI and fat mass did not change in subjects who received vitamin K_1 supplementation [25, 26, 29]. Similar MK-4 or MK-7 supplementation did not affect body weight and BMI (**Table 4**) [14, 15, 20, 27, 28].

The effects of vitamin K supplementation on leptin and adiponectin levels

Changes in leptin levels after vitamin K supplementation were measured in two studies [14, 26]. At baseline, in the intervention groups, the mean serum leptin concentrations varied from 6.20 ng/ml [14] to 28.59 ng/ml [26]. Similar results were observed in the control groups. Rasekhi et al. [26] observed that vitamin K_1 supplementation did not change the leptin levels. On the other hand, Koitaya et al. [14] reported that MK-4 supplementation increased serum leptin concentrations in the intervention group, but a similar effect was observed in the control group (**Table 5**).

The effect of vitamin K supplementation on adiponectin levels was assessed in three stud-

Table 4. Body weight (kg) and BMI (kg/m^2) changes during the intervention period in the intervention and the control groups in selected studies

Study	Intervention (dose of vit. K (µg/d))	Group	n[a]	Body weight (kg) Mean ± SD		BMI (kg/m^2) Mean ± SD		Fat mass (%) Mean ± SD	
				Pre-intervention	Post-intervention	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention
Fulton et al. [24]	MK-7 (100)	Intervention[b] Control	40 40	79.00 ±15.00 77.00 ± 13.00	N/A	N/A		N/A	
Rasekhi et al. [25, 26]	Vit. K_1 (1000)	Intervention[b] Control	39 43	71.21 ± 6.47 71.09 ± 6.59	70.72 ± 6.39 71.00 ± 6.76	28.34 ± 1.72 27.93 ± 1.53	28.19 ± 1.80 27.91 ± 1.61	38.77 ± 3.86 38.55 ± 3.99	38.46 ± 4.05 38.57 ± 4.10
Koitaya et al. [14]	MK-4 (1500)	Intervention[b] Control	24 24	52.20 ± 5.60 51.90 ± 4.70	52.90 ± 5.80[c] 52.50 ± 5.80[d] 52.20 ± 5.20[c] 52.00 ± 4.90[d]	22.00 ± 1.80 21.80 ± 2.20	22.30 ± 1.80[c] 22.10 ± 1.90[d] 21.90 ± 2.20[c] 21.70 ± 2.10[d]	N/A	
Nakamura et al. [27]	MK-4 (0–1500)	Intervention[b]	15	58.55 (50.55–68.25)[e]	57.95 (50.50–66.90)[e]	20.60 (18.50–24.10)[e]	20.10 (18.30–23.70)[e]	N/A	
Dalmeijer et al. [28]	MK-7 (180) MK-7 (360) Control	Intervention[b] Intervention[b] Control	22 18 20	N/A		24.90 ± 3.00 23.70 ± 1.90 24.40 ± 2.50	0.14 (0.50[f])[g] 0.18 (0.80[f])[g] -0.06 (-0.20[f])[g]	N/A	
Knapen et al. [20]	MK-7 (0–360)	Intervention[b]	20[a] 22[b]	81.30 ± 11.50[a*] 67.60 ± 7.40[b]	N/A	24.00 ± 2.50[a] 23.20 ± 2.70[b]	N/A	N/A	
	MK-4 (45000)	Intervention[b] Control	89 75	66.60 ± 8.10 66.70 ± 8.20	66.60 ± 8.90[*] 67.60 ± 8.70[#]	25.40 ± 2.80 25.50 ± 2.40	25.50 ± 3.00[*] 26.00 ± 2.50[#]		
Koitaya et al. [15]	MK-4 (1500)	Intervention[b] Control	20 20	50.20 ± 5.80 54.20 ± 7.80	50.00 ± 5.80 53.70 ± 7.50[#]	21.10 ± 2.20[*] 22.70 ± 2.60	21.00 ± 2.20 22.50 ± 2.50[#]	N/A	
Volpe et al. [29]	Vit. K_1 (600)	Intervention[b] Control	8 6	60.73 ± 9.78 63.00 ± 6.82	-0.14 ± 1.35[g] 0.50 ± 1.97[g]	22.86 ± 4.01 22.81 ± 2.95	N/A	25.04 ± 9.72 28.33 ± 6.94	1.66 ± 1.28[g] 1.50 ± 1.92[g]

[a] — Number of subjects who completed the study
[b] — Group receiving vit. K supplementation
[c] — Data after 6 months of intervention
[d] — Data after 12 months of intervention
[e] — Median (range)
[f] — %
[g] — Changes from baseline
[*] — p value (difference between intervention vs. control groups) < 0.05
[#] — p value (baseline vs. intervention) < 0.05
N/A — not available

ies [14, 20, 26]. In the vitamin K groups, the mean serum adiponectin concentrations ranged from 6.20 µg/ml [20] to 14.30 µg/ml [14] and similar values were noted in the control groups. The mean adiponectin levels increased after vitamin K_1 supplementation. In addition, significant differences between groups were observed [26]. Contrary, Knapen et al. [20] showed no effect of MK-4 supplementation on adiponectin levels, while Koitaya et al. [14] found a significant increase in adiponectin levels after 12 months of intervention. However, a similar effect was observed in the control group. MK-7 supplementation had no effect on serum adiponectin concentrations. Only for a dose of 180 µg/d a significant decrease in adiponectin levels was noted (**Table 5**) [20].

Discussion

Here we present the effect of vitamin K supplementation on changes in anthropometric parameters and adipokines levels in adults. While the results of the considered studies were equivocal, the findings of this systematic review showed no effect of vitamin K supplementation on body weight, BMI, leptin and adiponectin levels.

Osteocalcin (OC) is an abundant noncollagenous protein, which is synthesized by osteoblasts during bone formation and undergoes a posttranslational vitamin K dependent modification, in which 3 glutamic acid residues are carboxylated, which thereby allows the protein to bind calcium. The circulating measure of total OC, which includes both carboxylated osteocalcin (cOC) and ucOC forms, is used as a biomarker of bone formation, whereas serum ucOC concentrations are used as a marker of the vitamin K status [31]. Previous studies have shown that ucOC levels increase in response to vitamin K depletion and decrease after vitamin K supplementation [27, 32, 33]. These results are consistent with our finding showing that vitamin K supplementation might significantly reduce ucOC levels [15, 20, 25–27].

Studies in animal models have shown that OC might be the mediator of energy metabolism in the bone, pancreas and adipose tissue [24, 35]. It was also demonstrated that subjects with a high degree of cOC were leaner and had less body fat than those with lower OC carboxylation. These findings suggest that vitamin K status might be related to subjects' nutritional status [20]. Indeed, Shea et al. [36] showed that women with the high-

Table 5. Changes serum concentrations of leptin (ng/ml) and adiponectin (µg/ml) during the intervention period in the intervention and the control groups in selected studies

Study	Intervention (dose of vit. K (µg/d))	Group	n[a]	Leptin (ng/ml) Mean ± SD		Adiponectin (µg/ml) Mean ± SD	
				Pre-intervention	Post-intervention	Pre-intervention	Post-intervention
Rasekhi et al. [26]	Vit. K_1 (1000)	Intervention[b]	39	28.59 ± 9.61	28.29 ± 9.86	9.19 ± 1.80	10.44 ± 1.20[*#]
		Control	43	26.78 ± 10.33	25.62 ± 10.21	8.81 ± 1.54	8.54 ± 1.87
Koitaya et al. [14]	MK-4 (1500)	Intervention[b]	24	6.20 ± 3.60	7.20 ± 4.10[c#] 7.80 ± 4.90[d#]	14.30 ± 6.70	14.30 ± 7.70[c] 14.40 ± 7.70[d#]
		Control	24	5.20 ± 2.80	6.00 ± 2.40[c] 7.60 ± 3.40[d#]	14.30 ± 5.90	14.10 ± 6.10[c] 14.80 ± 6.40[d]
Knapen et al. [20]	MK-7 (10)	Intervention[b]	6	N/A		7.70[e]	7.60[e]
	MK-7 (20)	Intervention[b]	6			6.20[e]	6.30[e]
	MK-7 (45)	Intervention[b]	6			8.30[e]	8.30[e]
	MK-7 (90)	Intervention[b]	6			7.00[e]	7.40[e]
	MK-7 (180)	Intervention[b]	6			9.20[e]	7.80[e#]
	MK-7 (360)	Intervention[b]	6			8.10[e]	8.10[e]
		Control	6			8.40[e]	8.20[e]
	MK-4 (45000)	Intervention[b]	89	N/A		14.20 ± 9.70	-1.10 ± 3.80[f]
		Control	75			14.30 ± 9.50	- 1.10 ± 5.00[fh]

[a] – Number of subjects who completed the study
[b] – Group receiving vit. K supplementation
[c] – Data after 6 months of intervention
[d] – Data after 12 months of intervention
[e] – Data from figure
[f] – Change from baseline
[*] – p value (difference between intervention vs. control groups) < 0.05
[#] – p value (baseline vs. intervention) < 0.05
N/A – not available

est percentage of body fat had lower serum vitamin K concentrations and a poorer vitamin K status. In addition, Takeuchi et al. [37] presented evidence that MK-4 but not phylloquinone inhibited adipogenesis *in vitro*. However, here we did not show a significant effect of vitamin K supplementation on body weight, BMI and fat mass. Nevertheless, it is plausible that the unhealthy lifestyle of study participants might have attenuated the beneficial effect of vitamin K supplementation on body weight reduction.

It has been shown that adipokines levels might be associated with serum OC concentrations [38, 39] suggesting that vitamin K might also have an effect on adipokine levels. In addition, Kanazawa et al. [40] found that the ucOC/OC ratio positively correlated with serum adiponectin levels in men. On the other hand, Reinehr et al. [41] studied obese children and observed no significant relationship between serum adiponectin and OC concentrations. In addition, a recent meta-analysis did not demonstrate an effect of vitamin K supplementation on leptin and adiponectin levels. However, in their meta-analysis authors did not compare the effect of a different forms of vitamin K on adipokines levels [42]. Results obtained in this systematic review assessing the effect of vitamin K supplementation on adiponectin and leptin concentrations were equivocal. Vitamin K_1 supplementation did not change the leptin levels, but a significant increase in adiponectin levels was noted [26]. Koitaya et al. [14] reported that MK-4 supplementation increased serum leptin concentrations, but a similar effect was observed in the control group. On the other hand, MK-4 supplementation had no effect on adiponectin levels [14, 20], while MK-7 supplementation in a dose of 180 µg/d significantly reduced serum adiponectin concentrations [14]. The inconsistencies between studies might be related to variations in study design and intervention.

In this systematic review, we noted that the various vitamin K supplements seem to have partially antagonistic effects. Unfortunately, previous systematic reviews did not analyse a class effect of vitamin K supplements on anthropometric parameters and adipokines levels [42, 43]. Nevertheless, Takeuchi et al. [37] reported that MK-4, but not vitamin K_1, inhibited adipogenesis and stimulated osteoblastic differentiation *in vitro*. This is in line with a body of evidence that MK-4 has direct effects on a variety of metabolic and cellular processes by activating the steroid and xenobiotic receptors on the nuclear membrane [44]. On the other hand, Schurgers et al. [45] reported that MK-4 had a short serum half-life and a small area under the curve compared to vitamin K_1, whereas MK-9 displayed a long serum half-life compared to vitamin K_1 or MK-4. Sato et al. [46] also demonstrated that a nutritional dose of MK-7 was well absorbed in humans, and significantly increased serum MK-7 levels, whereas MK-4 had no effect on serum MK-4 concentrations. Therefore, the nutritional values of vitamin K homologues might be differentiated with regard to bioavailability and efficacy. In addition, several studies showed that the effects of long chain MK such as MK-7 on blood coagulation are greater and longer than vitamin K_1 and MK-4 [47, 48]. There is also evidence that MK-7 was much more effective than vitamin K_1 in increasing the degree of OC carboxylation [49].

There are several potential explanations as to why no significant effects of vitamin K supplementation on anthropometric parameters and adipokines levels were seen. In all studies included in this systematic review, a daily dose of vitamin K was above the RDI for vitamin K [14, 15, 20, 24–29], which in the United States of America is currently set at 90 µg/d for women and 120 µg/d for men [30]. However, it should be noted that the current RDI for vitamin K is based on saturation of the coagulation system [30] and a larger amount of vitamin K may be required to produce the significant effect on anthropometric parameters and adipokine levels [42, 43, 50]. In the United Kingdom, the Department for Health suggests that taking 1 mg or less of vitamin K supplements a day is unlikely to cause any harm in healthy individuals associated with intake of the recommended dose [51]. In addition, some epidemiological studies have suggested that recommended vitamin K levels required for maintaining health might vary according to age [50, 52]. Tsugawa et al. [52] found that the concentration of circulating vitamin K should be maintained at a higher level in the elderly than in young people. Moreover, no tolerable upper limit for vitamin K has been set with no known toxicity [30], which suggests that for most people, vitamin K supplementation is safe and had no side effects [14, 15,

20, 25–27]. Among studies included in this systematic review, only Fulton et al. [24] noted an excess of falls and gastrointestinal side effects in the vitamin K group compared to placebo, but no difference in serious adverse events or deaths was found. On the other hand, it is also probable that the lack effect of vitamin K supplementation on analysed parameters may be potentially due to the short supplementation period. It is also probable that vitamin K is not acting on pathways that improve anthropometric parameters and adipokine levels [42, 43]. Moreover, a possible explanation lack of response to vitamin K supplementation is that unhealthy diet and lifestyle of study participants attenuated any beneficial effect of vitamin K supplementation.

Several limitations should be listed regarding the study. Firstly, the number of studies that were included in this systematic review was relatively small. In addition, analysed studies had different designs, used different methods of exposure measurement and reported different outcomes. Moreover, our findings were limited to Caucasian and Asian descent and it is not clear if these results generalize to other ethnicities. In addition, we could not always analyse the reported outcomes of interest because information regarding variance was not always reported or provided by authors after attempts at contact. Eventually, despite a thorough search strategy, including grey literature and different databases, unavailable studies may exist, which have not been included.

Finally, the divergence between the outcomes of epidemiological and experimental supplementation studies should be noted. While epidemiological studies have long observation periods and use vitamin K rather as a proxy for certain lifestyles, for instance, healthy nutrition rich in vegetables and good sources of protein, supplementation studies use vitamin K as isolated agents. It might well be the case that it is the synergy of vitamin K with other substances that produce health effects that cannot be gleaned from isolated supplementation. This can only be clarified by long term supplementation studies in comparison with natural cohorts [53].

On the other hand, the strength of this systematic review includes details on the characteristics of the studies and study populations. Moreover, this is the first systematic review that assessed the effect of vitamin K supplementation on anthropometric parameters. Recent meta-analysis measured the effect of vitamin K supplementation on the cardiometabolic risk factor but did not take into account the effect of vitamin K supplementation on body weight, BMI and fat mass [54].

Conclusion

Currently available data showed no effect of vitamin K supplementation (K_1, MK-4 or MK-7) on body weight, BMI, fat mass, leptin and adiponectin levels. Nevertheless, further studies are needed to evaluate the role of vitamin K on nutrition status and adipokines levels.

Acknowledgements

Author contributions: M.J. searched databases, performed the selection of studies, analysed the data and wrote the manuscript. H.W. commented the manuscript. J.W. designed the study, searched databases, analysed the data and edited the manuscript. All authors reviewed and approved the final manuscript.

Conflict of interest statement
The authors declare no conflict of interest.

Funding sources
There are no sources of funding to declare.

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Acceptance for editing: 2019-11-09
Acceptance for publication: 2019-12-30