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# Exploring the effects of Cheddar cheese intake on vitamin K status and lipid profiles in overweight middle-aged adults

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**Background:** Cheese serves as a dietary source of vitamin K; however, its impact on vitamin K status biomarkers in humans and the role of dietary vitamin K in modulating lipid profiles have yet to be elucidated. **Objective:** To explore the effect of six weeks of daily consumption of pasture-derived and total mixed ration (TMR)-derived Cheddar cheese on vitamin K status biomarkers and lipid profiles. **Design:** Biobanked samples ( $n = 60$ ), including pasture-derived ( $n = 33$ ) and TMR-derived ( $n = 27$ ) Cheddar cheese groups from a previous human intervention study, were analysed. The original study examined the effects of six weeks of daily intake of 120 g of Cheddar cheese on metabolic health biomarkers in adults over 50 years with BMI  $\geq 25 \text{ kg m}^{-2}$ . Vitamin K-dependent proteins, including dephosphorylated-uncarboxylated matrix Gla protein (dp-ucMGP), undercarboxylated osteocalcin (ucOC) and carboxylated osteocalcin (cOC), were measured using ELISA kits. The dp-ucMGP level and the ucOC : cOC ratio were used as vitamin K status biomarkers. Lipid profiles, including triglycerides, total cholesterol, HDL, LDL, and VLDL cholesterol, and apolipoprotein B, were measured by NMR spectroscopy. **Results:** Overall, Cheddar cheese intake ( $n = 60$ ) led to decreases in dp-ucMGP ( $-34.73 \text{ pmol L}^{-1}$ ; 95% CI:  $-47.14, -22.33$ ) and ucOC : cOC ( $-0.047$ ; 95% CI:  $-0.07, -0.02$ ) after 6 weeks of consumption, with no differences between the groups. There were no differences in the changes in anthropometric markers or lipid profiles between groups. The sex-by-treatment interaction showed a significant impact on total cholesterol ( $P < 0.001$ ), HDL cholesterol ( $P < 0.001$ ) and LDL cholesterol ( $P = 0.002$ ) levels. Among males, the TMR-derived cheese group exhibited a significantly greater increase in HDL cholesterol ( $P < 0.05$ ). Among females, TMR-derived cheese consumption was associated with significantly greater decreases in total, HDL and LDL cholesterol levels ( $P < 0.05$ ) compared with the pasture-derived group. **Conclusion:** Cheddar cheese intake may improve vitamin K status, and vitamin K intake from cheese may induce sex-specific effects on blood lipid profiles in overweight middle-aged adults.

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## 1. Introduction

Vitamin K is a fat-soluble vitamin that exists primarily in two forms: phyloquinone (vitamin K1) and menaquinones (MK-4 to MK-13, collectively referred to as vitamin K2). Vitamin K1 is predominantly found in green leafy vegetables such as kale, spinach, and broccoli,<sup>1</sup> whereas vitamin K2 is mainly synthesized by bac-

teria and is present in foods such as animal products and fermented dairy products.<sup>2,3</sup> Historically, vitamin K has been recognized for its unique role in the blood clotting process, as it is required for the synthesis of key clotting factors, including prothrombin and factors VII, IX, and X.<sup>4-7</sup> Beyond this well-known function, its important roles in inhibiting vascular calcification, improving bone health, and preventing type 2 diabetes have been extensively studied and reported.<sup>8-12</sup> Emerging evidence also suggests that vitamin K plays roles in regulating hyperlipidemia.<sup>13,14</sup> However, most existing evidence comes from observational studies or clinical studies conducted in patient populations using vitamin K supplements.<sup>15-18</sup>

Cheese is a dietary source of vitamin K, primarily in the form of vitamin K2.<sup>19</sup> Cheese has been reported to provide different health benefits, including the prevention of cardiovascular disease and the improvement of bone health, due to

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its various nutrients such as calcium, proteins, bioactive peptides, fat, vitamins, and probiotics, as well as its unique structure, which can impact digestion and absorption.<sup>20–26</sup> The unique structure of cheese, encompassing its variety of nutrients and their interactions, is often described as the cheese matrix, and the health benefits that arise from the cheese matrix are described as cheese matrix health effects.<sup>27–29</sup>

To date, the specific contribution of vitamin K to the health effects of the cheese matrix, particularly its impact on human vitamin K status, has not been widely studied. As mentioned above, vitamin K has been reported to play a role in the regulation of hyperlipidemia. However, human studies investigating the effects of dietary vitamin K on lipid profiles in a healthy overweight population are scarce. Therefore, the aim of this exploratory study was to conduct a secondary analysis of a 6-week randomised controlled cheese trial, supplemented by original laboratory analysis using existing biobanked biological samples from the same study, to examine how different levels of vitamin K intake from different Cheddar cheese variants affect vitamin K status and lipid profiles in healthy, middle-aged individuals with a BMI  $\geq 25 \text{ kg m}^{-2}$ . Of note, a previous study conducting a secondary analysis in this population group suggested that sex differences may be an important consideration when examining the effects of cheese intake on blood lipids.<sup>30</sup> Therefore, this study also sought to investigate whether males and females exhibited different responses to varying levels of vitamin K intake from cheese.

## 2. Materials and methods

### 2.1 Population

In the analysis presented here, existing biobanked biological samples were utilised. These samples were collected from a randomised controlled trial which examined the effect of acute cheese consumption (120 g daily) or an equivalent amount of dairy fat (40 g) on markers of metabolic health.<sup>31</sup>

In this larger study, a total of 252 participants were recruited from Dublin, Ireland, and the surrounding areas. Participants were required to be aged 50 years or older, have a body mass index (BMI) of  $25 \text{ kg m}^{-2}$  or higher, have general good health, have no dairy intolerance or allergies, and consume an omnivorous diet.<sup>31</sup> Exclusion criteria included being on medications for cholesterol or blood pressure management, following prescribed or therapeutic diets, or actively attempting weight loss. All participants provided written informed consent before enrolling in the study, which was approved by the University College Dublin Human Research Ethics Committee (LS-19-78-Gibney). The trial was registered at ISRCTN as ISRCTN11913510.<sup>31</sup>

### 2.2 Study design

The overall study was a 6-week randomised parallel-arm design with four dietary intervention groups.<sup>31</sup> In the current analysis, biobanked samples from two of the groups were used: (A) 120 g per day of full-fat Cheddar cheese made from pasture-fed

cow's milk, and (D) 120 g per day of full-fat Cheddar cheese made from total mixed ration (TMR)-fed cow's milk. Cows fed the TMR diet received 9 kg of concentrate, 9 kg of maize silage, and 4.5 kg of grass silage available *ad libitum* per cow, on a dry matter intake basis, and were housed full-time. For the purposes of this paper, in the remaining sections where the cheese is referred to, these will be described as 'pasture-derived cheese' and 'TMR-derived cheese' for brevity. During the intervention, participants were asked to limit all other dairy intake to approximately 50 ml.

To select participants for this vitamin K exploratory analysis (Fig. 1), baseline levels of dephosphorylated-uncarboxylated matrix Gla protein (dp-ucMGP), undercarboxylated osteocalcin (ucOC) and carboxylated osteocalcin (cOC) were analysed for all participants in Group A and Group D. Participants with extremely high or low baseline levels of dp-ucMGP, cOC, and ucOC were excluded from the study, as they may have had very low or very high vitamin K daily intake before the study. To minimise interference from high vitamin K intake from other foods, participants from Group A and Group D who reported consuming more than  $200 \text{ g day}^{-1}$  of green vegetables rich in phylloquinone (such as spinach, broccoli, Brussels sprouts, and green cabbage) during the 6-week intervention study were excluded, based on their dietary intake records. Dietary intake was assessed using the validated EPIC-Norfolk Food Frequency Questionnaire (FFQ).<sup>31</sup> This exclusion criterion is consistent with that used in a previous study examining low-dose MK-7 intake on vitamin K status.<sup>32</sup> In Group A, several participants' serum samples had insufficient volume for triplicate ELISA analysis and were excluded from the analysis. A total of 60 participants were selected for the study, with the pasture-derived Cheddar cheese group having 33 participants and the TMR-derived Cheddar cheese group having 27 participants.

### 2.3 Intervention diets

All cheeses were consumed at a maturity of 8–12 months. The nutritional composition of these two Cheddar cheese variants was matched for energy, fat, protein, and calcium content and is shown in Table 1. Tirlán (formerly Glanbia) provided the pasture-derived cheese and Teagasc Food Research Centre, Moorepark, supplied the TMR-derived cheese for the study.<sup>31</sup> The vitamin K levels in these Cheddar cheeses were quantified by using the HPLC-FLD method reported by Zhou *et al.*<sup>33</sup> and are shown in Table 2.

### 2.4 Vitamin K-dependent proteins and lipid profile biomarkers

Blood plasma samples collected pre- and post-intervention were analysed for the inactive form of the vitamin K dependent protein dp-ucMGP using competitive enzyme immunoassay (MyBioSource, San Diego, USA). Serum ucOC and cOC concentrations were determined using dual-antibody ELISA tests (Takarabio, Paris, France). The detection limits of the dp-ucMGP, ucOC, and cOC ELISA assays are  $1.0 \text{ ng mL}^{-1}$ ,  $0.25 \text{ ng mL}^{-1}$ , and  $0.5 \text{ ng mL}^{-1}$ , respectively. For intra- and inter-assay precision, the coefficients of variation for all ELISA kits are



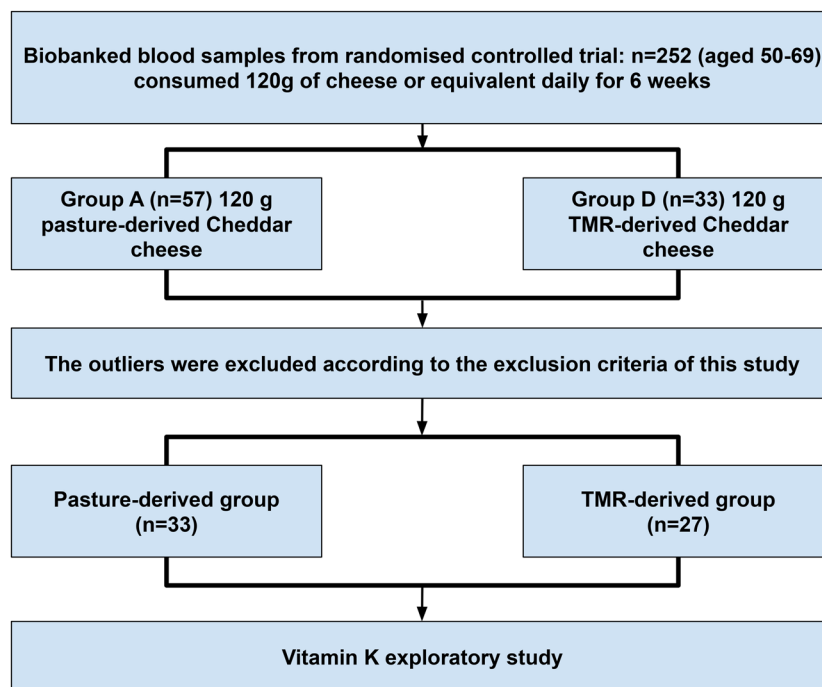


Fig. 1 Flowchart of screening participant samples for the vitamin K exploratory study.

Table 1 Nutritional composition of Cheddar cheese

Gross composition	Pasture-derived cheese	TMR-derived cheese
Energy (kcal per 100 g)	379 ± 13	376 ± 14
Fat (g per 100 g)	30.38 ± 0.96	31.07 ± 1.03
Protein (g per 100 g)	26.41 ± 1.24	26.04 ± 1.23
Calcium (g per 100 g)	0.57 ± 0.10	0.61 ± 0.06

below 10%. Both the dp-ucMGP level and the ratio of ucOC to cOC were considered as biomarkers of vitamin K status, with lower values indicating better vitamin K status.<sup>34,35</sup> Absorbance was measured at 450 nm using a VICTOR Nivo® Multimode Plate Reader (Revity, Massachusetts, USA). Lipid concentrations were measured in EDTA blood samples using nuclear magnetic resonance (NMR) spectroscopy (LabCorp, Morrisville, NC). LDL cholesterol was calculated using the Friedewald equation.<sup>36</sup>

## 2.5 Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics version 29. A Shapiro–Wilk test was used to assess the normality

of data to determine whether parametric or non-parametric methods should be applied. Baseline differences in biomarker values between groups were examined using the independent samples *t*-test or the Mann–Whitney *U*-test, as appropriate. The influence of treatment (cheese variants), sex and sex × treatment interaction on the absolute changes in different biomarkers after the intervention in the two groups was assessed *via* factorial analysis of covariance (ANCOVA) or Quade’s nonparametric ANCOVA, as appropriate. Bonferroni correction for multiple testing was applied to prevent Type I errors due to the large number of biomarkers. The absolute changes in different biomarkers after six weeks of intervention are shown in SI Table S1.

## 3. Results

Table 3 shows the baseline characteristics of the two intervention groups. The average age of the participants was 59.2 ± 5.7 years (S.D.). The percentages of males and females in this study were 43% and 57%, respectively. Overall, there were no significant differences in baseline values of different biomarkers between the two treatment groups, except for waist

Table 2 Vitamin K content in 120 g of Cheddar cheese

µg per 120 g	Vitamin K1	MK-4	MK-7	MK-9	Total
Pasture-derived cheese	4.23 ± 0.12 <sup>a</sup>	3.14 ± 0.4 <sup>a</sup>	1.12 ± 0.06	5.46 ± 0.22 <sup>b</sup>	13.95 ± 0.70 <sup>b</sup>
TMR-derived cheese	3.61 ± 0.26 <sup>b</sup>	1.41 ± 0.18 <sup>b</sup>	1.09 ± 0.17	21.37 ± 2.54 <sup>a</sup>	27.47 ± 3.10 <sup>a</sup>

Different superscripts (a,b) within each column indicate significant differences between the two groups ( $P < 0.05$ ) (levels are listed per 120 g since participants consumed 120 g of cheese daily, to better reflect daily vitamin K intake).



Table 3 Baseline characteristics

	Pasture-derived Cheddar cheese <i>n</i> = 33			TMR-derived Cheddar cheese <i>n</i> = 27			<i>P</i> <sup>d</sup>	<i>P</i> Male <sup>b</sup>	<i>P</i> Female <sup>c</sup>
	All	Male	Female	All	Male	Female			
Age (years)	59.09 ± 5.31	58.53 ± 6.10	59.56 ± 4.67	59.30 ± 6.31	57.36 ± 5.80	60.69 ± 6.41	0.841	0.312	0.581
Sex <i>n</i> (%)	33	15 (45.45)	18 (54.54)	27	11 (40.74)	16 (59.25)	0.714 <sup>d</sup>		
Weight (kg)	80.12 ± 14.30	91.16 ± 10.81	70.92 ± 9.55	83.53 ± 16.28	88.50 ± 11.15	80.11 ± 18.60	0.398	0.549	0.075
BMI (kg m <sup>-2</sup> )	27.65 ± 3.11	28.62 ± 3.17	26.85 ± 2.91	29.10 ± 5.08	27.84 ± 2.06	29.98 ± 6.32	0.281	0.760	0.117
Body fat (%)	32.93 ± 7.22	27.88 ± 6.76	37.13 ± 4.40	34.69 ± 9.02	25.46 ± 3.04	41.03 ± 5.45	0.405	0.281	<b>0.028</b>
Waist circumference (cm)	92.33 ± 11.21	100.17 ± 8.66	85.72 ± 8.46	98.21 ± 10.31	102.03 ± 8.81	95.59 ± 10.69	<b>0.039</b>	0.597	<b>0.005</b>
SBP (mmHg)	128.66 ± 18.55	134.87 ± 18.60	123.48 ± 17.33	130.83 ± 13.49	131.91 ± 13.1	130.08 ± 14.13	0.614	0.656	0.236
DBP (mmHg)	84.81 ± 10.15	86.38 ± 10.10	83.5 ± 10.30	84.85 ± 7.84	84.97 ± 8.90	84.77 ± 7.33	0.985	0.715	0.685
cOC (ng ml <sup>-1</sup> )	21.44 ± 4.10	21.00 ± 3.74	21.81 ± 4.46	22.22 ± 3.14	22.36 ± 3.74	22.13 ± 2.77	0.422	0.369	0.811
ucOC (ng ml <sup>-1</sup> )	5.81 ± 3.18	6.00 ± 3.36	5.66 ± 3.11	5.90 ± 3.26	4.18 ± 1.87	7.08 ± 3.52	0.92	0.118	0.220
ucOC : cOC	0.27 ± 0.15	0.30 ± 0.17	0.26 ± 0.13	0.27 ± 0.17	0.18 ± 0.08	0.33 ± 0.20	0.772	0.121	0.226
dp-ucMGP (pmol L <sup>-1</sup> )	387.59 ± 82.82	360.10 ± 73.56	410.50 ± 85.05	397.92 ± 80.87	401.98 ± 82.48	395.14 ± 82.34	0.302	<b>0.032</b>	0.772
Total cholesterol (mmol L <sup>-1</sup> )	5.83 ± 0.78	5.46 ± 0.72	6.14 ± 0.71	6.33 ± 1.32	5.54 ± 1.02	6.88 ± 1.25	0.074	0.823	<b>0.039</b>
HDL cholesterol (mmol L <sup>-1</sup> )	1.61 ± 0.42	1.43 ± 0.34	1.76 ± 0.43	1.71 ± 0.38	1.47 ± 0.19	1.87 ± 0.39	0.348	0.705	0.443
LDL cholesterol (mmol L <sup>-1</sup> )	3.73 ± 0.69	3.51 ± 0.70	3.92 ± 0.64	4.03 ± 1.11	3.42 ± 0.82	4.46 ± 1.11	0.312	0.683	0.081
LDL : HDL	2.47 ± 0.79	2.60 ± 0.85	2.36 ± 0.74	2.44 ± 0.77	2.25 ± 0.58	2.47 ± 0.78	0.923	0.610	0.772
VLDL cholesterol (mmol L <sup>-1</sup> )	0.49 ± 0.18	0.52 ± 0.17	0.46 ± 0.19	0.59 ± 0.34	0.65 ± 0.46	0.55 ± 0.25	0.452	0.959	0.281
Triglycerides (mmol L <sup>-1</sup> )	1.21 ± 0.43	1.29 ± 0.42	1.14 ± 0.44	1.43 ± 0.78	1.55 ± 1.06	1.35 ± 0.53	0.409	1.000	0.224
Apolipoprotein B (mg dL <sup>-1</sup> )	114.06 ± 17.32	107.87 ± 17.06	119.22 ± 16.20	124.74 ± 28.15	109.55 ± 23.70	135.19 ± 26.70	0.092	0.835	<b>0.041</b>

Data presented as mean ± standard deviation. Abbreviations: cOC – carboxylated osteocalcin; DBP – diastolic blood pressure; dp-ucMGP – dephosphorylated-uncarboxylated matrix Gla protein; HDL – high-density lipoprotein; LDL – low-density lipoprotein; SBP – systolic blood pressure; TMR – total mixed ration; ucOC – undercarboxylated osteocalcin; and VLDL – very low-density lipoprotein. <sup>a</sup> *P*-Value for the difference in baseline values between the two treatments. <sup>b</sup> *P*-Value for the difference in baseline values between the two treatments in males only. <sup>c</sup> *P*-Value for the difference in baseline values between the two treatments in females only. The *P*-values were calculated using the independent samples *t*-test or the Mann–Whitney *U*-test, as appropriate. <sup>d</sup> Chi-square test.

circumference ( $P < 0.05$ ). Among male participants, baseline dp-ucMGP levels differed significantly between the pasture-derived cheese and TMR-derived cheese groups ( $P < 0.05$ ), with higher baseline dp-ucMGP concentrations observed in the pasture-derived cheese group ( $401.98 \pm 82.48$  pmol L<sup>-1</sup>) compared with the TMR-derived cheese group ( $360.1 \pm 73.56$  pmol L<sup>-1</sup>) (Table 3). Among female participants, there were several differences in the baseline values of body fat, waist circumference, total cholesterol, and apolipoprotein B (apoB) between the treatment groups ( $P < 0.05$ ) (Table 3).

Table 4 presents an overview of all *P*-values for the effects of treatment, sex and sex-by-treatment interaction on both anthropometric and biochemical biomarkers. The treatment and sex have no significant impact on the measured biomarkers. A significant sex-by-treatment interaction effect was observed for total cholesterol ( $P < 0.001$ ), HDL cholesterol ( $P < 0.001$ ) and LDL cholesterol ( $P = 0.002$ ) (Table 4).

Fig. 2 shows the mean changes in total, HDL, LDL and VLDL cholesterol; triglycerides concentration (mmol L<sup>-1</sup>); apoB (mg dL<sup>-1</sup>); LDL:HDL ratio; dp-ucMGP (pmol L<sup>-1</sup>) and ucOC:cOC ratio after consumption of pasture-derived or TMR-derived Cheddar cheese for six weeks. No significant differences were observed between the two groups for these two vitamin K status biomarkers. Furthermore, no significant differences in vitamin K status biomarkers were observed between the two treatment groups after stratifying the data by sex.

In terms of blood lipid profiles, no significant differences were observed in the changes in total, HDL, LDL, and VLDL

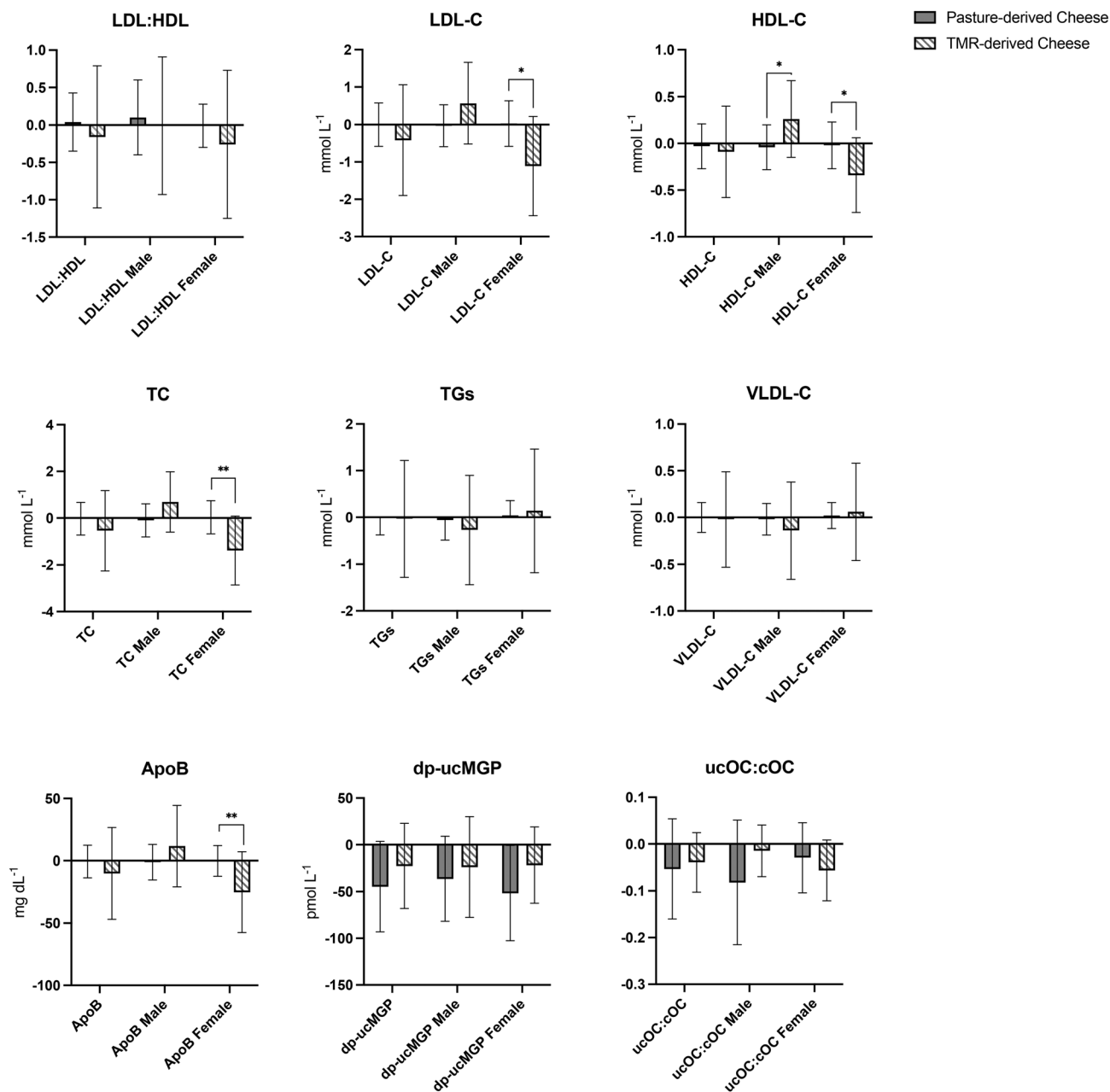
Table 4 *P*-Values for main effects and interaction effects in the analysis of anthropometric and biochemical biomarkers

	<i>P</i> treatment	<i>P</i> sex	<i>P</i> sex × treatment
Weight (kg)	0.327	0.289	0.260
BMI (kg m <sup>-2</sup> )	0.108	0.625	0.140
Body fat (%)	0.359	0.918	0.507
Waist circumference (cm)	0.056	0.433	0.006
SBP (mmHg)	0.052	0.805	0.480
DBP (mmHg)	0.012	0.719	0.875
ucOC : cOC	0.933	0.400	0.732
dp-ucMGP (pmol L <sup>-1</sup> )	0.057	0.808	0.758
Total cholesterol (mmol L <sup>-1</sup> )	0.834	0.241	<0.001*
HDL cholesterol (mmol L <sup>-1</sup> )	0.730	0.175	<0.001*
LDL cholesterol (mmol L <sup>-1</sup> )	0.528	0.115	0.002*
LDL : HDL	0.377	0.436	0.952
VLDL cholesterol (mmol L <sup>-1</sup> )	0.225	0.464	0.402
Triglycerides (mmol L <sup>-1</sup> )	0.216	0.536	0.631
Apolipoprotein B (mg dL <sup>-1</sup> )	0.901	0.259	0.009

The overall effects of treatment, sex and sex × treatment interaction (*P*-values) on absolute changes (visit 2-visit1) in anthropometric and biochemical biomarkers were calculated using ANCOVA or Quade's nonparametric ANCOVA. Baseline values were used as covariates. \* denotes significance after Bonferroni correction.

cholesterol, LDL:HDL ratio, triglycerides or apoB between the two groups after 6 weeks. However, the responses of several blood lipid biomarkers to the treatments were different between males and females. Among male participants, those who consumed TMR-derived Cheddar cheese for six weeks





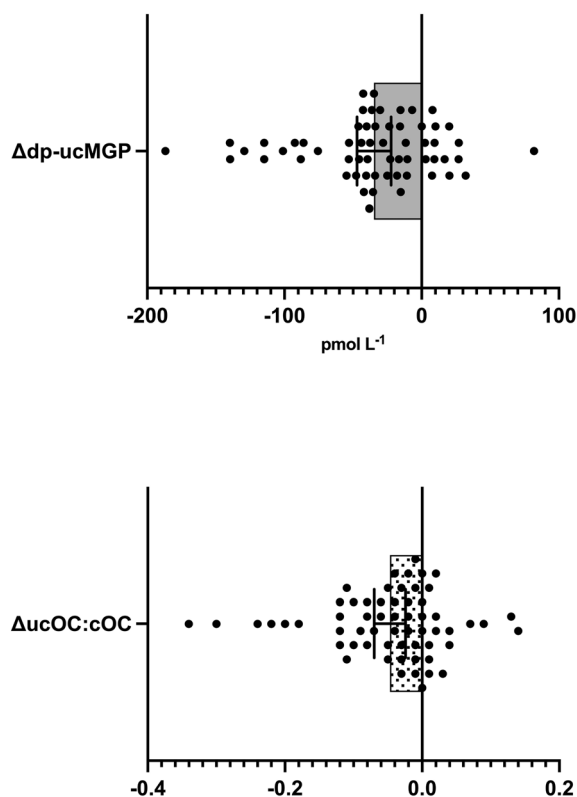
**Fig. 2** The mean changes in total cholesterol (TC), HDL cholesterol, LDL cholesterol, VLDL cholesterol; LDL : HDL ratio, triglycerides (TGs) ( $\text{mmol L}^{-1}$ ); apolipoprotein B (apoB) concentration ( $\text{mg dL}^{-1}$ ); dp-ucMGP level ( $\text{pmol L}^{-1}$ ) and ucOC : cOC ratio after consumption of pasture-derived or total mixed ration (TMR)-derived Cheddar cheese for 6 weeks. Differences between groups were assessed using the independent samples *t*-test or the Mann–Whitney *U*-test, as appropriate. \*\* denotes  $P$ -value < 0.01; \* denotes  $P$ -value < 0.05.

showed a significant increase in HDL cholesterol ( $P < 0.05$ ) compared with those who consumed pasture-derived Cheddar cheese. In contrast, among female participants, TMR-derived cheese intake significantly decreased HDL cholesterol ( $P < 0.05$ ) in comparison with pasture-derived cheese. Furthermore, female participants who consumed TMR-derived cheese for six weeks showed significant decreases in total cholesterol, LDL cholesterol, and apoB levels ( $P < 0.05$ ) compared with those who consumed pasture-derived cheese. In male participants,

there were no significant differences in the changes in these three biomarkers between the two groups.

Fig. 3 shows the pooled mean changes in the dp-ucMGP level ( $\text{pmol L}^{-1}$ ) and the ucOC : cOC ratio after 6 weeks of Cheddar cheese consumption. The data were pooled from the pasture- and TMR-derived cheese groups. The mean change in the dp-ucMGP level was  $-34.73 \text{ pmol L}^{-1}$  (95% CI:  $-47.14$ ,  $-22.33$ ), and the mean change in the ucOC : cOC ratio was  $-0.047$  (95% CI:  $-0.07$ ,  $-0.02$ ).





**Fig. 3** The pooled mean changes in the dp-ucMGP level ( $\text{pmol L}^{-1}$ ) and the ucOC : cOC ratio after consumption of Cheddar cheese for 6 weeks. The data were pooled from the pasture and TMR-derived groups. Error bars represent the 95% confidence interval (CI). Black dots represent individual data of each participant (total  $n = 60$ ) in the present study. The mean change in the dp-ucMGP level was  $-34.73 \text{ pmol L}^{-1}$  (95% CI:  $-47.14, -22.33$ ) and the mean change in the ucOC : cOC ratio was  $-0.047$  (95% CI:  $-0.07, -0.02$ ).

## 4. Discussion

### 4.1 Effects on vitamin K status

After six weeks, the levels of both vitamin K status biomarkers decreased, which may suggest an improvement in vitamin K status following Cheddar cheese consumption in general for this time period. Although both pasture-derived and TMR-derived cheeses have similar macronutrients, they have different vitamin K content. The total vitamin K content in TMR-derived cheese is approximately two times higher than that in pasture-derived cheese, and the MK-9 content is approximately four times higher. However, this did not result in a significantly greater effect on changes in vitamin K dependent proteins (VKDPs) compared with the pasture-derived group. VKDPs are characterized by the presence of  $\gamma$ -carboxylglutamate (Gla) residues, which are important for their function.<sup>37</sup> To become functional, VKDPs need to be activated by vitamin K-dependent carboxylation,<sup>38</sup> which is facilitated by the enzyme gamma-glutamyl carboxylase (GGCX) with cofactors including a reduced form of vitamin K ( $\text{KH}_2$ ), carbon dioxide ( $\text{CO}_2$ ), and oxygen ( $\text{O}_2$ ).<sup>39</sup> During the modification of

each glutamate residue,  $\text{KH}_2$  is oxidized to vitamin K 2,3-epoxide (KO), and then KO is converted back to  $\text{KH}_2$  through a two-step reduction process involving the enzymes vitamin K epoxide reductase (VKOR) and vitamin K reductase (VKR).<sup>39</sup> Therefore, vitamin K-dependent carboxylation is a complex process involving different enzymes. Furthermore, polymorphisms in the genes that encode the cycle enzymes may also affect individual response to vitamin K intake; it has been previously reported that total vitamin K intake showed a significant negative correlation with the ucOC : total OC ratio in individuals with the GG-type and GA-type of GGCX, but not in those with the AA-type of GGCX, suggesting that the requirement for vitamin K in gamma-carboxylation may vary depending on the GGCX genotype.<sup>40</sup> It is possible that differences in GGCX genotypes could partially explain the observation that higher vitamin K intake in the TMR group did not lead to a greater reduction in vitamin K status biomarkers. Unfortunately, genotypic data were not available for the participants in this study, and this could be an important consideration for future work in this area.

Dalmeijer *et al.* reported that after four weeks of supplementation with  $180 \mu\text{g day}^{-1}$  MK-7, the ucOC : cOC ratio decreased from 0.47 to 0.21; however, from week 4 to week 12, the mean ucOC : cOC ratio decreased only slightly further to 0.19.<sup>41</sup> A similar observation of a significant decrease during the first 4 weeks was also reported in the intervention group with  $360 \mu\text{g day}^{-1}$  MK-7 in the same study.<sup>41</sup> These may suggest that once the ucOC : cOC ratio decreases to a certain point, or when most OC is already carboxylated, increasing the dose or extending the intervention duration may have minimal additional effects on the carboxylation of VKDPs. The participants in the present study had relatively higher levels of carboxylated VKDPs, as reflected by the lower ucOC : cOC ratio at the baseline. The baseline ucOC : cOC ratio in both groups was 0.27, which is much lower than the reported baseline values in healthy populations in other studies (0.42–0.82).<sup>32,41,42</sup> Therefore, additional vitamin K intake may not have a significant effect on carboxylation of VKDPs because of the low baseline ucOC : cOC ratio.

### 4.2 Effects on lipid profiles

In this study, six weeks of TMR-derived cheese consumption resulted in a significant increase in HDL cholesterol in males and a significant reduction in total, HDL and LDL cholesterol levels in females compared with the pasture-derived cheese consumption. However, in both males and females, no significant change in LDL : HDL was observed compared with pasture-derived cheese consumption. The balanced LDL : HDL ratio suggests that the reductions in LDL and HDL levels may have occurred proportionally, thereby maintaining the overall lipoprotein balance. Although the apoB level showed a significant difference in changes between the two treatments in females (Fig. 2), the  $P$ -value for the interaction effect (Table 4) did not remain significant after Bonferroni correction. Therefore, this result should be interpreted with caution, as it may not represent a robust statistical finding. The observed



trend in the apoB level in females may be due to its strong correlation with the LDL cholesterol level,<sup>43</sup> as the apoB molecule is a component of LDL cholesterol.<sup>44</sup>

Among females in the TMR-derived group, the reduction in total cholesterol is likely attributed to the reduction in both HDL and LDL cholesterol. In the present study, the TMR-derived cheese contains twice the vitamin K content of the pasture-derived cheese. The higher vitamin K intake may have possibly contributed to the overall lipid-lowering effect. A randomised trial involving premenopausal women ( $n = 66$ ) aged 19.4–51.9 years who consumed 57 g day<sup>-1</sup> (46 µg day<sup>-1</sup> total vitamin K) of Jarlsberg cheese for 6 weeks reported similar decreases in total, HDL and LDL cholesterol, with no significant change in the LDL : HDL ratio after six weeks of consumption.<sup>42</sup> Furthermore, a number of different observational studies have also reported the role of vitamin K in regulating blood lipid profiles. An observational study in the US found that the HDL cholesterol level increased with higher dietary vitamin K1 intake among young adults.<sup>18</sup> Similarly, in a Dutch cohort study of healthy individuals aged 20–70 years, higher vitamin K2 intake was associated with increased HDL cholesterol.<sup>17</sup> Moreover, a recent study with sixty healthy Greek participants reported that a reduction in the LDL cholesterol level was associated with increased intake of vitamin K2.<sup>45</sup>

Vitamin K may regulate lipid metabolism through multifactorial mechanisms of action. It has been reported that the geranylgeraniol side chain of vitamin K2 may inhibit the synthesis of geranyldiphosphate, an intermediate metabolite in the cholesterol synthesis process.<sup>46</sup> Moreover, a recent animal study showed that vitamin K2 protects against non-alcoholic fatty liver disease and improves lipid metabolism disorder by inhibiting trihydroxy-3-methylglutaryl coenzyme A reductase, a key rate-limiting enzyme in cholesterol synthesis.<sup>47</sup> In addition to its effects on cholesterol synthesis, different randomised controlled trials have demonstrated that intake of 375 µg or 180 µg of MK-7 supplement per day for one or three years increased adiponectin levels in healthy postmenopausal women compared with the control group.<sup>48,49</sup> Adiponectin levels have also been reported to positively correlate with HDL cholesterol and negatively correlate with triglycerides, apoB, and non-HDL cholesterol.<sup>50–53</sup> Therefore, vitamin K is speculated to affect lipid profiles *via* inhibiting cholesterol synthesis and increasing the adiponectin level. However, further studies are needed to confirm the effect of vitamin K on the enzymes involved in cholesterol synthesis and adiponectin levels in healthy populations.

### 4.3 Sex differences

The present study demonstrated significant between sex-by-treatment (different cheddar cheese variants) interaction effects on blood lipid biomarkers. This finding suggests that males and females may respond differently to intake of Cheddar cheese containing vitamin K. Evidence from animal studies supports the possibility of sex-specific differences in vitamin K metabolism. Vitamin K2 has been shown to account for a large proportion of total vitamin K in the livers of both

male and female rats.<sup>54</sup> Moreover, female rats showed significantly higher vitamin K1 and K2 concentrations in their livers compared with male rats after administration of the same amount of vitamin K.<sup>54</sup> This indicates a potential sex-specific effect on the absorption and retention of vitamin K. This sex-specific difference may partly explain the different lipid profile responses observed between males and females in the present study after consuming the same Cheddar cheese, as females may have a higher proportion of vitamin K accumulated in the liver, which may inhibit cholesterol synthesis and affect lipid profiles, as discussed above. However, further human studies are needed to confirm this speculation.

Furthermore, some human intervention studies have reported sex-specific effects on blood profile responses after consuming dairy products with matched nutritional compositions. Brassard *et al.* reported that, in a middle-aged population with abdominal obesity, males showed a greater increase in HDL-mediated cholesterol efflux capacity than females after butter consumption.<sup>55</sup> Another study demonstrated that sex differences affected postprandial responses to different dairy products (butter, cheese, sour cream and whipped cream) in lipoprotein subclasses, including medium VLDL, small LDL, very large HDL, and large HDL particle concentrations.<sup>56</sup> The different responses between males and females in lipid profiles to food intake could potentially be explained by sex-specific differences in the methylome and transcriptome of the human liver, which are associated with hepatic *KDM6A* gene expression changes and HDL cholesterol levels.<sup>57</sup>

Therefore, it is speculated that biological or physiological differences between males and females lead to the different responses in blood lipid biomarkers to cheese intake. Additionally, genetic differences could also contribute to the different responses observed in this study. However, these speculations require additional research to confirm and explore the underlying mechanisms for these different lipid profile responses to dairy products or vitamin K intake between males and females.

## 5. Limitations of the study

This study was an exploratory study performed to investigate the potential for cheese consumption to improve vitamin K status in humans, as well as to explore the relationship between vitamin K intake and lipid-lowering effects. The analysis was conducted using existing data from a previous randomised controlled trial with additional measurements of vitamin K dependent proteins performed using biobanked blood samples. The primary study, from which the present analysis was derived, did not include a control group without vitamin K or dairy intake. Therefore, as no control group was included in the present study, the findings should be interpreted as indicative of associations rather than as conclusive evidence of a causal relationship.

Due to the unavailability of appropriate existing data for the power calculation, a power analysis was not performed for the



present study. Certain endpoints such as the significant difference observed in HDL-C for males between groups had a *post hoc* power below 0.80, indicating that the analysis may have been underpowered. Therefore, a replication of the experiment using a larger sample size is required in the future.

## 6. Conclusion

This exploratory study demonstrated that six weeks of consumption of Cheddar cheese variants was associated with improvements in vitamin K status. TMR-derived Cheddar cheese, which contained higher vitamin K content, also resulted in sex-specific effects on blood lipid profiles, with males showing increased HDL cholesterol and females exhibiting reductions in total, HDL, and LDL cholesterol compared with pasture-derived Cheddar cheese. The findings of this study suggest that dietary vitamin K from cheese may modulate lipid metabolism, but the responses are influenced by sex. Further randomized controlled studies with larger sample sizes are warranted to clarify the mechanisms underlying these different responses.

## Author contributions

Sitong Zhou: conceptualization, data curation, formal analysis, investigation, methodology, project administration, visualization, writing – review & editing, and writing – original draft. Heleena Moni Bottu: writing – review & editing, and methodology. Jean-Christophe Jacquier: writing – review & editing, and methodology. Raquel Cama-Moncunill: writing – review & editing, and methodology. Mark Timlin: writing – review & editing, and resources. Deirdre Hennessy: writing – review & editing, and resources. Michael O'Donovan: writing – review & editing, and resources. André Brodkorb: writing – review & editing, and resources. Jeremiah J. Sheehan: writing – review & editing, and resources. Eileen R. Gibney: data curation, funding acquisition, project administration, resources, and writing – review & editing. Peter Dunne: writing – review & editing, and supervision. Emma L. Feeney: conceptualization, data curation, funding acquisition, project administration, resources, supervision, and writing – review & editing.

## Conflicts of interest

There are no conflicts of interest to declare.

## Data availability

Data described in the manuscript, will not be made available, in line with current UCD HREC data storage and retention guidelines. The de-identified archived data are accessible only to study investigators and will not be accessible to others. Other supporting data are included as part of the supplementary information

(SI). Supplementary information showing the absolute changes in different biomarkers after six weeks of intervention is available. See DOI: <https://doi.org/10.1039/d5fo05631d>.

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