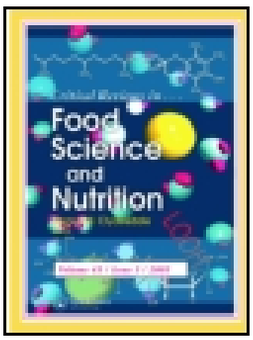

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REVIEW

The future is bright: Biofortification of common foods can improve vitamin D status

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ABSTRACT

Vitamin D deficiency is a global concern, linked to suboptimal musculoskeletal health and immune function, with status inadequacies owing to variations in UV dependent cutaneous synthesis and limited natural dietary sources. Endogenous biofortification, alongside traditional fortification and supplement usage is urgently needed to address this deficit. Evidence reviewed in the current article clearly demonstrates that feed modification and UV radiation, either independently or used in combination, effectively increases vitamin D content of primary produce or ingredients, albeit in the limited range of food vehicles tested to date (beef/pork/chicken/eggs/fish/bread/mushrooms). Fewer human trials have confirmed that consumption of these biofortified foods can increase circulating 25-hydroxyvitamin D [25(OH)D] concentrations ($n = 10$), which is of particular importance to avoid vitamin D status declining to nadir during wintertime. Meat is an unexplored yet plausible food vehicle for vitamin D biofortification, owing, at least in part, to its ubiquitous consumption pattern. Consumption of PUFA-enriched meat in human trials demonstrates efficacy ($n = 4$), lighting the way for exploration of vitamin D-biofortified meats to enhance consumer vitamin D status. Response to vitamin D-biofortified foods varies by food matrix, with vitamin D_3-enriched animal-based foods observing the greatest effect in maintaining or elevating 25(OH)D concentrations. Generally, the efficacy of biofortification appears to vary dependent upon vitamer selected for animal feed supplementation (vitamin D_2 or D_3, or 25(OH)D), baseline participant status and the bioaccessibility from the food matrix. Further research in the form of robust human clinical trials are required to explore the contribution of biofortified foods to vitamin D status.

KEYWORDS

25-hydroxyvitamin D (25(OH)D); feed supplementation; UV radiation; fortification; RCT; bioavailability; meat

Introduction

Biofortification, also referred to as 'bio-addition' or 'bio-enrichment', differs from exogenous or post-production fortification as the nutritional composition of a chosen food is naturally altered through a change in agronomic practices (Bouis and Saltzman 2017). In the case of animal production, for example, biofortification of primary produce can be achieved by altering the feed component or housing environment as part of animal husbandry. Alternative horticultural strategies and/or technologies have also been used in mushroom production, for example, to increase their nutritional value. Such strategies have successfully enhanced nutrient content of iron, vitamin A, zinc, selenium and vitamin D in a range of foodstuffs (for reviews, see Bouis and Saltzman 2017; Cardwell et al. 2018; Guo, Lovegrove, and Givens 2018; Jha and Warkentin 2020; Malagoli et al. 2015). The current review focuses on the different vitamin D biofortified foods researched to-date, the efficacy of these foods in human intervention trials and subsequently presents an argument for considering meat as a biofortification vehicle to improve population vitamin D status.

Vitamin D deficiency is a global public health priority issue as many populations fail to meet the recommended nutrient intake (RNI) and particularly during wintertime, at higher latitudes, vitamin D endogenous synthesis is at its nadir. However, estimates of the year-round prevalence of sub-optimal vitamin D status vary from 13% (increasing to 18% in winter) to 40% across Europe depending on whether deficiency is defined in accordance with the US Institute of Medicine (2011) as a 25-hydroxyvitamin D (25(OH)D) concentration in blood <30 nmol/l (12 ng/ml) or <50 nmol/l (20 ng/ml) as recommended by the Endocrine Society (Cashman et al. 2016a; Holick et al. 2011). These discrepancies are often owed to differences in the primary endpoint health outcome being considered (i.e. skeletal or non-skeletal benefits) as well as the lack of diversity in study populations which values were based upon (for reviews, see Bouillon et al. 2013; Holick et al. 2012; Pilz et al. 2019). Specifically in the UK, consumption rates are much lower than the recommended 10 µg/day (Scientific Advisory Committee on Nutrition (SACN) 2016) even when accounting for the contribution of supplements (approx. 3-4 µg/day) (Public Health England 2018). Hence, additional food-based strategies are

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required to bridge the gap between recommended vitamin D intakes and current 25(OH)D concentrations (Buttriss and Lanham-New 2020; Cashman 2020a; Cashman 2020b).

As animals synthesize vitamin D following natural or artificial ultraviolet-B (UVB) exposure and meat is a popular food in UK diets (Cocking et al. 2020; Public Health England 2018), this may be a feasible vitamin D biofortification vehicle to increase population vitamin D status. In recent years, there has been a decline in consumption levels of red and processed meats in UK populations (74 ± 57 g to 62 ± 51 g/day) (Public Health England 2018) owing to health and global sustainability concerns (Aune et al. 2013; Bouvard et al. 2015; World Cancer Research Fund 2018). Despite meat being a major contributor to vitamin D dietary intakes (Public Health England 2018), it is often under-valued and not widely recognized as a source of vitamin D (McNeill and Van Elswyk 2012). Accordingly, there is an opportunity to further enhance its nutritional profile through biofortification to ensure meat continues to remain one of the significant contributors to total vitamin D intakes despite lower quantities of meat being consumed. Moreover, it is not simply the concentration of vitamin D within the food source, but also the effects of food processing and the bioaccessibility from the food matrix which will impact upon bioavailability post-consumption which must be considered for biofortified sources. To date, numerous human studies have already demonstrated the bioavailability of vitamin D and subsequent status enhancement using the traditional exogenous, or post-production fortification routes (Black et al. 2012; Itkonen, Erkkola, et al. 2018; Pilz et al. 2018). However, the evidence surrounding the efficacy of endogenous vitamin D biofortification is less clear.

Therefore, the aims of the present review were to 1) summarize current evidence showing efficacy of vitamin D biofortification; 2) evaluate the efficacy of consumption of endogenously biofortified vitamin D-enriched products; 3) identify the feasibility of meat as a vehicle for endogenous nutrient biofortification.

Vitamin D biofortification in foodstuffs

Vertebrates as well as fungi and yeast are capable of synthesizing vitamin D_3 and vitamin D_2, respectively following exposure to UVB radiation (wavelength 290-315 nm) (Jäpelt and Jakobsen 2013; Wacker and Holick 2013). In humans and animals, 7-dehydrocholesterol (provitamin D_3) in the epidermis of skin is converted to pre-vitamin D_3 before undergoing thermal isomerization to cholecalciferol and then two hydroxylation steps in the liver and kidneys to produce 25-hydroxyvitamin D_3 ($25(OH)D_3$) and the final active metabolite, 1,25-dihydroxyvitamin D_3 ($1,25(OH)D_3$), respectively. A detailed overview of vitamin D pathology has been documented in detail elsewhere (Bikle 2014; Christakos et al. 2016). Considering this in-built endogenous synthesis, one effective method to enhance the vitamin D concentration of foodstuffs is to expose the animal or plant to UV radiation, either naturally or artificially.

Recent reviews have explored the impact of feed supplementation on vitamin D concentrations found in various animal-based foods (for reviews, see Barnkob, Argyraki, and Jakobsen 2020; Duffy et al. 2018a; Guo, Lovegrove, and Givens 2018), whilst others have extensively investigated how UV exposure impacts the vitamin D content of fresh mushrooms (for reviews, see Cardwell et al. 2018; Friedman 2016; Kohn 2016; Taofiq et al. 2017). These are collated and summarized alongside eighteen additional studies which are described and fully referenced in Table 1. UV exposure resulted in elevated vitamin D_2 concentrations in baker's yeast and mushrooms, with differences observed between UVA, UVB and UVC. Of those that specified UV wavelength, UVB was the most popular type of irradiation, followed by UVC and then UVA (75%, 31% and 25% of studies, respectively). Some recorded use of more than one UV form. Artificial irradiation was favored with 81% studies using lamps compared to 11% relying on natural exposure and the remainder investigating both forms. It is important, therefore, to be cognizant of variability regarding intensity, wavelength, narrowband and broadband lamps, the spectrum of broadband, and the duration of UV exposure which limits comparability of data. Supplementing animal feed with vitamin D_3 increased vitamin D_3 concentrations in tissue, blood and meat of beef cattle, pigs and fish, as well as in egg yolk and cow's milk. In view of this data, it can be concluded that biofortification through feed supplementation or UV radiation is effective at enhancing vitamin D content in a variety of foods, especially animal-based products.

Vitamin D biofortification in human trials

Despite many studies highlighting the feasibility of enhancing the vitamin D content of various foods, and particularly meat sources using biofortification methodologies, remarkably few randomized controlled trials (RCTs) to-date have investigated their efficacy in elevating concentrations of circulating serum 25(OH)D in human participants. Following a systematic approach (see Supplemental Material for search strategy), ten studies were identified that investigate how participants vitamin D status has been influenced following consumption of foods exposed to biofortification practices, namely enriched eggs (Hayes et al. 2016), bread baked with UV-treated yeast (Itkonen et al. 2016), fish (Graff et al. 2016) and mushrooms (Keegan et al. 2013; Mehrotra et al. 2014; Nieman et al. 2013; Shanely et al. 2014; Stephensen et al. 2012; Stepien et al. 2013; Urbain et al. 2011). Table 2 describes results from these vitamin D biofortification human RCTs. Notably, to-date mushrooms represent the most popular vehicle for biofortification studies and have been comprehensively reviewed by others (Cardwell et al. 2018; Cashman et al. 2016b; Kamweru and Tindibale 2016; Kohn 2016; Taofiq et al. 2017) so while not the focus of this review, they have been included in Table 2 for completeness.

Consumption of vitamin D_3 enriched eggs and fish had a positive impact on endpoint total 25(OH)D concentrations,

Table 1. Summary of studies investigating the outcome of feed supplementation or UV exposure on vitamin D enrichment in animals or plant-based foods.

	Biofortification method						
Food vehicle	D_3	25(OH)D_3	D_2	Mushroom D_2	UV	Summary of outcomes	Study reference
Beef cattle	X		X	X	X	Vitamin D_3 diet = ↑ vitamin D_3 in meat[1-2,4-7] UV exposure = ↑ vitamin D in milk[3] & blood[3]	Duffy et al. 2018b[1]; Duffy et al. 2017a[2]; Jakobsen et al. 2015[3]; Korn et al. 2013[4]; Montgomery et al. 2004[5]; Montgomery et al. 2002[6]; Montgomery et al. 2000[7]
Pigs	X	X	X	X	X	25(OH)D_3 diet = ↑ total vitamin D activity in LT[10] & higher 25(OH)D_3 in tissue[15], LT[10] & serum[10,15] Vitamin D_3 diet = ↑ vitamin D_3 in tissue[15,19], blood[12,16,18] & LT[10,17-18] UV exposure = ↑ total vitamin D content of loin tissue[9,13] & ↑ serum vitamin D_3[8-9,11,16] & 25(OH)D_3[8-9,11-13,16] & ↑ vitamin D_3 in skin[14,16]	Jakobsen, Nielsen, and Jakobsen 2020[8]; Barnkob et al. 2019[9]; Duffy et al. 2018c[10]; Alexander et al. 2017[11]; Kolp et al. 2017[12]; Larson-Meyer et al. 2017[13]; Barnkob et al. 2016[14]; Burild et al. 2016[15]; Burild et al. 2015[16]; Jakobsen et al. 2007[17]; Wilborn et al. 2004[18]; Clausen et al. 2003[19]
Chickens (egg yolk)	X	X	X	X	X	Vitamin D_3 diet = ↑ vitamin D_3 in yolk[21,23,26-27,30,32-36,40] 25(OH)D_3 diet = ↑ 25(OH)D_3 in yolk[23,27,32,37,42] & ↑ total vitamin D activity in egg[24] Vitamin D_2 diet = ↑ vitamin D in yolk[41] UV exposure = ↑ vitamin D or 25(OH)D_3 in plasma[22,25,29,31] & yolk[20,25,28-29,38-39]	Kühn et al. 2019[20]; Wen, Livingston, and Persia 2019[21]; Geng et al. 2018[22];Duffy et al. 2017b[23]; Cashman et al. 2015[24]; Kühn et al. 2015[25]; Plaimast et al., 2015; Browning and Cowieson 2014[27]; Kühn et al. 2014[28]; Schutkowski et al. 2013[29]; Yao et al. 2013[30]; Lietzow et al. 2012[31]; Mattila, Valkonen, and Valaja 2011[32]; Park et al. 2005[33]; Mattila et al. 2004[34]; Mattila et al. 2003[35]; Mattila et al. 1999a[36]; Terry et al. 1999[37]; Chiang, Hwang, and Holick 1997[38]; Chiang, Hwang, and Holick 1996[39]; Kawazoe et al. 1996[40]; Kawazoe et al. 1994[41]; Koshy and Van Der Slik 1979[42]
Chickens (meat)					X	UV exposure = ↑ vitamin D in meat[43]	Schutkowski et al. 2013[43]
Fish	X				X	Highest vitamin D_3 diet = ↑ vitamin D_3 in whole fish[46], fillet[44,48] & liver[46,49] No correlation between vitamin D_3 diet & rainbow trout muscle[47] UV exposure = ↑ vitamin D in skin[45]	Jakobsen, Melse-Boonstra, et al. 2019[44]; Pierens and Fraser 2015[45]; Graff et al. 2002[46]; Mattila et al. 1999b[47]; Horvli, Lie, and Aksnes 1998[48]; Vielma et al. 1998[49]
Dairy goats & sheep					X	UV exposure = ↑ 25(OH)D in serum[50]	Nemeth, Wilkens, and Liesegang 2017[50]
Cows (milk)	X	X			X	25(OH)D_3 diet = ↑ 25(OH)D_3 in serum[52] Vitamin D_3 diet = ↑ vitamin D_3 & 25(OH)D_3 in plasma[53] & milk[54-5] UVB exposure = ↑ 25(OH)D_3 in plasma[51] & ↑ vitamin D_3 & 25OHD_3 in milk[51]	Jakobsen et al. 2015[51]; Weiss et al. 2015[52]; McDermott et al. 1985[53]; Reeve, Jorgensen, and Deluca 1982[54]; Hollis et al. 1981[55]
Baker's yeast*					X	UV exposure = ↑ vitamin D in yeast[56-57]	Degre and Zhang 2014[56]; Degre, Zhang, and Edwards 2008[57]
Fresh mushrooms					X	UVA or UVC exposure = ↑ vitamin D_2 in mushrooms[58,63-64,76,82,86,91,95-99,101] UVB exposure = ↑ vitamin D_2 in mushrooms[59-62,65-75,77-90,92-94,98,100-101] (extended exposure/dose = ↓ vitamin D_2[61,70]) UVC exposure = ↑ vitamin D_2 in mushrooms vs UVA exposure[96] Post-harvest UVB exposure = ↑ vitamin D_2 vs exposure during growth phase[84] Gills facing UV source = ↑ vitamin D_2 vs caps facing UV source[99]	Hu et al. 2020[58]; Bilbao-Sainz et al. 2017[59]; Chien et al. 2017[60]; Won et al. 2018[61]; Banlangsawan and Sanoamuang 2016[62]; Guan et al. 2016[63]; Huang, Cai, and Xu 2017[64]; Lee and Aan 2016[65]; Nölle et al. 2017[66]; Sławińska et al. 2016[67]; Urbain, Valverde, and Jakobsen 2016[68]; Huang, Lin, and Tsai 2015[69]; Urbain and Jakobsen 2015[70]; Zhang et al. 2015[71]; Krings and Berger 2014[72]; Mehrotra et al. 2014[73]; Sapozhnikova et al. 2014[74]; Wu and Ahn 2014[75]; Bennett et al. 2013[76]; Calvo et al. 2013[77]; Keegan et al. 2013[78]; Phillips and Rasor 2013[79]; Stepien et al. 2013[80]; Wittig, Krings, and Berger 2013[81]; Kalaras, Beelman, and Elias 2012a[82]; Kalaras et al. 2012b[83]; Kristensen, Rosenqvist, and Jakobsen 2012[84]; Stephensen et al. 2012[85]; Koyyalamudi et al. 2011[86]; Phillips et al. 2011[87]; Ruslan, Reza, and Damayanti 2011[88]; Simon et al. 2011[89]; Urbain et al. 2011[90]; Koyyalamudi et al. 2009[91]; Lee et al. 2009[92]; Ko et al. 2008[93]; Roberts, Teichert, and McHugh 2008[94]; Jasinghe, Perera, and Sablani 2007[95]; Teichmann et al. 2007[96]; Jasinghe, Perera, and Barlow 2006[97]; Jasinghe and Perera 2006[98]; Jasinghe and Perera 2005[99]; Perera et al. 2003[100]; Mau, Chen, and Yang 1998[101]

LT, *Longissimus thoracis*; vitamin D activity = vitamin D_3 + (25(OH)D_3 × 5). Superscript numerals correspond with study outcomes and their respective references.

*The European Food Safety Authority (EFSA Panel on Dietetic Products and Nutrition and Allergies (NDA) 2014) and U.S. Food and Drug Administration (FDA, 2012) have approved the use of UV-irradiated baker's yeast (*Saccharomyces Cerevisiae*), patented by LALLEMAND, USA Inc (Montreal, Canada).

Table 2. Study characteristics of randomized controlled trials investigating the effect of biofortified foods on vitamin D status [a].

Study	Location	Age, y [b]	BMI, kg/m^2 [b]	Duration, wk	Season	Study groups (type of food)	Vitamin D dose, μg/d [c]	25(OH)D outcome, nmol/L [d]
Bread (yeast) Itkonen et al. 2016 (n = 33, 0% M)	Helsinki, Finland (60°N)	27.2 ± 5.1	22.2 ± 2.3	8	Winter (Feb-April)	Placebo capsule + bread	0	No change
						Vitamin D_2 supplement + bread	24.4 D_2	Δ + 9.6
						Vitamin D_3 supplement + bread	25.0 D_3	Δ + 17.0*
						Placebo capsule + UV-bread	26.3 D_2	No change
Eggs Hayes et al. 2016 (n = 51, 49% M)	Cork, Ireland (51°N)	45–70	25.6 ± 4.1	8	Winter (Jan-March)	Placebo eggs	≤6.8 D	41.2 ± 14.1 → 34.8 ± 11.4*
						Vitamin D_3-eggs	24.5 D	48.2 ± 18.9 → 50.4 ± 21.4
						25(OH)D_3-eggs	31.5 D	49.4 ± 15.8 → 49.2 ± 16.5
Fish Graff et al. 2016 (*n* = 122, 0% M)	Bergen, Norway (60°N)	55.0 (5.0) [e]	24.6 (5.0) [e]	12	Spring (Feb-May)	High vitamin D_3 + high vitamin K_1 salmon (+ Ca supplement)	16.3 D_3	Δ + 11.4 ± 16.0*
						High vitamin D_3+ low vitamin K_1 salmon (+ Ca supplement)	15.0 D_3	Δ + 12.1 ± 16.8*
						Low vitamin D_3+ high vitamin K_1 salmon (+ Ca supplement)	3.9 D_3	Δ −1.2 ± 12.3
						Vitamin D + calcium supplement	15.0 D_3	Δ + 13.7 ± 17.0*
Mushrooms Mehrotra et al. 2014 (*n* = 36, 42% M)	New York, United States (41°N)	49 ± 12	>25	16	Winter + Spring (Nov-April)	Placebo capsule + (low) UV-mushroom	12.1 D_2	NR
						Placebo capsule + (high) UV-mushroom	65.2 D_2	42.5 ± 12.3 → 46.3 ± 10.3
						Vitamin D_3 supplement (low) + mushroom	31.1 D_3	40.3 ± 8.8 → 71.3 ± 2.8*
						Vitamin D_3 supplement (high) + mushroom	183.0 D_3	47.0 ± 10.5 → 81.3 ± 9.5*
Mushrooms Shanely et al. 2014 (*n* = 33, 100% M)	North Carolina, United States (36°N)	16.2 ± 1.1	23.4–24.7	6	Winter (Jan–Feb)	UV-mushroom capsule	15.0 D_2	62.2 ± 12.9 → 69.0 ± 12.6*
						Placebo mushroom capsule	Below limit of detection	64.5 ± 20.1 → 62.0 ± 20.7
Mushrooms Keegan et al. 2013 (*n* = 25, 24% M)	Massachusetts, United States (42°N)	35.2	NR	12	Winter (NR)	Vitamin D_2 supplement	50.0 D_2	48.5 ± 5.8 → 73.0 ± 5.0*
						Vitamin D_3 supplement	50.0 D_3	42.8 ± 3.5 → 86.0 ± 3.3*
						UV-mushroom capsule	50.0 D_2	51.5 ± 6.0 → 75.3 ± 6.5*
Mushrooms Nieman et al. 2013 (*n* = 28, 100% M)	North Carolina, United States (36°N)	27.2 ± 4.5	28.2–29.8	6	Winter (Oct–Jan)	UV-mushroom powder	95.0 D_2	91.5 ± 15.3 → 93.5 ± 17.1
						Placebo mushroom powder	0	102 ± 20.3 → 96.5 ± 17.4
Mushrooms Stepien et al. 2013 (*n* = 85, 35% M)	Dublin, Ireland (53°N)	40–65	25.2–26.0	4	Winter (Feb–March)	UV-mushroom powder	15.0 D_2	49.0 ± 19.0 → 36.8 ± 16.6
						Placebo mushroom powder	0	39.8 ± 12.7 → 30.6 ± 15.1
						Vitamin D_3 supplement	15.0 D_2	47.8 ± 17.2 → 57.3 ± 17.7*
						Placebo capsule	0	54.9 ± 21.1 → 41.7 ± 20.1
Mushrooms Stephensen et al. 2012 (n = 35, 34% M)	California, United States (39°N)	20–59	22.5–24.7	6	Summer + Autumn (June–Nov)	Vitamin D_2 supplement + mushroom	28.2 D_2	Δ − 7.3 ± 2.9
						Placebo capsule + (low) UV-mushroom	8.8 D_2	Δ − 6.5 ± 3.7
						Placebo capsule + (high) UV-mushroom	17.1 D_2	Δ − 10.5 ± 6.0*
						Placebo capsule + mushroom	0.8 D_2	Δ + 2.6 ± 3.3
Mushrooms Urbain et al. 2011 (*n* = 26, 35% M)	Freiburg, Germany (48°N)	30.8 ± 5.8	22.1 ± 2.5	5	Winter (Jan–March)	Vitamin D_2 supplement + mushroom	100.2 D_2	27.3 ± 6.0 → 65.3 ± 15.0*
						Placebo capsule + UV-mushroom	100.0 D_2	37.6 ± 5.0 → 59.6 ± 12.2*
						Placebo capsule + mushroom	0.2 D_2	30.4 ± 6.0 → 26.2 ± 5.6*

BMI, Body Mass Index; 25(OH)D, 25-hydroxyvitamin D; *n*, number of participants completed study; M, males; NR, not reported; Ca, calcium.
All studies analyzed serum 25(OH)D by Liquid Chromatography–Mass Spectrometry (LC-MS/MS). Urbain et al. (2011) initially analyzed by radioimmunoassay (RIA) but reanalyzed by LC-MS/MS (Cashman et al. 2016b), results of which are provided.
aUnless otherwise specified, data is presented as mean ± SD.
bAge and BMI is reported as range where mean ± SD was unavailable.
cWhen daily vitamin D dose was not presented in original data, concentration was calculated from weekly dosage; study by Hayes et al. (2016) is presented as mean total vitamin D activity [vitamin D3 + (25(OH)D3 x 5)].
dDemonstrates significant effect of dietary regime (*$P < 0.05$).
eData reported as median (interquartile range).

compared to control groups (Graff et al. 2016; Hayes et al. 2016). Vitamin D_3 and 25(OH)D_3-enriched eggs maintained wintertime total serum 25(OH)D concentrations at around 50 nmol/l (a non-significant change from baseline, $P > 0.05$) whereas, the group receiving placebo eggs observed the expected 25(OH)D seasonal decline (mean ± SD; 41.2 ± 14.1 to 34.8 ± 11.4 nmol/l, $P = 0.001$). There was no significant difference between endpoint 25(OH)D concentrations in vitamin D_3 and 25(OH)D_3-enriched egg groups, however both groups were significantly higher in endpoint 25(OH)D from control ($P \leq 0.005$). In the study by Graff et al. (2016), participants offered fish with the highest vitamin D_3 content observed a significant treatment effect in serum 25(OH)D concentrations from baseline to endpoint (median (IQR); 74.2 (32.5) to 84.0 (15.6) nmol/l, $P < 0.001$). This differs to the 25(OH)D maintenance reported by Hayes et al. (2016) with enriched eggs; however, the weekly vitamin D_3 dose from enriched fish was much greater than the highest vitamin D_3 egg group (114 vs. 7.28 µg). Contrasting with traditional vitamin D_2 fortification in bread which has shown positive outcomes (Mocanu and Vieth 2013; Natri et al. 2006; Nikooyeh et al. 2016), consuming bread baked with UV-treated yeast had no impact on participant total 25(OH)D concentrations compared to baseline or compared to control (placebo) bread (Itkonen et al. 2016). As the vitamin D_2 supplement group in the same study observed an increase in endpoint total 25(OH)D concentration (+9.6 nmol/l; +14.7%), even with relatively equivalent dosage to vitamin D_2-enriched bread (24.4 µg D_2/supplement; 26.3 µg D_2/bread portion), it has been proposed this may in part be caused by the baking process or digestibility of the yeast preventing liberation of vitamin D_2. Lastly, response to vitamin D_2-enriched mushrooms varied. All studies observed increasing 25(OH)D_2 concentrations, suggesting enriched mushrooms do not have to overcome the same vitamin D_2 entrapment limitation reported within UV-treated yeast; however only two studies (Nieman et al. 2013; Urbain et al. 2011) were deemed successful in elevating total 25(OH)D concentrations post-consumption of biofortified mushrooms compared to control. In all studies, little to no difference was observed in circulating parathyroid hormone (PTH) or calcium concentrations in any of the bio-enriched food intervention groups over time.

Taken together, these findings indicate that biofortification, particularly vitamin D_3-enrichment in animal-based foods, may be a viable concept to offer consumer protection against the expected decline in vitamin D status to nadir during winter. The complexity of vitamin D human intervention studies, however, must be acknowledged, both in terms of study design, and in drawing comparisons between trials. Such research is often conducted during the winter months to avoid confounding by sun exposure, and thus a significant seasonal decline in the control group is often observed which is at variance to that typically expected in a micronutrient trial. Interpretation therefore can be complicated by differing hypotheses, in particular whether the desired outcome is to maintain or increase 25(OH)D concentrations within the intervention groups. Moreover, many other reasons may exist for the observed heterogeneity of results in the present review however, arguably, the main factors include efficacy differences between vitamin D_2 and D_3, as well as different vitamin D responses between parental vitamin D_3 and its metabolite, 25(OH)D_3, the effect of participants baseline status and the impact of the food matrix in which vitamin D is encompassed.

Relative effectiveness of parent forms, vitamin D_2 and D_3

Both vitamin D parental forms, vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol) have been enriched in biofortification studies for mushroom/bread and animal-based foods, respectively. Within the present review, eight RCTs included at least one vitamin D_2 study arm (Itkonen et al. 2016; Keegan et al. 2013; Mehrotra et al. 2014; Nieman et al. 2013; Shanely et al. 2014; Stephensen et al. 2012; Stepien et al. 2013; Urbain et al. 2011) and six studies included vitamin D_3 (Graff et al. 2016; Hayes et al. 2016; Itkonen et al. 2016; Keegan et al. 2013; Mehrotra et al. 2014; Stepien et al. 2013), albeit only two studies increased vitamin D_3 by biofortification (Graff et al. 2016; Hayes et al. 2016) whilst the remaining included supplemental vitamin D_3 as a comparison to a biofortified product. Participants serum responses differ depending on the specific vitamer which was either enhanced in the food item or provided in supplement form as seen in Table 2. Prohormones vitamin D_2 and D_3 differ only by side chain structure, with the former containing an extra double bond. Much research has questioned if both are equipotent and interchangeable, however accumulating evidence suggests otherwise (Armas, Hollis, and Heaney 2004; Binkley et al. 2011; Glendenning et al. 2009; Heaney et al. 2011; Jakobsen et al. 2017; Leventis and Kiely 2009; Logan et al. 2013; Melhem, Aiedeh, and Hadidi 2015; Oliveri et al. 2015; Wetmore et al. 2016) and has been reviewed elsewhere (Tripkovic et al. 2012; Wilson et al. 2017). From the current review, where comparative vitamin D_2 vs. D_3 intervention groups exist, mainly within a supplement matrix, vitamin D_3 has always resulted in higher total serum 25(OH)D concentrations at endpoint ($n = 4$ studies) (Itkonen et al. 2016; Keegan et al. 2013; Mehrotra et al. 2014; Stepien et al. 2013).

Specifically, it has been postulated that a competitive situation may exist between the two metabolites. Vitamin D_2 is reported to escalate at the apparent expense of vitamin D_3, meaning as dietary vitamin D_2 intake and serum 25(OH)D_2 increases, a concomitant decrease is observed in vitamin D_3 and its vitamers, thus affecting the overall total vitamin D pool (Hammami et al. 2019; Martineau et al. 2019). The suggested mechanisms have been presented elsewhere (Armas, Hollis, and Heaney 2004; Hammami et al. 2019; Houghton and Vieth 2006; Jones et al. 2014; Shieh et al. 2016). This may, in part, offer an explanation for the lack of change or lower total 25(OH)D concentrations post-intervention compared to baseline in a number of the biofortification studies, which have been enriched with vitamin D_2

(Mehrotra et al. 2014; Nieman et al. 2013; Stephensen et al. 2012; Stepien et al. 2013).

In general, participants assigned to vitamin D_2-enriched groups observed significant increases in circulating 25(OH)D_2 compared to baseline (range +45.0 to +5.0 nmol/l) but either a decrease (range −16.5 to −20.6 nmol/l) or no significant change was observed in circulating 25(OH)D_3 (Itkonen et al. 2016; Keegan et al. 2013; Mehrotra et al. 2014; Nieman et al. 2013; Shanely et al. 2014; Stephensen et al. 2012; Stepien et al. 2013). The impact of vitamin D_2 biofortified foods, however, on total 25(OH)D concentration compared to baseline varies. There was either no change or a decrease in circulating total 25(OH)D concentrations in five studies (Itkonen et al. 2016; Mehrotra et al. 2014; Nieman et al. 2013; Stephensen et al. 2012; Stepien et al. 2013), whilst three mushroom studies observed a significant increase in 25(OH)D concentrations compared to baseline (Keegan et al. 2013; Shanely et al. 2014; Urbain et al. 2011). Vitamin D biofortified bread baked with UV-treated yeast was not effective in elevating vitamin D status in human participants (Itkonen et al. 2016). Whilst serum 25(OH)D_2 observed a mean change of +6.4 nmol/l, total 25(OH)D and 25(OH)D_3 concentrations remained unchanged amongst the vitamin D_2-enriched bread group. These findings, therefore, potentially confirm the assertion from previous studies that vitamin D_2 is less potent (Heaney et al. 2011; Wilson et al. 2017), with an inverse relationship existing between vitamin D_2 and D_3 (Cashman et al. 2016b). Human studies investigating biofortified animal products (eggs and fish) and thus, enrich with vitamin D_3 rather than vitamin D_2, only reported on total 25(OH)D. As such, comments regarding the specific impact of its consumption on 25(OH)D_3 and 25(OH)D_2 are limited. However, based on supplemental data, a similar inverse relationship would be assumed.

Despite extensive research investigating supplemental vitamin D_2 vs D_3 (for reviews, see Bouillon, Verlinden, and Verstuyf 2016; Tripkovic et al. 2012; Wilson et al. 2017), research directly comparing the effect of vitamin D_2 and D_3 from biofortified foods on 25(OH)D concentrations is lacking. Unlike supplementation trials, however, where the form of vitamin D can be controlled, the selected biofortification food vehicle will naturally determine whether vitamin D_2 or D_3 is predominantly increased. As such, differing food matrices will limit direct comparisons between vitamin D_2 and D_3 from biofortified sources.

Whilst some uncertainty remains as to the impact of dosing-schedule, sex, age, ethnicity and genetic variation (Hammami and Yusuf 2017; Nimitphong et al. 2013) on vitamin D_2 and D_3 potency, the consensus to date, predominantly from supplemental studies may provide validation to vitamin D_3 being the more common vitamer when fortifying or biofortifying food. Nonetheless, the value of vitamin D_2 biofortified products should not be overlooked, especially amongst those who follow a vegan or vegetarian diet as well as consumers with cultural considerations who rely on plant sources or consciously limit their intake of animal products and/or sun exposure, and to whom the vitamin D_3 metabolite will most likely be lacking.

Relative effectiveness of parent form, vitamin D_3 and its metabolite, 25(OH)D_3

When supplementing animal feed for biofortification, either parental vitamin D or its hydroxylated form (25(OH)D) may be selected to increase the vitamin D content within the end food product. This demands careful consideration when implementing biofortification practices, as evidence suggests that these vitamers affect vitamin D status differently. Within the present review, only one study compared vitamin D_3 and 25(OH)D_3 biofortification. In Hayes et al. (2016), both vitamin D enhanced eggs resulted in higher post-intervention participant serum 25(OH)D concentrations compared to control, with a similar response noted between groups (vitamin D_3 eggs vs 25(OH)D_3 eggs). Nevertheless, regarding acute pharmacokinetics, 25(OH)D_3 would be expected to reach its peak significantly earlier, around 11 hours compared to 22 hours for equivalent vitamin D_3, depending on the dosage (Guo et al. 2017; Jetter et al. 2014). This may be owed to polar 25(OH)D_3 having higher solubility than parental vitamin D_3 (Cesareo et al. 2019; Cianferotti et al. 2015). Consumption of 25(OH)D_3 negates the hepatic metabolism of vitamin D_3 within the liver, and thus may be advantageous for those with impaired liver function (Guo, Lovegrove, and Givens 2019; Sosa Henríquez and Gómez de Tejada Romero 2020). Furthermore, 25(OH)D is less dependent on bile acids and micelle formation for absorption (Maislos, Silver, and Fainaru 1981; Maislos and Shany 1987). This accumulated evidence has stimulated debate on the exact potency of 25(OH)D in comparison to vitamin D, with ranges from 1 to 9 proposed, depending on dermal synthesis, host-related characteristics such as baseline status or genotype, dose, intervention duration and study design (for reviews, see Cashman et al. 2017; Guo, Lovegrove, and Givens 2018; Jakobsen, Melse-Boonstra, et al. 2019; Quesada-Gomez and Bouillon 2018). As no international consensus exists, national food composition tables vary in the factor used to quantify total vitamin D activity [vitamin D_3 + (25-OH-D_3 × n)]. Some food databases, including the United Kingdom, Denmark and Switzerland apply a factor of five, whilst others use a factor of one or do not account for concentration of 25(OH)D, such as the Netherlands, Canada and the United States (Federal Department of Home Affairs 2019; Health Canada 2015; National Food Institute 2019; NEVO online version 6.0 2019; Public Health England 2019; U.S. Department of Agriculture (USDA), Agricultural Research Service 2019).

Commercial perspective of vitamin D biofortification

From an industry perspective, there may be additional concerns when deciding whether to enrich with vitamin D or 25(OH)D as The European Food Safety Authority (EFSA) currently only recognizes and regulates the presence of vitamin D_3 and D_2 (cholecalciferol and ergocalciferol, respectively) within a product when establishing a health claim (EFSA Panel on Dietetic Products and Nutrition and Allergies (NDA) 2010), and not total vitamin D activity (including 25(OH)D content within the product). Further

well-designed long-term RCTs are required to cement this concept and generate legislative change. Albeit convincing data exists to suggest intake of 25(OH)D is of greater advantage owing to a more rapid increase in vitamin D status (Bischoff-Ferrari et al. 2012), increased potency (Barger-Lux et al. 1998; Cashman et al. 2012; Jetter et al. 2014; Navarro-Valverde et al. 2016; Shieh et al. 2017; Vaes et al. 2018), higher intestinal absorption efficacy (Davies, Mawer, and Krawitt 1980; Sitrin and Bengoa 1987) and less fluctuations in serum 25(OH)D compared to vitamin D_3 after intermittent intake (Quesada-Gomez and Bouillon 2018; Russo et al. 2011). Considering animal-based products, EFSA has approved and informed the quantity of vitamin D and 25(OH)D permitted in feed of all animal species, of which Hayes et al. (2016) adhered to and thus reflected commercial application (European Food Safety Authority 2009; European Food Safety Authority 2017). From a business perspective, selecting to supplement animal feed with vitamin D_3 could result in an end-product meeting the quantitative requirement for a front-of-pack vitamin D health claim. This marketing may increase the likelihood of a consumer purchasing a biofortified product, compared to a similar 25(OH)D_3 enriched food without such advertising, and thus regulations may also dictate the vitamer most suitable for biofortification.

Impact of baseline status on serum response

When investigating the efficacy of vitamin D biofortified foods, a participant's baseline status may elucidate varying levels of intervention response (for reviews, see Jakobsen, Melse-Boonstra, et al. 2019; Mazahery and von Hurst 2015; Quesada-Gomez and Bouillon 2018). Although some research suggests the baseline status has little to no effect, recent large-scale randomized control trials have confirmed different serum 25(OH)D responses between deficient and sufficient participants, cementing the general consensus that those with lower baseline vitamin D status would be expected to observe a greater effect on health outcomes than individual's with higher baseline status (Borel, Caillaud, and Cano 2015; Manson et al. 2019; Pittas et al. 2019; Scragg 2019). Participants consuming enriched bread baked with UV-treated yeast had relatively high mean baseline vitamin D concentrations (64.6 ± 15.1 nmol/l) which reflects the status of the Finnish population but may underrepresent the effectiveness of UV-treated yeast (Itkonen et al. 2016). As the study was carried out in Finland, where the majority of liquid milk products (1 µg vitamin D/100g) and fat spreads (20 µg vitamin D/100g) are fortified based on voluntary recommendations (National Nutrition Council 2010), this will naturally have repercussions on the vitamin D status of the selected study population. Interestingly, participants assigned enriched salmon also had high total 25(OH)D baselines status (median (IQR); 75.4 (30.5) nmol/l) yet significant changes in serum 25(OH)D were still observed (Graff et al. 2016). This elevated status will likely be owed to the popularity of cod liver oil supplements in Norway (Brustad, Braaten, and Lund 2004; Brustad et al. 2003), alongside modest voluntary fortification of some types of low-fat milk (0.4 µg vitamin D/100g), margarine and butter (10 µg vitamin D/100g) (Itkonen et al. 2020), resulting in higher vitamin D concentrations compared to other European regions (Hilger et al. 2014). From mushroom studies, when baseline status was higher, increases in vitamin D_2 also observed similar decreases in vitamin D_3, whereas when baseline concentrations were lower, vitamin D_2 increases were accompanied with more modest reductions in vitamin D_3 and resulted in significant response on serum 25(OH)D (Cashman et al. 2016b). As noted previously, the complexity in directly comparing vitamin D RCTs with different hypotheses is also relevant here. Modest or no increase in participant vitamin D concentrations may not necessarily reflect an unviable biofortification vehicle, rather that the participant's baseline status may be at such a level, a significant change is not observed. In light of this, widespread vitamin D biofortification of staple foods may be of particular benefit to populations with sub-optimal status who would observe a greater response comparatively to those with sufficient vitamin D status prior to the inclusion of biofortified products within their diet.

Bioaccessibility and bioavailability of vitamin D from food matrix

Understanding the bioaccessibility and bioavailability of nutrients is paramount to recognizing its availability for physiological activity. Often these terms are wrongly used interchangeably. Bioaccessibility refers to the release of bioactive compounds from its encapsulating matrix in the gastrointestinal tract allowing for absorption, whilst bioavailability determines the rate of absorption efficiency and availability of metabolic utilization for physiological functions or storage (Benito and Miller 1998; Fairweather-Tait 1993; Fernández-García, Carvajal-Lérida, and Pérez-Gálvez 2009; Godber 1990; Hedrén, Mulokozi, and Svanberg 2002; Jackson 1997; Saura-Calixto, Serrano, and Goñi 2007). Thus, considering the food vehicle is an important factor when assessing the effectiveness of biofortified foods.

Biofortification studies vary in how vitamin D enriched sources are provided to participants, either as a mushroom extract within a capsule (Keegan et al. 2013; Shanely et al. 2014), within a meal as was the case for five mushroom studies (Mehrotra et al. 2014; Nieman et al. 2013; Stephensen et al. 2012; Stepien et al. 2013; Urbain et al. 2011), or left to the discretion of the participant to decide how to consume as part of the habitual diet as instructed for studies investigating biofortified fish, eggs and bread baked with UV-treated yeast (Graff et al. 2016; Hayes et al. 2016; Itkonen et al. 2016).

Vitamin D-enriched yeast has also been used in animal and in vitro studies, but with equivocal results (Hohman et al. 2011; Itkonen et al. 2016; Itkonen, Pajula, et al. 2018; Lipkie, Ferruzzi, and Weaver 2016). In vitro research shows 6-7% vitamin D bioaccessibility of yeast-fortified breads, with no difference between whole wheat and white wheat bread (Lipkie, Ferruzzi, and Weaver 2016). This contrasts

starkly with 71-85% vitamin D bioaccessibility from bovine milks and infant formula. In vitro and rat in vivo digestion suggests yeast vitamin D_2 fortified bread has ~4x and ~2x lower bioaccessibility than bread fortified with crystalline vitamin D_2, respectively (Hohman et al. 2011; Lipkie, Ferruzzi, and Weaver 2016). Such evidence suggests that vitamin D_2 is not fully released as simulation of oral, gastric and small intestine digestions resulted in unchanged yeast cells (Lipkie, Ferruzzi, and Weaver 2016). The same research group postulated that harsher lyophilization, autolysis or purification may enhance digestive release of vitamin D_2 from yeast.

Both studies providing capsules of UV-exposed mushrooms observed significant increases in vitamin D status (Keegan et al. 2013; Shanely et al. 2014). It could be hypothesized that the single, dried food component was advantageous to meal settings as it negated the more complex digestion and release required from food matrices. The array of additional nutritional components in food meal settings, together with the multiplicity of interactions, warrants bioaccessibility implications, as unlike supplemental isolated vitamin D forms, it must be released from the incorporated food matrix in the human gastrointestinal tract (Aguilera 2019). Being a fat-soluble vitamin, dietary fat content may be of particular interest to vitamin D and the food matrix context. Some evidence to date suggests that neither the amount of fat consumed alongside vitamin D, nor the food matrix, have any impact on the bioavailability of fortified food and supplemental forms of vitamin D and are extraneous to total vitamin D activity (for reviews, see Borel, Caillaud, and Cano 2015; Jakobsen, Melse-Boonstra, et al. 2019). However, in healthy older adults, ingesting a vitamin D_3 supplement alongside a low-fat meal resulted in increased absorption compared to a high-fat meal or no meal (Dawson-Hughes et al. 2013). In addition, a prospective cohort study observed improved absorption when a vitamin D supplement was consumed with the largest meal of the day (Mulligan and Licata 2010). Fatty acids, vitamins A, E and K, and dietary fibers may require specific consideration as they have previously demonstrated an affect on vitamin D absorption efficiency (Maurya and Aggarwal 2017), however it is doubtful these would have influenced the current biofortification studies. The heterogeneity of vitamin D biofortification vehicles proves difficult to confirm the exact influence of the matrix on bioaccessibilty and bioavailability, and is an area which demands future research to confirm the optimal food group. If pursuing biofortification, industries must be conscious of not simply the nutrient of interest but the use of a matrix which ensures physiological relevance to the consumer.

In essence, with the exception of mushrooms, research regarding the efficacy of biofortified foods to increase serum 25(OH)D concentrations in humans is in its infancy but some encouraging results have been observed (see Table 2). Additional RCTs in other foods/food groups are required to add to the body of evidence in support of vitamin D biofortification efficacy and allow a greater understanding of the long-term implications for both healthy and disease-state populations.

Meat as biofortification vehicle

Enriching food vehicles via biofortification, namely eggs, fish and mushrooms, with vitamin D can result in a positive response on participant status. Poultry and red meat, naturally a source of protein, B-vitamins, zinc and iron (Marangoni et al. 2015; Williams 2007), could be another plausible vehicle for vitamin D biofortification. It is evident that UV exposure and feed supplementation can improve the vitamin D content in animals, however it is critical to understand its implication on human participants 25(OH)D concentrations. We conducted a systematic review which identified four human intervention trials investigating enriched meat via feed alterations. All of the eligible studies increased PUFA concentrations in meat (see Supplementary Table 1). To the best of the authors' knowledge, no studies have investigated the impact of biofortified meat on human participant vitamin D status, however evidence exists on the efficacy of this food vehicle choice from PUFA models.

Encouragingly, the majority of meat biofortification studies showed that the increased presence of PUFA within the meat matrix effectively improved fatty acid status in human participants (Coates et al. 2008; Haug et al. 2012; McAfee et al. 2011), with the exception of one study which only reported a decrease in total cholesterol and no concurrent change in circulating fatty acids (Sandström et al. 2000). Direct comparison proves limited owing to different fatty acid sources targeted across the studies and substantial variation in the quantified markers (see Supplementary Table 2). Overall, consuming enriched meat increased participants' fatty acid profiles, albeit the specific fatty acids which did so differed across studies.

Biofortification aligns with the need to optimize the nutritional quality of meat products, especially within the broader context of health and environmental advice to limit red and processed meat consumption (Godfray et al. 2010; Scientific Advisory Committee on Nutrition (SACN) 2010; Springmann et al. 2018; Willett et al. 2019).

Impact of meat product on human participant response

The form of meat offered to participants may have impacted upon their fatty acid response. Higher PUFA concentration was apparent in homogenous products, such as mince and sausage meat than that in unprocessed cuts of meat (182 ± 29 vs. 89 ± 5 mg/100 g), most probably owing to the inclusion of multiple meat cuts from a larger range of animals processed with added higher fat (Haug et al. 2012; McAfee et al. 2011; Sioutis et al. 2008). This suggests that food processing impacts upon PUFA concentrations in meat offered to participants. In addition, inter- and intra-variation may be prevalent amongst meat, depending on the quantity of supplemented feed consumed by the respective animal. Naturally this would then impact the nutritional content of meat which could have repercussions on human status if the

enriched meat product offered to participants does not include a combination of animal samples. Furthermore, these findings may hint toward a substantial limitation in human feeding studies, whereby processed products offer an arguably more homogenized study design, yet may not be reflective of normal, or indeed, recommended consumption patterns. One example meal plan provided participants with three sausage-based eating occasions per day (Sandström et al. 2000) and another successfully increased PUFA concentrations but required participants to consume supra-physiological quantities (1000 g pork/week) (Coates et al. 2008), neither of which are reflective of typical 'real-life' intakes and would contradict current health advice in its translational application. Both studies, however, do highlight proof of concept, given the popularity of pork consumption globally (OECD 2020) and stimulate thought that biofortification could enhance *n*-3 concentration, or other nutrients, albeit within smaller portion sizes. Considering long-term public health implications, small changes across multiple products may be more realistic.

Vitamin D biofortification in meat

Increasing the vitamin D biofortification portfolio has been suggested by many as a viable way to address poor status globally (Cashman 2020b; Guo, Lovegrove, and Givens 2019; Guo et al. 2017; Hayes and Cashman 2017; Saternus, Vogt, and Reichrath 2019). The positive results from *n*-3 PUFA-enriched meat arguably justifies the plausibility of vitamin D biofortification of meat as a vehicle to safely elevate 25(OH)D status in participants. Although, a paucity of data exists on the effect of consuming vitamin D-enriched meat, on-farm evidence has clearly demonstrated that supplementing feed and/or exposing animals to UV light significantly increases vitamin D concentrations in meat (see Table 1). For example, Duffy et al. (2017a) observed a 145% increase in total vitamin D activity in the *Longissimus thoracis* of beef heifers offered the EU limit of enriched vitamin D_3 feed (4000 IU/kg) compared to those receiving no vitamin D_3. In another example, considering UV exposure, an 18-fold difference was observed in lean meat vitamin D_3 concentration between control pork and the highest UV-exposed pork meat (0.2 ± 0.03 vs 3.7 ± 1.0 ng/g) (Barnkob et al. 2019). While meat naturally contains both vitamin D_3 and 25(OH)D_3, the quantities of each and the vitamin D_3:25(OH)D_3 ratio likely vary by species as well as by part of animal (e.g. muscle and offal) and season (Cashman et al. 2020). Consequently, such inherent variability coupled with downstream effects of food processing, have implications for the success of any biofortification strategy. Offsetting this, biofortification merits greater consumer acceptability as it could be perceived as a more natural option (Kotta et al. 2015). Animals for example, naturally synthesize vitamin D endogenously and are capable of self-regulation owing to the negative feedback system involving PTH secretion and 1,25-dihydroxyvitamin D (1,25$(OH)_2$D) (Bikle 2009; Nussey and Whitehead 2001). Consequently, reducing the risk of vitamin D toxicity within the animal and ensuring a maximum plateau concentration, thus limiting the risk of consumers over-dosing from a portion of biofortified meat, which may be a cause of concern when using vitamin D supplements (Galior, Grebe, and Singh 2018).

Owing to the popularity of meat in many Western countries, particularly in the UK (108 ± 68 g/day) (Cocking et al. 2020; Public Health England 2018), a beneficial and realistic dose could theoretically be ingested. Nevertheless, it is important to acknowledge the recent shift toward lower meat intakes owing to environmental and public health concerns. If the trend toward lower consumption rates continues, it may appear questionable to use meat as a vitamin D biofortification vehicle. However, whilst striving to reduce potentially detrimental effects of excessive meat consumption, it is important that the health-benefiting nutritional composition of meat are still preserved; thus, ensuring vitamin D levels can be maintained even with fewer eating occasions or smaller portions of meat. Furthermore, those with lower incomes are less likely to access sustainable healthy diets (Drewnowski et al. 2020), consume red and processed meats more often (Clonan, Roberts, and Holdsworth 2016) and are at greater risk of low vitamin D status (Lin et al. 2021). A range of vitamin D biofortified meat products may therefore provide a more meaningful contribution to lower socioeconomic status consumers. Whilst vitamin D biofortification alone will not solve the vitamin D crisis, it may offer an additional, feasible, potentially cost-effective strategy to contribute toward its eradication in certain subgroups.

Determining the long-term efficacy of including realistic portion sizes of vitamin D biofortified meat in diets to reduce rates of hypovitaminosis D and maintain optimal 25(OH)D concentrations year-long, will necessitate validation by high-quality RCTs. Moreover, dietary modeling facilitates the opportunity to explore at a population level, the impact on vitamin D status if such bio-enriched meats were widely available and consumed.

Future research

Evidence regarding the effectiveness of consuming biofortified products is clearly lacking, and challenges exist in replicating habitual consumption patterns or imitating expected home preparations in a robust scientific study design. However, biofortification warrants undeniable potential to complement public health policies to improve population nutritional status. Additional factors requiring attention to ensure the successful implementation of biofortification include assessing consumer acceptability, shelf-life, stability of vitamin D-enriched food over time and manufacturing costs (Buttriss and Lanham-New 2020). Demonstration of bioaccessibility and status impact from vitamin D biofortified meat via feed supplementation and/or UV exposure awaits conclusive outcomes from RCTs. Moreover, further research should also consider the role of free 25(OH)D as an additional marker of vitamin D bioactivity (Shieh et al. 2016). In vitro research may be considered to screen potential vitamin D meat biofortification approaches prior to

human interventions. As discussed, future research demands careful consideration toward the selected form of vitamin D, participants baseline status and the food matrix to allow robust application of beneficiary outcomes.

Conclusion

Biofortification can be a simple, noninvasive, convenient way in which to increase nutritional intake amongst participants and may offer preventative health benefits in the longer-term. Vitamin D_3-enriched animal products, specifically eggs and fish, are effective in elevating or maintaining wintertime human vitamin D status, compared to enriched-mushrooms and bread baked with UV-treated yeast which produced heterogenous outcomes. Biofortified meat is an unexploited area in human research which, based on results from vitamin D on-farm work and PUFA-enriched meat RCTs, may offer an exciting opportunity. Nevertheless, the greatest benefit from consuming either vitamin D_3 or D_2 biofortified foods will be observed amongst those with lower baseline status. In combination with traditional fortification processing, biofortification and supplement usage may help to reduce the prevalence of vitamin D deficiency.

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