Title: Adherence to the infant vitamin D supplementation policy in Ireland

Author names: Hemmingway A[1,2], Fisher D[1], Berkery T[1], Murray DM[1,3], Kiely ME[1,2]

Affiliations and Addresses: [1]INFANT Research Centre, University College Cork, Ireland.

[2]Cork Centre for Vitamin D and Nutrition Research, School of Food and Nutritional Sciences, University College Cork, Cork, Ireland.

[3]Department of Paediatrics and Child Health, University College Cork, Cork, Ireland.

Corresponding author: Professor Mairead Kiely, m.kiely@ucc.ie, +353 214903394

Acknowledgments: The authors wish to gratefully acknowledge the families of the COMBINE and BASELINE birth cohort studies for their participation.

Abstract

Purpose

From September 2010 until November 2019, Ireland's infant vitamin D supplementation policy recommended administration of 5µg/day of vitamin D_3 from birth to 12 months to all infants, regardless of feeding method. This study aims to examine policy adherence.

Methods

In the prospective COMBINE birth cohort study (recruited 2015-2017), detailed longitudinal supplement data were examined in 364 infants across the first year of life, according to product type, dose, frequency and duration. Vitamin D supplement use at 2, 6 and 12 months in COMBINE was compared with the BASELINE cohort (recruited 2008-2011, *n*=1949).

Results

In COMBINE, 92% of infants initiated supplementation at birth. The median supplementation duration was 51 (40, 52) weeks, with a range of 3-52 weeks. While supplementing, most parents (92%) used an exclusive vitamin D supplement as recommended and 88% gave 5µg/day. Half (51%) gave vitamin D daily and a further 33% supplemented at least 3-6 times/week. Overall, 30% adhered fully to the policy, providing 5µg vitamin D_3 daily from birth to 12 months. A further 16% were broadly compliant, giving 5µg frequently for the full 12 months. Vitamin D supplement use at 2, 6 and 12 months in COMBINE was 93%, 89% and 72%, considerably higher than our earlier BASELINE cohort at 49%, 64% and 44% at the same time points (all $P<0.001$).

Conclusions

We report a high level of vitamin D supplementation initiation at birth, with full to broad policy adherence among more than half of infants. There is scope to improve overall compliance by focusing on supplementation frequency.

Key words: vitamin D, supplementation, policy, adherence, infancy, birth cohort

Introduction

Pregnancy and early life are periods of particular vulnerability to vitamin D deficiency [1]. Many authors around the world have reported low vitamin D status (indicated by serum 25-hydroxyvitamin D [25(OH)D] concentrations) among women during pregnancy [2,3]. A high prevalence of low 25 (OH)D (<25 – 50 nmol/L) has been reported in pregnant women in countries such as Scotland [4], the Netherlands [5] and Sweden [6], which are at relatively high northerly latitudes. For example, in Scotland, at 57ºN, 22% of a cohort of pregnant women had a 25(OH)D below 25 nmol/L [4]. Around the world, particularly among people with darker pigmented skin tones, nutritional rickets has re-emerged as a public health problem [7].

Ireland is a useful exemplar of a country at high latitude (53ºN) with no national antenatal vitamin D supplementation policy. In a large prospective cohort of women in Cork (51ºN) using gold-standard 25(OH)D analysis, we reported that 44% of women had a circulating 25(OH)D concentration < 50 nmol/L, 17% had a 25(OH)D < 30 nmol/L and 11% were below 25 nmol/L [8]. Given that fetal vitamin D status is determined by maternal circulating 25(OH)D, this is of great concern [1]. The Cork data showed that 46% of infants born to the mothers in the prospective cohort had umbilical cord 25(OH)D < 30 nmol/L and 35% had 25(OH)D < 25 nmol/L [9], similar to estimates from Saraf et al. [3].

Because 25(OH)D has a short half-life [10] and sun exposure is not recommended for infants [11], vitamin D intake is crucial in early life for maintenance of adequate vitamin D status [12]. The IOM and EFSA have both set an adequate intake of 10 µg/day in the first year of life [10,13], while the Scientific Advisory Committee on Nutrition in the UK set a safe intake of 8.5-10 µg/day [14]. Exclusive breastfeeding is recommended for the first 6 months of life, with continuation thereafter [15]. However, breastmilk has been reported to be a poor source of vitamin D [16,17].

Many countries have implemented infant vitamin D supplementation policies. Such policies are safe and can be effective in improving vitamin D status and reducing incidence of nutritional rickets [18]. However, their effectiveness is dependent on adherence, which can be poor for reasons such as inaccessibility and lack of awareness among healthcare professionals and/or parents [19], and substantial differences in supplementation rates have been reported across Europe [20]. In 2007, in response to several cases of nutritional rickets in Dublin, mainly among the increasing immigrant population, the Food Safety Authority of Ireland published an infant vitamin D supplementation policy, recommending that ‘all infants, from birth to 12 months, whether breastfed or formula fed, be given a daily supplement of 5 µg (200 IU) vitamin D. This should be provided by a supplement containing vitamin D exclusively’ [21]. The policy, including a clear implementation plan, was implemented by the Health Services Executive in 2010, following stakeholder involvement from health promotion, medical, midwifery, dietetic and pharmacy experts and remained unchanged until November 2019 [22].

Following implementation of the vitamin D supplementation policy, specifically designed supplement products became widely available in pharmacies and supermarkets for purchase without prescription. Continuous monitoring of policy uptake [20], as well as detailed investigation of supplementation practices are necessary to ensure maximum public health benefit without risk of excessive vitamin D intakes. To date, adherence to this policy has not been monitored.

Here, using data from the prospective COMBINE birth cohort study, we report adherence with the infant vitamin D policy recommendations. Our secondary aim was to examine trends in the use of supplemental vitamin D in infants over time, using our mature BASELINE birth cohort study.

Methods

Study Design

The COMBINE (Cork Nutrition and Development Maternal-Infant) study, based in Cork, Ireland, is a longitudinal, prospective birth cohort study. Participants of the Improved Pregnancy Outcomes via Early Detection (IMPROvED) study (http://www.clinicaltrials.gov; trial ID: NCT01891240) formed the recruitment pool for the COMBINE cohort [23]. Recruitment for COMBINE commenced in late 2015 and finished in late 2017; 456 IMPROvED participants were recruited to postnatal follow-up in COMBINE, which included 7 research midwife-led study visits in the first 12 months of life, at hospital discharge/day 2, 1 month, 2, 4, 6, 9 and 12 months.

Data collection

Specific information on infant nutritional supplementation practices were collected longitudinally using interviewer-led questionnaires at each study visit, and included supplement type, brand name, frequency of use and dose. Where applicable, the age supplementation started and/or stopped was collected to the nearest week, and any changes in supplementation practices were carefully recorded. Participants were excluded from this analysis if they had dropped-out of the study before 12 months, as their vitamin D supplementation data could not be verified past the point of drop-out, or had missed a study visit with subsequent unverifiable supplementation data; complete 12-month data were available for 364 COMBINE participants.

Supplementation policy adherence

Implemented in 2010, the Irish vitamin D supplementation policy stipulated that all infants should be supplemented with 1) an exclusive vitamin D_3 supplement, 2) containing 5 µg vitamin D, 3) daily, 4) from birth to 12 months [22]. Initiation of supplementation at birth was defined as beginning supplementation on week 0 or 1. Full policy adherence was defined as adherence to the product type, supplement dose and frequency recommendations from birth to 12 months. In addition to overall adherence to 12 months, longitudinal adherence to 2 months (≥ 8 weeks), 4 months (≥ 17 weeks), 6

months (≥ 26 weeks) and 9 months (≥ 39 weeks) was also examined to capture trends in policy adherence. For this purpose, full adherence was defined as longitudinal adherence to product type, dose and frequency aspects from birth to each time point. Adherence to type and dose recommendations, where 5 µg vitamin D was given at least often (3-6 times/week) but not always daily, was classed as substantial adherence and indicates broad compliance. Partial adherence refers to giving vitamin D from birth to the time-point of interest, although at least one other factor (type, dose and/or frequency) was not met and not providing vitamin D supplementation for the complete duration of interest (from birth to the particular time-point) was defined as non-adherence.

Time trends in supplement use

The BASELINE (Babies after SCOPE Evaluating the Longitudinal Impact on Neurological and Nutritional Endpoints) birth cohort study recruited participants in Cork, Ireland, in the same setting as the COMBINE cohort, between 2008 and 2011 [24]. In the BASELINE cohort, use of vitamin D-containing supplements was collected in 1949 participants, with data available for 1902 participants at 2 months, 1817 participants at 6 months and 1704 participants at 12 months. The national vitamin D supplementation policy was implemented in May 2010 while the BASELINE study was ongoing; 70.5% attended their 2 month visit after policy implementation, 79.7% did so at 6 months and 89.9% of participants attended their 12 month visit after implementation of the vitamin D supplementation policy.

Statistical Analysis

Statistical analysis was performed using IBM SPSS® version 24.0 (IBM Corp., Armonk, NY, USA) software for Windows™. Normality testing indicated that descriptive data were non-parametric and data are presented as median (IQR), with categorical data presented as percentage (%). Chi-square or Fisher's Exact tests were used, as appropriate, in comparisons of categorical variables between participant groups. Differences in continuous variables were assessed using the Mann-Whitney U test.

Results

Maternal and infant characteristics

Characteristics of COMBINE participants included in this analysis (n = 364) are presented in **Table 1**. Median (IQR) maternal age at delivery was 33 (30, 34) years. There was a high proportion of white (97%) and Irish-born (81%) mothers and 77% had a third level qualification (ordinary bachelor degree or greater). Forty-eight percent were breastfeeding solely at hospital discharge and the respective percentages at 6 and 12 months were 24%, and 16%. Participants included in the analysis were slightly older [33 (30, 35) vs. 30 (25, 33) years], more likely to be in a stable relationship (96 vs. 89%

partner/married) and to have breastfed at hospital discharge (48 vs. 28%) than those not included (all $P < 0.05$), but other maternal and infant characteristics did not differ.

Adherence to the vitamin D supplementation policy in the COMBINE cohort

Product type

Supplements used in the cohort were largely in dropper format, although pump, spray and twist-off capsule products were also used. All supplements, with the exception of one multi-vitamin product, used during the COMBINE study contained vitamin D_3 (cholecalciferol). Most parents (94.2%) provided an exclusive vitamin D supplement. In those who used a multi-vitamin, the median (IQR) age at which this was first provided was 36 (21, 46) weeks. Participants who supplemented with vitamin D in a multi-vitamin preparation were less likely to have always provided a 5 µg dose of vitamin D (5.0% vs. 92.9%, $P < 0.001$). These multi-vitamin products typically contained > 5 µg (68.0%), although 24.0% contained less than 5 µg.

Dose

As per the recommendation, 87.9% used a product containing 5 µg for the duration of supplementation. Few (1.7%, 6 participants) ever gave < 5 µg, while supplements containing > 5 µg vitamin D were used by 9.8%. Mothers who supplemented with > 5 µg were less likely to have been born in Ireland (63% vs. 83%, $P = 0.003$) and were more likely to be breastfeeding at 6 months (39% vs. 23%, $P = 0.034$), suggesting a lower vitamin D intake from formula products.

Supplement doses in products containing more than 5 µg ranged from 7.5 – 25 µg, with 88.9% containing 10 µg or less. These higher dose supplements were commonly English or Eastern European brand products, likely designed to meet supplementation recommendations in the country of origin. Two participants in this study reported exceeding the recommended 5 µg dose with use of products designed in line with the Irish policy. One participant, who had previously used a non-Irish supplement containing 10 µg, reported giving a 10 µg dose and another reported providing 2-3 times the recommended 5 µg/day dose for the first 2 months of life by mistake; attendance at their General Practitioner confirmed no adverse effects of this.

Frequency

While using supplements, 50.6% of COMBINE participants always gave vitamin D daily and a further 33.3% reported supplementing not less than often. Only 3.3% consistently provided vitamin D less than 3 times/week.

Duration

The rate of initiation of vitamin D supplementation at birth was 92.3% and a further 3.3% had started supplementation by week 2. Participants supplemented for a median duration of 51.0 (40.3, 52.0) weeks, although there was a wide range (3.0 – 52.0 weeks).

Overall adherence

Table 2 details adherence with the vitamin D supplementation policy in COMBINE. From birth to 2 months, 64.3% gave 5 µg vitamin D daily, and the rate of full adherence decreased thereafter to 57.9% to 4 months, 52.2% to 6 months and 42.7% to 9 months. The rate of substantial adherence from birth to these follow-up visits was 17.9–22.5%. Approximately one-third (30.3%) of participants adhered fully to the policy, providing an exclusive 5 µg vitamin D supplement daily from birth to 12 months. A further 16.1% gave 5 µg vitamin D not less than often for the full 12 month duration, adhering substantially with the policy.

By 12 months, 15.6% of participants, who provided vitamin D for the full 12 month duration but had used a multi-vitamin preparation, provided a dose other than 5 µg and/or given a supplement < 3 times/week, were classed as partially adhering. Within these participants, 44.4% had given vitamin D less than 3 times/week, 22.2% had not always adhered to the dosage recommendation and 31.5% had not complied with two or more recommendations (type, dose and/or frequency). The rate of longitudinal non-adherence for the complete duration of birth to 2 months was 7.2%; most of these participants (88.0%) initiated supplementation after week 1. One-quarter (25.6%) of parents did not supplement for the complete duration of birth to 9 months, and the median duration of supplementation in these participants was 26.5 (19.3, 33.0) weeks. The rate of longitudinal non-adherence for the complete duration of birth to 12 months was 38.0%; the median supplementation duration in these participants was 33.0 (24.0, 45.0) weeks.

Maternal and infant characteristics and adherence

There were no differences in maternal demographics, including age, white ethnicity, Irish nationality, education or marital status between those who adhered to the policy and those who did not (all $P > 0.05$) (**Table 3**). Policy adherence did not differ depending on infant sex, gestational age or birthweight (all $P > 0.05$). Similarly, the proportion who breastfed was comparable between the two groups ($P > 0.05$).

Changes over time: comparison of COMBINE and BASELINE at 2, 6 and 12 months

As shown in Table 1, mothers in COMBINE (recruited 2015-2017) were slightly older (all $P < 0.001$) than mothers in BASELINE (recruited 2008-2011), but participants in the two cohorts did not differ in ethnicity, nationality, relationship status or education level (all $P > 0.05$). The breastfeeding rate was significantly higher (all $P < 0.05$) in the COMBINE cohort compared to the BASELINE cohort at hospital discharge (47.9 vs 40.9%), 2 months (36.1 vs 27.1%), 6 months (24.4 vs 12.3%) and 12 months (15.5 vs 4.7%).

While 69.4% of parents in the BASELINE cohort gave their infant a vitamin D-containing supplement at some stage during the first year of life, 99.2% did so in COMBINE ($P < 0.001$). As the BASELINE study spanned the policy implementation, it is interesting to note the difference between participant use of a vitamin D-containing supplements pre and post policy implementation (3.9 vs 48.7% at 2 months, 15.2 vs. 64.4% at 6 months and 10.9 vs 43.6% at 12 months, all $P < 0.001$), as shown in **Figure 1**. Compared with BASELINE participants assessed after implementation of the supplementation policy, a higher proportion in COMBINE supplemented with vitamin D at 2 months (93.1 vs. 48.7%), 6 months (88.7 vs. 64.4%) and 12 months (71.6 vs. 43.6%), all $P < 0.001$.

Discussion

This is the first detailed analysis of adherence with the national infant vitamin D supplementation policy in Ireland. These data from the recent COMBINE cohort showed that almost all participants supplemented with vitamin D at some point during the first year of life and there was a high initiation rate of supplementation at birth, indicating widespread awareness of the policy. Adherence with dosing recommendations was also high, suggesting a low risk of excess intakes. Both frequency and duration of vitamin D supplementation had the greatest effects on overall longitudinal adherence to the policy. In comparison to our mature BASELINE cohort, we found substantial increases in supplement use since the policy introduction, suggesting that the infant vitamin D supplementation policy has become well established since its introduction in 2010.

In 2017, Uday and colleagues published an exploration of adherence to vitamin D supplementation programmes in Europe [20]. Of the 29 included countries, only 3 (Denmark, Turkey and Israel) monitored policy adherence nationally. While an adherence rate of ≥ 80% was indicated by 59% of countries, 31% reported moderate adherence (50-79%) and 10% low adherence (< 50%). An adherence rate of 59%, estimated from a regional study, was reported for Ireland, although the source of these data was not provided. Cross-sectional analyses of cohort studies highlight wide variation in supplementation policy adherence, ranging from < 10% in America at multiple time-points during the first year of life [25] to 80% in Canada at 2 months of age [26] and 97% in Denmark at 9 months [27]. Secondary analysis of an infant feeding trial estimated daily (defined as 4-7 times/week) vitamin D supplementation in ~1% of infants in Australia, ≥ 60% in Southern Europe and ≥ 80% in Northern and Central Europe [28]. Given that 93% of infants in COMBINE received supplemental vitamin D at 2 months, 89% at 6 months and 72% at 12 months, our data indicates high rates of supplementation. However, prospective longitudinal data can provide a more in-depth examination of supplementation practices. Accounting for dose, type, frequency and duration of supplementation, reflecting a strict definition of policy adherence, we report a rate of 30%, approximately half that reported by Uday et al [20].

In recommending universal supplementation with a low dose 5 µg/day supplement, compared to the more commonly recommended 10 µg/day, the Food Safety Authority of Ireland determined that this would prevent serum 25(OH)D concentrations < 25 nmol/L in breastfed infants, whilst ensuring that intakes in formula fed infants (the majority of infants in Ireland), would not exceed the tolerable upper intake level (UL) [21]. Adherence to the dose recommendation was high in COMBINE, with almost 90% always providing 5 µg/day while supplementing. Non-adherence to this recommendation generally reflected use of products not designed to meet the Irish vitamin D supplementation policy, typically where parents born outside of Ireland were using supplements available in their native countries or where multi-vitamin products were used. Vitamin D excess in infants has generally been associated with very large single bolus doses and toxicity is rare [29]. In 2018, EFSA increased the UL to 35 µg/day for infants aged 6-12 months [30], reinforcing the safety of low dose supplemental vitamin D for infants. Given the high adherence to the 5 µg dose recommendation, risk of vitamin D over-exposure resulting from a low dose universal vitamin D supplementation policy appears low.

Maternal awareness and knowledge influences uptake of infant vitamin D supplementation [19] and our data indicates that the policy has become well established, with a high level of policy awareness. This may be attributed to a clear implementation plan and strong communication by clinical and midwifery staff. During pregnancy and again after birth, midwifery staff explain the vitamin D supplementation policy to families and they are provided with an information leaflet, with information also available online on the health services website. To increase policy reach to at risk minority groups, the information leaflet has been translated to 9 languages, including French, Arabic, Polish and Chinese. In addition to promoting its initiation, healthcare professionals play an important role in encouraging continuation of vitamin D supplementation [31]. In COMBINE, the largest increases in non-adherence occurred towards the end of the first year of life. The first year of life is unique in the provision of scheduled public health check-ups and immunisation visits. Harnessing this established network for ongoing dissemination could provide a sustainable platform for ensuring continued awareness to the vitamin D supplementation policy, particularly from 6 months onwards. Because monitoring at child health visits has been associated with increased policy adherence [20], national monitoring may be an effective strategy to increase and maintain policy adherence, as well as providing useful data, and should be considered in Ireland and elsewhere. As in other studies [32], our breastfeeding rates did not differ between those who adhered fully to the policy and those who did not. This likely reflects the universality of the supplementation policy, which is an advantage in providing clarity and improving overall uptake.

Understanding which specific aspects of a particular policy represent the main barriers to adherence allows creation of informed supports. In a cross-sectional Canadian analysis, consideration of dose and frequency substantially lowered vitamin D supplementation policy adherence rates [33]. Here, frequency of supplementation represented the main driver of incomplete adherence; one-fifth of

participants never gave vitamin D daily. Frequency of supplementation can affect serum 25(OH)D concentration achieved [34], thus directly influencing policy effectiveness. Highlighting the importance of daily supplementation to the sub-group who substantially adhered to the policy but gave vitamin D frequently, rather than daily, should prove effective in increasing full adherence rates and encouragement to establish a habitual supplementation routine may be especially beneficial [25,35].

While some studies have reported a variety of maternal demographics, including education, age and ethnicity to relate to infant vitamin D supplementation practices [28,33], we and others [26] did not find that adherence differed depending on maternal characteristics. Policy adherence also did not differ depending on feeding method. A universal supplementation policy, independent of feeding mode, has been associated with good policy adherence [20] and may be especially beneficial in countries like Ireland, where changes in feeding patterns across the first year of life are common [36]. However, since November 2019, in response to new EU Directives increasing the minimum allowable vitamin D content of infant formula from 1 to 2 µg/100 kcal [37,38], Ireland now recommends daily supplementation with 5 µg vitamin D only for breastfed infants and those consuming < 300 mL of formula [39]. Careful monitoring of the effects of this change on both policy adherence and infant vitamin D intakes is required, to ensure the risk of vitamin D deficiency and nutritional rickets continues to be effectively minimised. Data from the UK, which recommends 8.5-10 µg/day vitamin D for breastfed infants or those consuming < 500ml/day of infant formula [14,40], indicates very low supplementation rates [20], which may be partly attributable to the complexity of the recommendation. Given this, both the role of healthcare staff in policy promotion and parental awareness, which have previously been identified as essential in Irish studies [32,41], will be of increasing importance.

The strengths of this analysis include detailed longitudinal data collection in COMBINE, which facilitated detailed examination of vitamin D supplementation practices and policy adherence in the cohort. Examination of supplementation according to product type, dose, frequency and duration allowed identification of policy strengths and target areas for further improvement. In addition, the prospective nature of both cohorts, which had a similar demographic profile and were conducted in the same setting, allowed examination of time trends in vitamin D supplementation over a 5-10 year period. Well-educated women were highly-represented in COMBINE and the demographic profile of mothers excluded from analysis differed slightly from those included, which may limit generalisability of findings. However, neither tertiary education levels, nor other characteristics, differed with overall adherence in this analysis. Although frequent closely-spaced study visits and interviewer-led questionnaires minimised the potential for recall bias and misreporting, by nature, this study required self-report, which may introduce some uncertainty to the results. Because circulating 25(OH)D concentrations were not measured in infants in COMBINE, the effect of supplementation on vitamin D status could not be examined. Data on changes in the incidence of nutritional rickets and hypocalcaemic

seizures in Ireland over this period is of interest. As recent data from the British Paediatric Surveillance Unit refer to this period of time (42), future adherence studies will have a benchmark.

To conclude, in this well-educated cohort we report a high level of initiation of vitamin D supplementation at birth, with full to broad policy adherence among more than half of infants. Adherence with supplement dose and type was high during the first year of life, but there is scope to improve overall compliance by focusing on frequency of dosing. Given the current lack of an antenatal vitamin D supplementation policy for pregnant women in Ireland and the widely reported high prevalence of maternal and infant vitamin D deficiency, a simple, universal infant vitamin D supplementation policy should be retained to promote continued uptake.

316 Table 1. Participant characteristics in the COMBINE (recruited 2015-2017) and BASELINE
317 (recruited 2008-2011) birth cohort studies

Characteristic	COMBINE (n = 364)	BASELINE (n = 1949)	P-value
Maternal			
Age at delivery (years)	33.0 (30.0, 34.3)	31.0 (29.0, 34.0)	< 0.001
< 25 years at delivery	4.4	8.5	0.012
> 35 years at delivery	15.2	14.9	0.941
White ethnicity	96.7	98.2	0.097
Born in Ireland	80.8	82.9	0.373
Partner (married/defacto relationship)	96.2	94.0	0.131
Education (≥ 13 years primary and secondary education)	89.0	87.6	0.512
BMI at 15 weeks' gestation (kg/m^2)[a]	25.1 (22.9, 27.9)	24.0 (22.1, 26.9)[1]	< 0.001
Infant			
Sex - female	43.4	48.9	0.059
Gestational age (weeks)	40.3 (39.3, 41.0)	40.3 (39.1, 41.0)	0.091
Birthweight (kg)	3.5 (3.2, 3.8)	3.5 (3.2, 3.8)	0.598
Breastfed[b]			
Hospital discharge	47.9	40.9	0.016
2 months	36.1	27.1	0.001
6 months	24.4	12.3	< 0.001
12 months	15.5	4.7	< 0.001

Data are presented as median (IQR) or percentage (%) as appropriate

[a]n = 1185

[b]Breastfed solely

318

Table 2. Longitudinal adherence (from birth to each time-point) with the Irish vitamin D supplementation policy in the COMBINE birth cohort study.

	2 months	4 months	6 months	9 months	12 months
Full adherence[a]	64.3	57.9	52.2	42.7	30.3
Substantial adherence[b]	20.2	22.5	20.7	17.9	16.1
Partial adherence[c]	8.4	9.8	12.4	13.8	15.6
Non-adherence[d]	7.2	9.8	14.7	25.6	38.0

[a]Adherence to type, dose and frequency

[b]Adherence with type and dose where vitamin D was given at least often (3-6 times/week) but not always daily

[c]Vitamin D given but at least one other factor (type, dose or frequency) was not met

[d]Did not give vitamin D for the complete duration of interest (from birth to each time-point)

323 Table 3. COMBINE cohort characteristics stratified by adherence to the vitamin D supplementation
324 policy

Characteristic	Overall adherence[a]		*P*-value
	Yes (*n* = 105)	No (*n* = 245)	
Age at delivery (years)	33.0 (31.0, 35.0)	33.0 (30.0, 34.0)	0.415
< 25 years at delivery	3.8	4.9	0.785
> 35 years at delivery	19.2	13.9	0.212
White ethnicity	96.2	97.1	0.640
Born in Ireland	82.9	80.8	0.653
Partner (married/defacto relationship)	94.3	96.7	0.371
Education (third level qualification)[b]	78.8	75.6	0.516
Family income (euro)			0.219
< 42,000	18.4	23.4	
43-84,000	50.5	54.0	
≥85,000	31.1	22.6	
Smoked at 2 months post-partum	6.8	7.7	0.780
Infant sex - female	47.1	41.4	0.324
Gestational age (weeks)	40.3 (39.4, 40.7)	40.3 (39.3, 41.0)	0.284
Birthweight (kg)	3.5 (3.2, 3.8)	3.5 (3.2, 3.8)	0.861
Breastfed[c]			
Hospital discharge	45.2	49.4	0.474
2 months	35.0	36.6	0.862
6 months	20.8	26.0	0.312
12 months	15.3	15.7	0.937

Data are presented as median (IQR) or percentage (%) as appropriate

[a]Full adherence to dose, frequency and type aspects from birth to 12 months

[b]Ordinary bachelor degree or greater

[c]Breastfed solely

325

Declarations

Funding

COMBINE is funded through a grant from Science Foundation Ireland (grant number INFANT/B3067), which is co-funded by the European Regional Development Fund (ERDF) under Ireland's European Structural and Investment Funds Programmes 2014-2020. The Cork BASELINE Birth Cohort Study was funded by the National Children's Research Centre Ireland.

Conflicts of interest

The authors have no conflicts of interest to report.

Ethical standards

Ethical approval for the COMBINE cohort was obtained from the UCC Clinical Research Ethics Committee [ECM4(hh)06/01/15 and ECM3(bbb)10/04/18]. Ethical approval for the BASELINE birth cohort study was obtained from the Clinical Research Ethics Committee of the Cork Teaching Hospitals [ECM 5 (9) 01/07/2008]. COMBINE and BASELINE were conducted in accordance with the Declaration of Helsinki guidelines and written informed consent was obtained for all participants prior to study commencement. Both cohorts are registered at http://www.birthcohorts.net/.

Author's contributions

MEK designed the COMBINE cohort study and is Principal Investigator. AH and MEK conceptualized and designed this research. DF conducted COMBINE study visits. DMM provided clinical advice and governance to COMBINE and is Principal Investigator of BASELINE. TB and AH conducted quality control and constructed the database. AH analysed the data and drafted the manuscript. All authors read and approved the final manuscript.

Fig. 1 Use of vitamin D-containing supplements at 2, 6 and 12 months in the BASELINE (recruited 2008-2011) and COMBINE (recruited 2015-2017) birth cohort studies. The vitamin D supplementation policy was implemented in May 2010 while the BASELINE cohort was ongoing. *$P < 0.001$

References

1. Kiely M, Hemmingway A, O'Callaghan KM (2017) Vitamin D in pregnancy: current perspectives and future directions. Ther Adv Musculoskelet Dis 9 (6):145-154. doi:10.1177/1759720X17706453

2. Palacios C, Gonzalez L (2014) Is vitamin D deficiency a major global public health problem? J Steroid Biochem Mol Biol 144 Pt A:138-145. doi:10.1016/j.jsbmb.2013.11.003

3. Saraf R, Morton SM, Camargo CA, Jr., Grant CC (2016) Global summary of maternal and newborn vitamin D status - a systematic review. Matern Child Nutr 12 (4):647-668. doi:10.1111/mcn.12210

4. Haggarty P, Campbell DM, Knox S, Horgan GW, Hoad G, Boulton E, McNeill G, Wallace AM (2013) Vitamin D in pregnancy at high latitude in Scotland. Br J Nutr 109 (5):898-905. doi:10.1017/s0007114512002255

5. Vinkhuyzen AAE, Eyles DW, Burne TH, Blanken LME, Kruithof CJ, Verhulst F, Jaddoe VW, Tiemeier H, McGrath JJ (2016) Prevalence and predictors of vitamin D deficiency based on maternal mid-gestation and neonatal cord bloods: The Generation R Study. J Steroid Biochem Mol Biol 164:161-167. doi:10.1016/j.jsbmb.2015.09.018

6. Bärebring L, Schoenmakers I, Glantz A, Hulthén L, Jagner Å, Ellis J, Bärebring M, Bullarbo M, Augustin H (2016) Vitamin D status during pregnancy in a multi-ethnic population-representative Swedish cohort. Nutrients 8 (10):pii: E655. doi:10.3390/nu8100655

7. Shaw NJ (2016) Prevention and treatment of nutritional rickets. J Steroid Biochem Mol Biol 164 (Supplement C):145-147. doi:https://doi.org/10.1016/j.jsbmb.2015.10.014

8. Kiely ME, Zhang JY, Kinsella M, Khashan AS, Kenny LC (2016) Vitamin D status is associated with uteroplacental dysfunction indicated by pre-eclampsia and small-for-gestational-age birth in a large prospective pregnancy cohort in Ireland with low vitamin D status. Am J Clin Nutr 104 (2):354-361. doi:10.3945/ajcn.116.130419

9. Kiely M, O'Donovan SM, Kenny LC, Hourihane JO, Irvine AD, Murray DM (2017) Vitamin D metabolite concentrations in umbilical cord blood serum and associations with clinical characteristics in a large prospective mother-infant cohort in Ireland. J Steroid Biochem Mol Biol 167:162-168. doi:10.1016/j.jsbmb.2016.12.006

10. Institute of Medicine (2011) Dietary reference intakes for Calcium and Vitamin D. National Academies Press, Washington (DC)

11. Health Service Executive (2018) Child safety in the sun. https://www.hse.ie/eng/health/child/childsafety/csap-sun.html. Accessed 7/12/2018

12. Högler W (2015) Complications of vitamin D deficiency from the foetus to the infant: one cause, one prevention, but who's responsibility? Best Pract Res Clin Endocrinol Metab 29 (3):385-398. doi:https://doi.org/10.1016/j.beem.2015.03.003

13. EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), (2016) Scientific opinion on dietary reference values for vitamin D. EFSA Journal 14 (10):4547, 4145 pp. doi:10.2903/j.efsa.2016.4547

14. Scientific Advisory Committee on Nutrition (2016) Vitamin D and Health. TSO, London

15. World Health Organisation, UNICEF (2003) Global strategy for infant and young child feeding. World Health Organisation, Geneva

16. Food Standards Agency (2015) McCance and Widdowson's The composition of foods (7th summary ed.). Cambridge Royal Society of Chemistry, UK

17. við Streym S, Højskov CS, Møller UK, Heickendorff L, Vestergaard P, Mosekilde L, Rejnmark L (2016) Vitamin D content in human breast milk: a 9-mo follow-up study. Am J Clin Nutr 103 (1):107-114. doi:10.3945/ajcn.115.115105

18. Hatun Ş, Ozkan B, Bereket A (2011) Vitamin D deficiency and prevention: Turkish experience. Acta Paediatr 100 (9):1195-1199. doi:10.1111/j.1651-2227.2011.02383.x

19. Millette M, Sharma A, Weiler H, Sheehy O, Bérard A, Rodd C (2014) Programme to provide Quebec infants with free vitamin D supplements failed to encourage participation or adherence. Acta Paediatr 103 (10):e444-449. doi:10.1111/apa.12727

20. Uday S, Kongjonaj A, Aguiar M, Tulchinsky T, Högler W (2017) Variations in infant and childhood vitamin D supplementation programmes across Europe and factors influencing adherence. Endocr Connect 6 (8):667-675. doi:10.1530/ec-17-0193

21. Food Safety Authority of Ireland (2007) Recommendations for a national policy on vitamin D supplementation for infants in Ireland. FSAI. https://www.fsai.ie/resources_publications.html

22. Health Service Executive (2010) Policy on vitamin D supplementation for infants in Ireland. https://www.hse.ie/eng/health/child/vitamind/vitamin%20d%20policy.pdf

23. Navaratnam K, Alfirevic Z, Baker PN, Gluud C, Grüttner B, Kublickiene K, Zeeman G, Kenny LC (2013) A multi-centre phase IIa clinical study of predictive testing for preeclampsia: improved pregnancy outcomes via early detection (IMPROvED). BMC Pregnancy Childbirth 13:226. doi:10.1186/1471-2393-13-226

24. O'Donovan SM, Murray DM, Hourihane JO, Kenny LC, Irvine AD, Kiely M (2015) Cohort profile: The Cork BASELINE Birth Cohort Study: Babies after SCOPE: Evaluating the Longitudinal Impact on Neurological and Nutritional Endpoints. Int J Epidemiol 44 (3):764-775. doi:10.1093/ije/dyu157

25. Perrine CG, Sharma AJ, Jefferds ME, Serdula MK, Scanlon KS (2010) Adherence to vitamin D recommendations among US infants. Pediatrics 125 (4):627-632. doi:10.1542/peds.2009-2571

26. Crocker B, Green TJ, Barr SI, Beckingham B, Bhagat R, Dabrowska B, Douthwaite R, Evanson C, Friesen R, Hydamaka K, Li W, Simmons K, Tse L (2011) Very high vitamin D supplementation rates among infants aged 2 months in Vancouver and Richmond, British Columbia, Canada. BMC Public Health 11:905. doi:10.1186/1471-2458-11-905

27. Østergård M, Arnberg K, Michaelsen KF, Madsen AL, Krarup H, Trolle E, Mølgaard C (2011) Vitamin D status in infants: relation to nutrition and season. Eur J Clin Nutr 65 (5):657-660. doi:10.1038/ejcn.2010.285

28. Lehtonen E, Ormisson A, Nucci A, Cuthbertson D, Sorkio S, Hyytinen M, Alahuhta K, Berseth C, Salonen M, Taback S, Franciscus M, González-Frutos T, Korhonen TE, Lawson ML, Becker DJ, Krischer JP, Knip M, Virtanen SM (2014) Use of vitamin D supplements during infancy in an international feeding trial. Public Health Nutr 17 (4):810-822. doi:10.1017/s1368980013001122

29. Vogiatzi MG, Jacobson-Dickman E, DeBoer MD (2014) Vitamin D supplementation and risk of toxicity in pediatrics: a review of current literature. J Clin Endocrinol Metab 99 (4):1132-1141. doi:10.1210/jc.2013-3655

30. EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), Turck D, Bresson J-L, Burlingame B, Dean T, Fairweather-Tait S, Heinonen M, Hirsch-Ernst KI, Mangelsdorf I, McArdle HJ, Naska A, Nowicka G, Pentieva K, Sanz Y, Siani A, Sjödin A, Stern M, Tomé D, Van Loveren H, Vinceti M, Willatts P, Fewtrell M, Lamberg-Allardt C, Przyrembel H, Arcella D, Dumas C, Fabiani L, Martino L, Tomcikova D, Neuhäuser-Berthold M (2018) Scientific opinion on the update of the tolerable upper intake level for vitamin D for infants. EFSA Journal 16 (8):5365

31. Taylor JA, Geyer LJ, Feldman KW (2010) Use of supplemental vitamin D among infants breastfed for prolonged periods. Pediatrics 125 (1):105-111. doi:10.1542/peds.2009-1195

32. Doolan A, Cousins J, Sheridan-Pereira M (2012) Vitamin D supplementation in babies. Opinions of mothers. Ir Med J 105 (1):2

33. Gallo S, Jean-Philippe S, Rodd C, Weiler HA (2010) Vitamin D supplementation of Canadian infants: practices of Montreal mothers. Appl Physiol Nutr Metab 35 (3):303-309. doi:10.1139/h10-021

34. Pludowski P, Socha P, Karczmarewicz E, Zagorecka E, Lukaszkiewicz J, Stolarczyk A, Piotrowska-Jastrzebska J, Kryskiewicz E, Lorenc RS, Socha J (2011) Vitamin D supplementation and status in infants: a prospective cohort observational study. J Pediatr Gastroenterol Nutr 53 (1):93-99. doi:10.1097/MPG.0b013e318216920f

35. de Nooijer J, Onnink M, van Assema P (2010) Vitamin D supplementation in young children: associations with Theory of Planned Behaviour variables, descriptive norms, moral norms and habits. Public Health Nutr 13 (8):1279-1285. doi:10.1017/s1368980010000777

36. Hemmingway A, Fisher D, Berkery T, Dempsey E, Murray DM, Kiely ME (2020) A detailed exploration of early infant milk feeding in a prospective birth cohort study in Ireland: combination feeding of breastmilk and infant formula and early breastfeeding cessation. Br J Nutr:1-28. doi:10.1017/S0007114520001324

37. European Commission (2016) Commission Delegated Regulation (EU) 2016/127 of 25 September 2015 supplementing Regulation (EU) No 609/2013 of the European Parliament and of the Council as regards the specific compositional and information requirements for infant formula and follow-on formula and as regards requirements on information relating to infant and young child feeding. Official Journal L (25):1-29

38. European Commission (2019) Commission Delegated Regulation (EU) 2019/828 of 14 March 2019 amending Delegated Regulation (EU) 2016/127 with regard to vitamin D requirements for infant formula and erucic acid requirements for infant formula and follow-on formula Official Journal L (137):12-14

39. Health Service Executive (2020) Vitamin D for babies 0 to 12 months. Accessed 01/04/2020 https://www2.hse.ie/wellbeing/child-health/vitamin-d-for-babies-0-12-months.html

40. Public Health England (2016) PHE publishes new advice on vitamin D. https://www.gov.uk/government/news/phe-publishes-new-advice-on-vitamin-d. Accessed 20/01/2020

41. McSwiney E, Moran P, Garvey A, Quet J, Kelly T, Watson M, Kiely M, Hourihane J (2013) Compliance with the HSE policy on vitamin D supplementation for infants. Ir Med J 106 (3):93

42. Julies P, Lynn RM, Pall K, Leoni M, Calder A, Mughal Z, Shaw N, McDonnell C, McDevitt H, Blair M (2020) Nutritional rickets under 16 years: UK surveillance results. Arch Dis Child 105(6):587-592.