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**University College Cork, Ireland**  
Coláiste na hOllscoile Corcaigh

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

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9

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11 BASELINE birth cohort studies for their participation.

12 **Abstract**

13 *Purpose*

14 From September 2010 until November 2019, Ireland's infant vitamin D supplementation policy  
15 recommended administration of 5µg/day of vitamin D<sub>3</sub> from birth to 12 months to all infants, regardless  
16 of feeding method. This study aims to examine policy adherence.

17 *Methods*

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

22 *Results*

23 In COMBINE, 92% of infants initiated supplementation at birth. The median supplementation duration  
24 was 51 (40, 52) weeks, with a range of 3-52 weeks. **While supplementing**, most parents (92%) used an  
25 exclusive vitamin D supplement as recommended and 88% gave 5µg/day. Half (51%) gave vitamin D  
26 daily and a further 33% supplemented at least 3-6 times/week. Overall, 30% adhered fully to the policy,  
27 providing 5µg vitamin D<sub>3</sub> daily from birth to 12 months. A further 16% were broadly compliant, giving  
28 5µg frequently for the full 12 months. Vitamin D supplement use at 2, 6 and 12 months in COMBINE  
29 was 93%, 89% and 72%, considerably higher than our earlier BASELINE cohort at 49%, 64% and 44%  
30 at the same time points (all *P*<0.001).

31 *Conclusions*

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

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

36

## 37 **Introduction**

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

46 Ireland is a useful exemplar of a country at high latitude (53°N) with no national antenatal vitamin D  
47 supplementation policy. In a large prospective cohort of women in Cork (51°N) using gold-standard  
48 25(OH)D analysis, we reported that 44% of women had a circulating 25(OH)D concentration < 50  
49 nmol/L, 17% had a 25(OH)D < 30 nmol/L and 11% were below 25 nmol/L [8]. Given that fetal vitamin  
50 D status is determined by maternal circulating 25(OH)D, this is of great concern [1]. The Cork data  
51 showed that 46% of infants born to the mothers in the prospective cohort had umbilical cord 25(OH)D  
52 < 30 nmol/L and 35% had 25(OH)D < 25 nmol/L [9], similar to estimates from Saraf et al. [3].

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

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

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

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

## 79 **Methods**

### 80 **Study Design**

81 The COMBINE (Cork Nutrition and Development Maternal-Infant) study, based in Cork, Ireland, is a  
82 longitudinal, prospective birth cohort study. Participants of the Improved Pregnancy Outcomes via  
83 Early Detection (IMPROVED) study (<http://www.clinicaltrials.gov>; trial ID: NCT01891240) formed  
84 the recruitment pool for the COMBINE cohort [23]. Recruitment for COMBINE commenced in late  
85 2015 and finished in late 2017; 456 IMPROVED participants were recruited to postnatal follow-up in  
86 COMBINE, which included 7 research midwife-led study visits in the first 12 months of life, at hospital  
87 discharge/day 2, 1 month, 2, 4, 6, 9 and 12 months.

### 88 **Data collection**

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

### 97 **Supplementation policy adherence**

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

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

## 112 **Time trends in supplement use**

113 The BASELINE (Babies after SCOPE Evaluating the Longitudinal Impact on Neurological and  
114 Nutritional Endpoints) birth cohort study recruited participants in Cork, Ireland, in the same setting as  
115 the COMBINE cohort, between 2008 and 2011 [24]. In the BASELINE cohort, use of vitamin D-  
116 containing supplements was collected in 1949 participants, with data available for 1902 participants at  
117 2 months, 1817 participants at 6 months and 1704 participants at 12 months. The national vitamin D  
118 supplementation policy was implemented in May 2010 while the BASELINE study was ongoing;  
119 70.5% attended their 2 month visit after policy implementation, 79.7% did so at 6 months and 89.9%  
120 of participants attended their 12 month visit after implementation of the vitamin D supplementation  
121 policy.

## 122 **Statistical Analysis**

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

## 128 **Results**

### 129 **Maternal and infant characteristics**

130  
131 Characteristics of COMBINE participants included in this analysis ( $n = 364$ ) are presented in **Table 1**.  
132 Median (IQR) maternal age at delivery was 33 (30, 34) years. There was a high proportion of white  
133 (97%) and Irish-born (81%) mothers and 77% had a third level qualification (ordinary bachelor degree  
134 or greater). Forty-eight percent were breastfeeding solely at hospital discharge and the respective  
135 percentages at 6 and 12 months were 24%, and 16%. Participants included in the analysis were slightly  
136 older [33 (30, 35) vs. 30 (25, 33) years], more likely to be in a stable relationship (96 vs. 89%

137 partner/married) and to have breastfed at hospital discharge (48 vs. 28%) than those not included (all  $P$   
138  $< 0.05$ ), but other maternal and infant characteristics did not differ.

### 139 **Adherence to the vitamin D supplementation policy in the COMBINE cohort**

#### 140 *Product type*

141 Supplements used in the cohort were largely in dropper format, although pump, spray and twist-off  
142 capsule products were also used. All supplements, with the exception of one multi-vitamin product,  
143 used during the COMBINE study contained vitamin D<sub>3</sub> (cholecalciferol). Most parents (94.2%)  
144 provided an exclusive vitamin D supplement. In those who used a multi-vitamin, the median (IQR) age  
145 at which this was first provided was 36 (21, 46) weeks. Participants who supplemented with vitamin D  
146 in a multi-vitamin preparation were less likely to have always provided a 5 µg dose of vitamin D (5.0%  
147 vs. 92.9%,  $P < 0.001$ ). These multi-vitamin products typically contained  $> 5$  µg (68.0%), although  
148 24.0% contained less than 5 µg.

#### 149 *Dose*

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

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

#### 163 *Frequency*

164 While using supplements, 50.6% of COMBINE participants always gave vitamin D daily and a further  
165 33.3% reported supplementing not less than often. Only 3.3% consistently provided vitamin D less than  
166 3 times/week.

#### 167 *Duration*

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

#### 171 *Overall adherence*

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

179 By 12 months, 15.6% of participants, who provided vitamin D for the full 12 month duration but had  
180 used a multi-vitamin preparation, provided a dose other than 5 µg and/or given a supplement < 3  
181 times/week, were classed as partially adhering. Within these participants, 44.4% had given vitamin D  
182 less than 3 times/week, 22.2% had not always adhered to the dosage recommendation and 31.5% had  
183 not complied with two or more recommendations (type, dose and/or frequency). The rate of longitudinal  
184 non-adherence for the complete duration of birth to 2 months was 7.2%; most of these participants  
185 (88.0%) initiated supplementation after week 1. One-quarter (25.6%) of parents did not supplement for  
186 the complete duration of birth to 9 months, and the median duration of supplementation in these  
187 participants was 26.5 (19.3, 33.0) weeks. The rate of longitudinal non-adherence for the complete  
188 duration of birth to 12 months was 38.0%; the median supplementation duration in these participants  
189 was 33.0 (24.0, 45.0) weeks.

#### 190 **Maternal and infant characteristics and adherence**

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

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

196 As shown in Table 1, mothers in COMBINE (recruited 2015-2017) were slightly older (all  $P < 0.001$ )  
197 than mothers in BASELINE (recruited 2008-2011), but participants in the two cohorts did not differ in  
198 ethnicity, nationality, relationship status or education level (all  $P > 0.05$ ). **The breastfeeding rate was**  
199 **significantly higher (all  $P < 0.05$ ) in the COMBINE cohort compared to the BASELINE cohort at**  
200 **hospital discharge (47.9 vs 40.9%), 2 months (36.1 vs 27.1%), 6 months (24.4 vs 12.3%) and 12 months**  
201 **(15.5 vs 4.7%).**



202 While 69.4% of parents in the BASELINE cohort gave their infant a vitamin D-containing supplement  
203 at some stage during the first year of life, 99.2% did so in COMBINE ( $P < 0.001$ ). As the BASELINE  
204 study spanned the policy implementation, it is interesting to note the difference between participant use  
205 of a vitamin D-containing supplements pre and post policy implementation (3.9 vs 48.7% at 2 months,  
206 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**.  
207 Compared with BASELINE participants assessed after implementation of the supplementation policy,  
208 a higher proportion in COMBINE supplemented with vitamin D at 2 months (93.1 vs. 48.7%), 6 months  
209 (88.7 vs. 64.4%) and 12 months (71.6 vs. 43.6%), all  $P < 0.001$ .

## 210 **Discussion**

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

220 In 2017, Uday and colleagues published an exploration of adherence to vitamin D supplementation  
221 programmes in Europe [20]. Of the 29 included countries, only 3 (Denmark, Turkey and Israel)  
222 monitored policy adherence nationally. While an adherence rate of  $\geq 80\%$  was indicated by 59% of  
223 countries, 31% reported moderate adherence (50-79%) and 10% low adherence ( $< 50\%$ ). An adherence  
224 rate of 59%, estimated from a regional study, was reported for Ireland, although the source of these data  
225 was not provided. Cross-sectional analyses of cohort studies highlight wide variation in  
226 supplementation policy adherence, ranging from  $< 10\%$  in America at multiple time-points during the  
227 first year of life [25] to 80% in Canada at 2 months of age [26] and 97% in Denmark at 9 months [27].  
228 Secondary analysis of an infant feeding trial estimated daily (defined as 4-7 times/week) vitamin D  
229 supplementation in  $\sim 1\%$  of infants in Australia,  $\geq 60\%$  in Southern Europe and  $\geq 80\%$  in Northern and  
230 Central Europe [28]. Given that 93% of infants in COMBINE received supplemental vitamin D at 2  
231 months, 89% at 6 months and 72% at 12 months, our data indicates high rates of supplementation.  
232 However, prospective longitudinal data can provide a more in-depth examination of supplementation  
233 practices. Accounting for dose, type, frequency and duration of supplementation, reflecting a strict  
234 definition of policy adherence, we report a rate of 30%, approximately half that reported by Uday et al  
235 [20].

236 In recommending universal supplementation with a low dose 5 µg/day supplement, compared to the  
237 more commonly recommended 10 µg/day, the Food Safety Authority of Ireland determined that this  
238 would prevent serum 25(OH)D concentrations < 25 nmol/L in breastfed infants, whilst ensuring that  
239 intakes in formula fed infants (the majority of infants in Ireland), would not exceed the tolerable upper  
240 intake level (UL) [21]. Adherence to the dose recommendation was high in COMBINE, with almost  
241 90% always providing 5 µg/day while supplementing. Non-adherence to this recommendation generally  
242 reflected use of products not designed to meet the Irish vitamin D supplementation policy, typically  
243 where parents born outside of Ireland were using supplements available in their native countries or  
244 where multi-vitamin products were used. Vitamin D excess in infants has generally been associated  
245 with very large single bolus doses and toxicity is rare [29]. In 2018, EFSA increased the UL to 35  
246 µg/day for infants aged 6-12 months [30], reinforcing the safety of low dose supplemental vitamin D  
247 for infants. Given the high adherence to the 5 µg dose recommendation, risk of vitamin D over-exposure  
248 resulting from a low dose universal vitamin D supplementation policy appears low.

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

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

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

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

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

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

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

315

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

Characteristic	COMBINE ( <i>n</i> = 364)	BASELINE ( <i>n</i> = 1949)	<i>P</i> -value
<b>Maternal</b>			
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 <sup>2</sup> ) <sup>a</sup>	25.1 (22.9, 27.9)	24.0 (22.1, 26.9) <sup>1</sup>	< 0.001
<b>Infant</b>			
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 <sup>b</sup>			
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

<sup>a</sup>*n* = 1185

<sup>b</sup>Breastfed solely

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

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

<sup>a</sup>Adherence to type, dose and frequency

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

<sup>c</sup>Vitamin D given but at least one other factor (type, dose or frequency) was not met

<sup>d</sup>Did not give vitamin D for the complete duration of interest (from birth to each time-point)

321

322

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

Characteristic	Overall adherence <sup>a</sup>		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) <sup>b</sup>	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 <sup>c</sup>			
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

<sup>a</sup>Full adherence to dose, frequency and type aspects from birth to 12 months

<sup>b</sup>Ordinary bachelor degree or greater

<sup>c</sup>Breastfed solely

325

326 **Declarations**

327

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333 **Conflicts of interest**

334 The authors have no conflicts of interest to report.

335 **Ethical standards**

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

342 **Author's contributions**

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

348



349 **Fig. 1** Use of vitamin D-containing supplements at 2, 6 and 12 months in the BASELINE (recruited  
350 2008-2011) and COMBINE (recruited 2015-2017) birth cohort studies. The vitamin D supplementation  
351 policy was implemented in May 2010 while the BASELINE cohort was ongoing. \* $P < 0.001$

352

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