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Cholesterol at ages 6, 12 and 24 months: Tracking and associations with diet and maternal cholesterol in the Infant Cholesterol Study

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ABSTRACT

Background and aims: There are indications for tracking of circulating total cholesterol concentration (TC) from childhood to later in life. An increased lifelong TC exposure increases the risk of developing atherosclerosis, however little is known about the determinants of TC early in life. We aimed to describe TC in Norwegian offspring aged 6, 12 and 24 months, and to explore if maternal TC, breastfeeding and offspring diet are associated with offspring TC.

Methods: In this cross-sectional study, mothers of offspring aged 6 (n = 629), 12 (n = 258) and 24 (n = 263) months completed a questionnaire of the offspring's diet and took home-based dried blood spot samples from themselves and their offspring. The mothers and offspring participating at age 12 months also participated at age 6 months of the offspring.

Results: Offspring TC showed a wide range in all three age groups. Twenty one percent of the offspring had TC ≥ 5.1 mmol/l. There was significant tracking of offspring TC from 6 to 12 months of age ($r = 0.42$, $p < 0.001$). Maternal and offspring TC was positively associated in all age groups ($0.20 \leq \beta \leq 0.40$, $p < 0.001$ for all). Breastfeeding was positively associated with offspring TC at ages 6 and 12 months ($0.05 \leq \beta \leq 0.26$, $0.001 \leq p \leq 0.03$), but not at age 24 months.

Conclusions: The wide range in TC and probable tracking of TC from infancy to later in life highlights the importance of early identification of children with elevated TC who can benefit from preventive measures.

1. Introduction

Atherosclerosis is a progressive disease involving retention of lipids and an inflammatory response in the arterial wall [1]. It may begin as early as in childhood [2,3]. Both the circulating concentration of total cholesterol (TC) [4] and low-density lipoprotein cholesterol [1] are well-known risk factors for atherosclerosis. We have previously shown that TC is 1.4 mmol/l in newborns [5] and three times as high in infants around one year of age [6]. Furthermore evidence for tracking of TC from childhood to adulthood has been observed in multiple studies [7,8]. This suggests that infant TC can provide a glimpse into the future of an individual's lifelong cholesterol exposure [9]. Thus, it is of public health relevance to first elucidate the determinants of TC in early life, and secondly to identify children who might benefit from preventive measures. Previous studies have shown positive associations between the concentration of maternal cholesterol before or in early pregnancy and offspring cholesterol in childhood or adulthood [10–12]. In adults, a diet consisting of a higher ratio of polyunsaturated fatty acids (PUFA) to

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saturated fatty acids (SFA) is associated with lower TC and is protective against cardiovascular disease (CVD) [13]. There are some studies indicating that both a higher ratio of dietary PUFA to SFA and breastfeeding during infancy are associated with lower TC in adult life [14,15]. In the present Infant Cholesterol Study, we aimed to describe TC in Norwegian offspring aged 6, 12 and 24 months, and to explore if maternal TC, breastfeeding and offspring diet are associated with offspring TC.

2. Patients and methods

The Infant Cholesterol Study had both a prospective cohort design ("population 1") and a cross-sectional design ("population 2"). In "population 1", 2099 mothers of offspring aged 6 months participating in the nationwide dietary survey among infants in Norway "Spedkost 3" [16] were invited to participate in the Infant Cholesterol Study (Supplementary Fig. 1). The mothers who provided blood samples in "population 1" were invited to participate for a second time six months later when the offspring were 12 months of age. In "population 2", 1349 mothers of offspring participating in the nationwide dietary survey among 2-year-olds in Norway "Småbarnskost 3" [17] were invited to participate in the Infant Cholesterol Study. In the "Spedkost 3" and the "Småbarnskost 3" dietary studies, a nationwide selection was drawn from the Norwegian National Registry. Only offspring of mothers born in Norway, Sweden, or Denmark were invited. Recruitment and data collection in the two studies were performed at the University of Oslo, Norway, from September 2018 to June 2019.

2.1. Dietary questionnaires

Offspring diet during the preceding 14 days was assessed by semi-quantitative food frequency questionnaires (FFQs) containing 44–50 questions. The FFQs and the results of the "Spedkost 3" and the "Småbarnskost 3" dietary studies have been published previously [16–18]. The FFQ for offspring aged 6 months contained questions regarding breastfeeding frequency, formula feeding and supplementary feeding. Absolute intake of nutrients could not be calculated as portion sizes were mostly not assessed. The FFQs for offspring aged 12 and 24 months included use of approximately 200 foods, and were used to calculate average daily intake of energy and nutrients, using the "Kostberegningssystem" (KBS) version 7.3 and the food database AE18 developed at the University of Oslo, Norway. At age 12 and 24 months, breastfeeding status (yes/no), but not the quantity of breastmilk given, was assessed and could therefore not be included in the calculation of energy and nutrients. All three FFQs included questions about the offspring's sex, body weight and length, and maternal age, education and smoking status. Breastfeeding frequency (at 6 months of age) and status (yes/no, at 12 months of age) were also assessed at the time of blood sampling in "population 1", and these data are used in the presentation of the breastfeeding results at 6 and 12 months of age.

2.2. Dried blood spot samples

As part of the Infant Cholesterol Study (Supplementary Fig. 1), the subjects received a "dried blood spot" (DBS) kit by mail, allowing home-based blood sampling from the fingertips of both mother and offspring at ages 6, 12 and 24 months. Capillary blood drops were placed on DBS cards, which were dried at room temperature for 2–4 h, placed in a sealed aluminum bag and returned by mail. The DBS cards were frozen (−80°) within 10 days after blood sampling. A maximum of three months passed between completion of the FFQ and blood sampling. TC (primary endpoint) was measured at an accredited medical laboratory (Vitas AS, Oslo, Norway). We have previously found a strong correlation between TC from venous blood samples analyzed by the DBS method and routine laboratory methods at accredited medical laboratories ($r = 0.94$, $p < 0.001$) [6]. The American College of Cardiology and American Heart Association has defined TC $\geq$ 5.1 mmol/l as abnormal among children [19].

2.3. Ethics

The Infant Cholesterol Study was approved by the Regional Committees for Medical and Health Research Ethics southeast region of Norway (no. 2017/980), and mothers and fathers with parental responsibility provided written informed consent. The "Spedkost 3" and "Småbarnskost 3" dietary studies were approved by the Norwegian Centre for Research Data (ref. 58855 and 60537), and parents provided written informed consent. All the studies were conducted according to the principles of the Declaration of Helsinki.

2.4. Statistics

Data are presented as mean (standard deviation [SD]) for continuous variables and frequency (%) for categorical variables. Kernel density plots are used to visualize the distribution of TC in the three age groups. Change in TC was calculated in offspring and mothers participating at both age 6 and 12 months. Tracking of TC from 6 to 12 months of age was assessed by Pearson's correlation coefficient. Univariable and multivariable linear regression analyses with offspring TC as outcome were stratified by age groups. Maternal TC, maternal higher education (yes vs no), offspring sex (girls vs boys) and offspring weight/length were included in the regression analyses in all age groups. Additionally, breastfeeding (frequency/day) was included in the model with offspring aged 6 months, and breastfeeding status (yes *vs* no) was included in the models with offspring aged 12 months and 24 months. The exposures were selected based on previous knowledge and directed acyclic graphs. Univariable linear regression analyses were also used to explore the association between offspring dietary intake of fat and TC. The residuals were examined to check model assumptions. Regression results are presented in a table as univariable and multivariable regression (β) coefficients with 95% confidence intervals (CIs) and p-values. A selection of the correlation and multivariable regression results are presented in scatter plots and box plots. p-values <0.05 were considered significant. The statistical analyses were performed in R version 3.6.1 with RStudio IDE version 1.3.1073 [20].

3. Results

3.1. Characteristics

Of the 2099 invited mothers in "population 1", 629 (30%) mother-offspring pairs provided blood samples at age 6 months of the offspring, and of these 258 (41%) provided blood samples again at age 12 months of the offspring. Of the 1349 invited mothers in "population 2", 263 (19%) mother-offspring pairs provided blood samples at age 24 months of the offspring (Supplementary Figure 1). The blood samples were drawn mean (SD, min-max) 42 (21, 4–98) days after the FFQs were completed. In "population 1" and "population 2", the mean age of the mothers was 32 and 33 years, and 77% and 78% had higher education, respectively (Table 1). One percent of the mothers were regular/daily smokers. BMI was mean 24.9 kg/m^2 in the mothers in "population 2". Age, education and smoking prevalence were similar as in mothers participating only in the dietary studies ("Spedkost 3" and "Småbarnskost 3") (Supplementary Table 1). The offspring's weight and length for age were between the 50th and the 75th percentiles [21].

3.2. Maternal and offspring TC

The mean (SD) offspring TC was 4.2 (0.9), 4.4 (0.8), and 4.9 (0.9) mmol/l at age 6, 12 and 24 months, respectively (Table 1). There were wide ranges in offspring TC in all three age groups (min-max: 1.7–8.4 mmol/l) (Fig. 1). TC was $\geq$5.1 mmol/l in 186 (21%) offspring and >6

Table 1
Subject characteristics.

	Population 1				Population 2	
	6 months		12 months		24 months	
	Offspring	Mothers	Offspring	Mothers	Offspring	Mothers
n	629	629	258	258	263	263
Age, years, mean (SD)		32 (4)		32 (4)		33 (5)
Female, n (%)	273 (43.4)		110 (42.6)		128 (48.7)	
Body weight, kg, mean (SD)	8.0 (1.0)		9.9 (1.1)		12.8 (1.4)	70.2 (13.3)
Length, cm, mean (SD)	68.0 (2.5)		76.1 (2.8)		87.8 (3.7)	168.0 (5.9)
Weight/Length, kg/m, mean (SD)	11.8 (1.2)		12.9 (1.2)		14.6 (1.3)	
Breastfeeding[a], n (%)	489 (77.7)		100 (38.8)		26 (10.0)	
Higher education, n (%)		481 (76.5)		207 (80.2)		205 (77.9)
Regular smokers, n (%)		8 (1.3)		3 (1.2)		3 (1.1)
TC, mmol/l[a], mean (SD)	4.2 (0.9)	4.9 (0.9)	4.4 (0.8)	4.9 (0.9)	4.9 (0.9)	5.0 (0.9)

SD, standard deviation; TC, circulating concentration of total cholesterol. [a]TC was measured mean 42 days after completion of the dietary questionnaire. In population 1, breastfeeding status was measured simultaneously to TC.

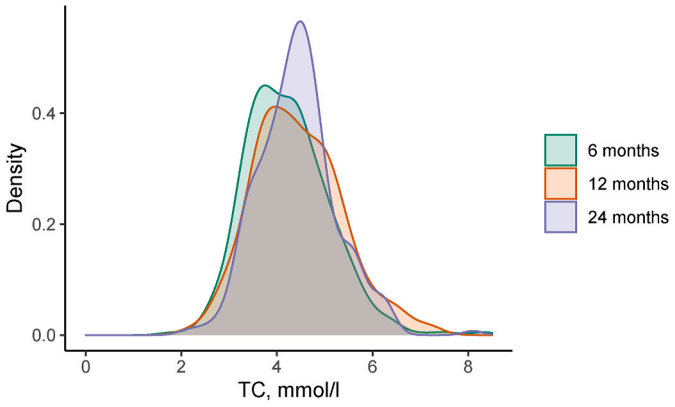

Fig. 1. Density plot of distributions of offspring TC at ages 6, 12 and 24 months.
TC, circulating concentration of total cholesterol.

mmol/l in 40 (5%) offspring. The distribution of maternal TC was similar in the three age groups (Supplementary Figure 2). Changes in TC from 6 to 12 months of age ranged between −2.3 and 3.3 mmol/l in the offspring and −3.4 to 3.4 mmol/l in the mothers (n = 258). Offspring and maternal TC showed significant tracking from 6 to 12 months of age (r = 0.42 and r = 0.51, $p < 0.001$ for both, Fig. 2 and Supplementary Figure 3). Maternal and offspring TC were positively associated in all age groups (multivariable $0.20 \leq \beta \leq 0.40$, $p < 0.001$ for all), after adjustment for maternal education, offspring sex, offspring body weight/length, and breastfeeding (Fig. 3 and Supplementary Table 2). Changes in maternal and offspring TC from 6 to 12 months of age were also positively associated (multivariable $\beta = 0.27$, $p < 0.001$, data not shown).

3.3. Breastfeeding and offspring TC

The prevalence of any (partial or exclusive) breastfeeding was 78% at age 6 months, 39% at age 12 months and 10% at age 24 months (Table 1). The prevalence of exclusive breastfeeding was 9% at age 6 months (data not shown). Breastfeeding frequency at age 6 months and offspring TC were positively associated (multivariable $\beta = 0.05$, $p < 0.001$, Fig. 4A and Supplementary Table 2). Offspring who were breastfed at age 12 months had significantly higher TC than offspring who were not breastfed at this age (multivariable $\beta = 0.26$, $p = 0.03$, Fig. 4B and Supplementary Table 2). There was no significant difference in TC between offspring who were breastfed compared to not breastfed at age 24 months (multivariable $\beta = -0.12$, $p = 0.50$, Fig. 4C and Supplementary Table 2).

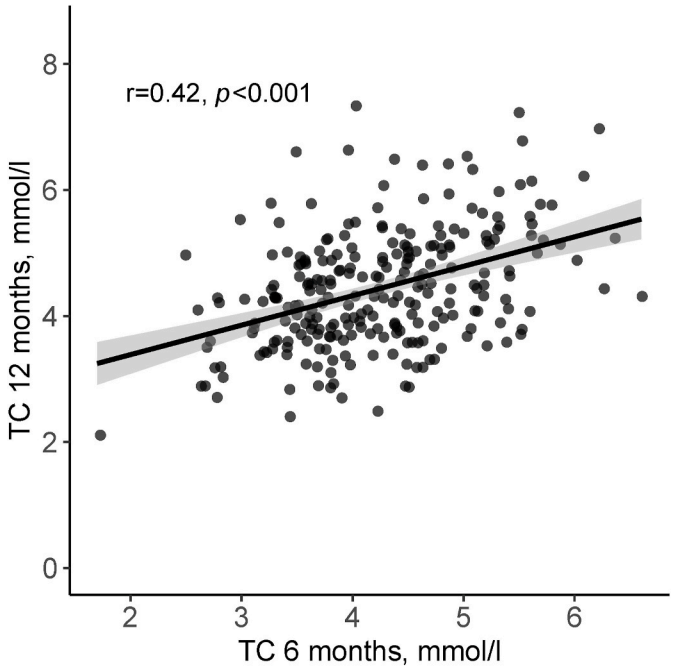

Fig. 2. Tracking of offspring TC from age 6–12 months (n = 258).
Results are presented as Pearson's correlation coefficient (r) and *p*-value. TC, circulating concentration of total cholesterol.

3.4. Offspring diet and TC

Dietary intake of macronutrients was calculated at ages 12 months and 24 months (Supplementary Figure 4). The mean (SD) intake of energy was 4.5 (1.5) MJ at age 12 months and 5.4 (1.5) MJ at age 24 months. At ages 12 and 24 months, 113 (44%) and 225 (86%) got ≥ 10% of energy from SFA in the diet. We found no significant associations between offspring dietary intake of SFA, monounsaturated fatty acids, PUFA or cholesterol and TC at age 12 months and 24 months (univariable $0.11 \leq p \leq 0.91$, Supplementary Table 2). The results were similar when excluding infants who were breastfed (data not shown). Thus, dietary intake of fat was not included in the multivariable analyses.

4. Discussion

We found a positive association between maternal and offspring TC in all age groups, and between breastfeeding and TC in offspring aged 6 and 12 months, but not in offspring aged 24 months. Offspring TC

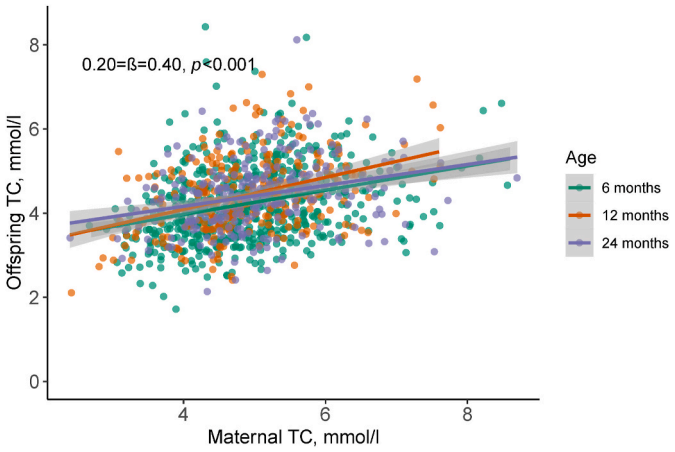

Fig. 3. Associations between maternal and offspring TC.
Results are presented as multivariable regression coefficients (β) and *p*-values, after adjustment for maternal education, offspring sex, offspring body weight/length, and breastfeeding. TC, circulating concentration of total cholesterol.

showed a wide range, and we found significant tracking of TC from 6 to 12 months of age. The current study, together with our previous work [5], indicates large inter-individual differences in the cholesterol exposure during the first two years of life.

TC increases with age and the largest increase in TC through life occurs before adulthood [9]. Mean offspring TC observed in the present study is a bit higher than German paediatric references [22]. Mean maternal TC is similar to TC measured in average Norwegian women between 30 and 39 years [23]. As many as 21% of the offspring in the current study had abnormal TC [19]. Large inter-individual differences in TC appear to be present from infancy throughout life [22,24,25]. Our finding of tracking of TC during infancy is important as others have shown tracking of TC from infancy to childhood [26] and from childhood to adulthood [7,8], thus affecting the lifelong cholesterol exposure [9]. Furthermore, atherosclerosis begins already in childhood [2,3], and a 1 mmol/l reduction in low-density lipoprotein cholesterol over 30–40 years may half the risk of developing atherosclerotic CVD [27]. Hence, early identification of children with elevated TC is important to facilitate preventive measures such as dietary adjustments.

In agreement with the current study, a relation between maternal and offspring TC has previously been found in infancy [28], childhood [10,11,26] and adult life [12]. In the present study, a 20% increase in maternal TC corresponded to about 5–10% increase in offspring TC in all age groups. The mother-offspring TC associations can be attributed to genetics [29], epigenetics [30], and shared lifestyle. The results were similar before and after adjustment for breastfeeding. About 20% of the variance in TC in young children can be explained by known single nucleotide polymorphisms [29]. Moreover, maternal TC might alter the epigenetic pattern of the offspring, affecting their susceptibility to hypercholesterolemia and CVD [30]. A cholesterol-lowering diet during pregnancy has been shown to lower maternal TC [31]. Thus, identifying and treating women with gestational hypercholesterolemia might provide short- and long term benefits for both mother and offspring. However, there is no consensus regarding the definition of gestational hypercholesterolemia as TC naturally rises during pregnancy [32]. TC > 7.2 mmol/l has been suggested as a cut-off for gestational supraphysiological hypercholesterolemia [33].

Offspring who were breastfed had 0.3 mmol/l higher TC than offspring who were not breastfed at age 12 months in the current study. Others have found similar associations in infancy [15,34], but inverse associations in adult life [15]. The TC increasing effect has been suggested to persist only as long as breastfeeding is continued [35]. We found no difference in TC between offspring aged 24 months who were breastfed compared to not breastfed, however, few offspring aged 24

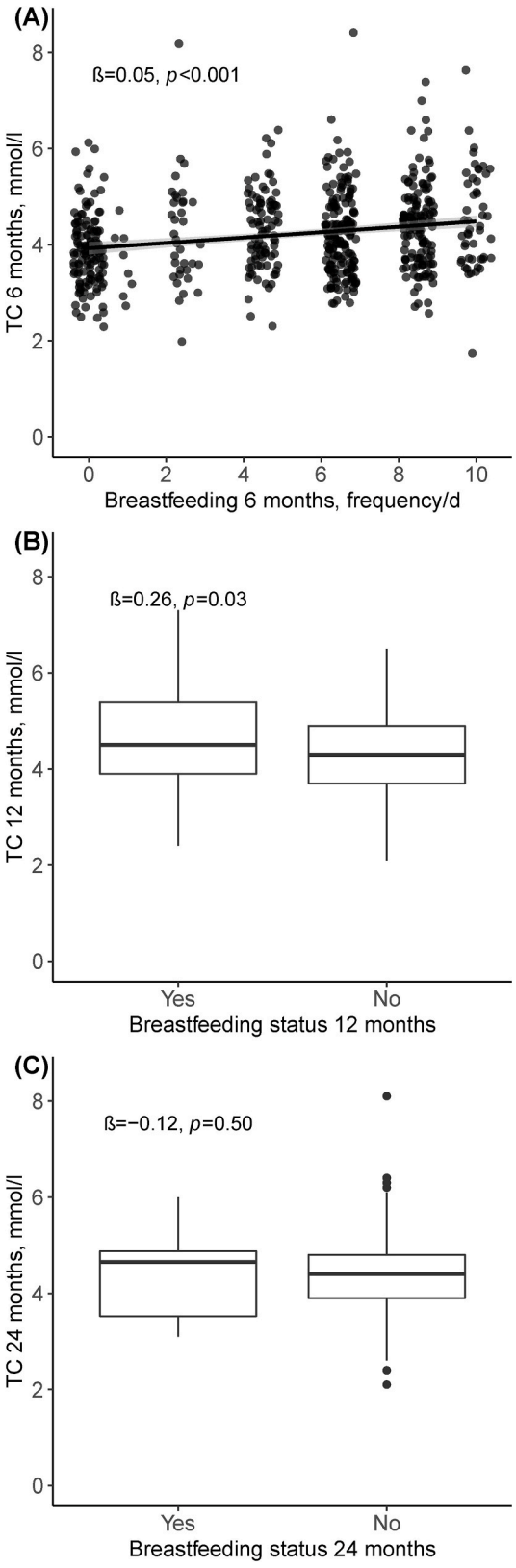

Fig. 4. Associations between breastfeeding and offspring TC at ages 6 (A), 12 (B) and 24 (C) months.
Results are presented as multivariable regression coefficients (β) and *p*-values, after adjustment for maternal TC, maternal education, offspring sex, and offspring body weight/length. TC, circulating concentration of total cholesterol.

months were breastfed. The lipid quality and quantity in breastmilk vary greatly, however, infant formulas commonly used in Norway are within the normal ranges of breastmilk [36,37]. The most likely reason for the increased TC associated with breastfeeding is that breastmilk contains more cholesterol than infant formulas [15,36]. Maternal dietary fat quality has a market effect on the lipid composition of breastmilk [36, 38], but whether this affects offspring TC should be further explored. Nutritional programming has been suggested as an explanatory mechanism for the beneficial effect of breastfeeding on adult TC [15]. However, there is insufficient evidence regarding the association between breastfeeding and later CVD [39].

In the present study, a large proportion of the offspring got more SFA from the diet than recommended [40]. However, intake of SFA and PUFA showed a small range which might explain the non-significant associations with offspring TC. A higher ratio of dietary PUFA to SFA from 6 to 12 months of age has previously been associated with lower TC at 12 months of age in a cohort study [41] and a randomized controlled trial [42]. In the latter study, the cholesterol-lowering effect persisted until 20 years of age [14]. Replacing dietary SFA with PUFA is safe and recommended in children from two years of age throughout life [13,19, 43].

Limitations of our study are that one cannot exclude recall bias in the completion of the FFQs. The FFQ for offspring at 12 months of age has been shown to overestimate energy intake and absolute nutrient intake in a validation study [44], thus we chose to include intake of nutrients in percentage of energy in the regression analyses. Of the sample drawn from the Norwegian National Registry, the dietary studies included 73% at 6 months [16], 66% at 12 months [18] and 47% at 24 months of age [17], while the Infant Cholesterol Study only included 21% at 6 months, 9% at 12 months and 9% at 24 months of age, making selection bias possible. The mothers in the current study gave birth at a similar age as average Norwegian women [45], but a higher proportion had higher education (77–80% vs 60%) [46] and fewer were smokers (1% vs 5%) [47] compared to average Norwegian women in their age range. Thus, our selection is probably healthier than the average. Other epidemiological studies also find higher participation rate among non-smoking subjects with higher education [48]. As the study focused on cholesterol, conditions such as hypercholesterolemia or heart disease in the family may also have motivated participation. Due to the high prevalence of breastfeeding, intake of nutrients was not assessed in offspring aged 6 months. The logistics of the study did not allow simultaneous completion of the FFQ and blood sampling. Thus, the offspring's anthropometrics and diet may have changed between completion of the FFQ and blood sampling. Strengths in the study are the use of simple, resource effective and non-invasive techniques to collect both dietary data and TC from a large number of subjects. The current study adds novel information about TC in Norwegian infants and toddlers and how it is related to breastfeeding, diet and maternal TC.

4.1. Conclusions

In the current study we found a positive association between maternal and offspring TC in all age groups, and between breastfeeding and TC in offspring aged 6 and 12 months, but not in offspring aged 24 months. Thus, maternal TC and breastfeeding are probable determinants of offspring TC in early life. The wide ranges in TC and probable tracking of TC from infancy to later in life, highlight the importance of early identification of children with elevated TC who can benefit from preventive measures. Further studies should explore if a dietary intervention early in life may lower the lifelong cholesterol exposure and incidence of premature CVD. Moreover, routine measurement of TC during childhood at least once should be considered.

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Author contributions

Conceived and designed the study: LKLØ, ALK, MPB, KBH. Collected the data: LKLØ, MPB, ALK, JBM, HA, LFA, KBH. Performed the analyses: LKLØ. Drafted the paper: LKLØ, MPB, KBH. All authors (LKLØ, MPB, ALK, JBM, HA, KR, HKB, JRVL, LFA, KBH) contributed to the interpretation of the data and critically reviewed the paper. LKLØ, MPB, and KBH hold primary responsibility for the content.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: During the past five years, MPB reports grants and personal fees from Amgen, grants and personal fees from Sanofi, personal fees from MSD, personal fees from Boehringer Ingelheim, grants and personal fees from Mills AS, and grants from Kaneka, none of which are related to the content of this manuscript. KR reports personal fees from Amgen, personal fees from Mills AS, personal fees from The Norwegian Medical Association, personal fees from The Norwegian Directorate of Health, personal fees from Sanofi, personal fees from Takeda, personal fees from Chiesi, personal fees from Bayer, and personal fees from MSD, none of which are related to the content of this manuscript. JRVL has received research grants from Amryt, which are not related to the content of this manuscript. KBH has received research grants or honoraria from Mills AS, Tine SA, Olympic Seafood, Amgen, Sanofi, and Pronova, none of which are related to the content of this manuscript. LKLØ, ALK, JBM, HA, HKB, and LFA declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2021.04.017.

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