Cord blood leptin and gains in body weight and fat mass during infancy

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Abstract

Objectives: Low early-life leptin concentrations may promote faster weight gain in infancy. We aimed to examine the associations between cord blood leptin concentrations and changes in weight and body composition during infancy.

Design and methods: Serum leptin was measured at 15 weeks gestation, in umbilical cord blood collected at delivery and at 2 years in 334 children from the Cork Baseline Birth Cohort Study. Body composition was measured at 2 days and 2 months using air displacement plethysmography. Conditional change in weight standard deviation scores over a number of age intervals in the first 2 years and conditional change in fat mass index (FMI) and fat-free mass index (FFMI) (kg/(length)m²) between birth and 2 months were calculated and associations with cord blood leptin were examined using linear regression.

Results: At birth, cord blood leptin was positively correlated with FMI ($r=0.48$, $P<0.001$) and showed a weaker correlation with FFMI ($r=0.12$, $P=0.05$). After adjustment for confounders, higher cord blood leptin (per ng/mL) was associated with slower conditional weight gain between birth and 2 months (β (95% CI): -0.024 (-0.035 , -0.013), $P<0.001$) but not over subsequent age intervals. Cord blood leptin was also inversely associated with conditional change in FMI (-0.021 (-0.034 , -0.007 , $P=0.003$) but not FFMI between birth and 2 months.

Conclusions: These are the first data to show that associations between higher cord blood leptin and slower weight gain during infancy are driven by lower increases in adiposity, at least in early infancy.

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Introduction

Rapid weight gain in infancy is associated with an increased risk of obesity in childhood and adulthood (1, 2) and may affect subsequent metabolic health (3, 4). Currently, there are few data on determinants of rapid weight gain in infancy, but both prenatal and early-life factors have been implicated (5, 6). Leptin, a product of the *ob* gene, is a 16 kDa hormone secreted primarily by adipocytes, but is also produced in other sites, including fetal and placental tissues (7, 8). In adults, the primary role of leptin is in energy homeostasis through the regulation of appetite and energy expenditure via a number of neuronal signals (9, 10). There is now emerging evidence to suggest that

low fetal leptin concentrations mediate faster weight gain during infancy and play a role in the development of obesity (11, 12, 13).

Evidence from animal models suggests that lower umbilical cord blood leptin may be a marker of adverse intrauterine conditions including placental insufficiency and fetal growth restriction, resulting in lower fat mass at birth, permanent changes in appetite regulation and faster postnatal growth (10, 14, 15). In rodents, leptin plays a role in the programming of hypothalamic appetite regulation in the early postnatal period, and it has been demonstrated that disruption in the action of leptin by leptin antagonists

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during this critical period of hypothalamic development leads to long-term consequences including hyperphagia, obesity and leptin resistance in adulthood (15, 16, 17). In humans, development of the hypothalamic feeding circuits occurs primarily *in utero* during the final trimester (18) and thus leptin during the pre- and perinatal periods may be important. Umbilical cord blood leptin has been consistently shown to be positively associated with birth weight and has been widely accepted as a marker of neonatal adiposity (13, 19, 20). Cord blood leptin concentrations have also been shown to be inversely associated with weight gain in infancy (11, 12, 21) and with body mass index (BMI) in early childhood (20). However, weight and BMI are limited as proxies of adiposity as they correlate with both fat and lean mass. To date, no study has examined cord leptin in relation to changes in direct measures of body composition in infancy. The aim of this study was to examine the associations between umbilical cord blood leptin concentrations collected at delivery and changes in both weight and adiposity in early infancy.

Subjects and methods

Study subjects were participants of the Cork BASELINE (Babies after SCOPE: Evaluating the Longitudinal Impact using Neurological and Nutritional Endpoints) Birth Cohort Study (22). This mother–infant prospective birth cohort study based in Cork, Ireland, was initiated in 2008 as a follow-up to the SCOPE (Screening for Pregnancy Endpoints) Ireland study, as part of a major multicenter prospective pregnancy study involving primiparous low-risk women. The SCOPE study is registered with the Australian New Zealand Clinical Trials Registry (<http://www.anzctr.or.au>), ID: ACTRN12607000551493. A detailed description of the SCOPE methodology has been provided elsewhere (23).

A total of 1768 women were recruited to SCOPE Ireland from Cork University Maternity Hospital (CUMH). During the 20 week gestation visit, 1537 SCOPE participants provided informed consent for their infants to participate in the BASELINE study. During a second stream of recruitment, a further 600 infants were recruited after delivery from the postnatal wards of CUMH, with the last infant recruited in 2011. Pediatric follow-up with in-person assessments were conducted at birth, 2, 6 and 12 months and at 2 years. Data on the child's early-life environment, diet, health and development were recorded at each assessment. A detailed description of the cohort and pediatric assessments has been provided by O' Donovan *et al.* (22). Ethical approval for the Cork BASELINE Birth

Cohort Study was granted by the Clinical Research Ethics Committee of the Cork Teaching Hospitals, ref ECM 5 (9) 01/07/2008, and the study is registered with the United States National Institutes of Health Clinical Trials Registry (<http://www.clinicaltrials.gov>), ID: NCT01498965.

Of the 2137 infants recruited to the Cork BASELINE Birth Cohort Study, 1954 infants continued with the study and had follow-up information collected after the initial assessment at birth. Umbilical cord blood was only collected from those recruited from the SCOPE study. At the time of the current analysis, cord blood was available for 1050 infants. A total of 1537 children attended the 2 year assessment, of which 742 (48%) had a serum sample collected at 2 years. Cord blood and 2 year leptin concentrations were only measured in those with both a cord and 2 year blood sample available ($n=346$). In the current analysis, preterm infants ($n=12$) were excluded due to potential differences in their early growth patterns, leaving a cohort of 334 infants.

Anthropometry

Naked weight was measured using digital scales (seca 384, seca, Birmingham, UK) at birth and at 2 months correct to the nearest 0.01 kg and at 6 and 12 months and at 2 years correct to the nearest 0.1 kg. Supine length correct to the nearest 0.1 cm was measured at birth, 2, 6 and 12 months (seca 210). At 2 years, standing height was measured using a wall mounted stadiometer (seca 206). Age- and sex-specific weight standard deviation scores (SDS) were generated using LMS growth software (24) and the UK-World Health Organization (WHO) 0–4 year growth reference data (25). BMI (kg/m^2) and BMI SDS at 2 years were calculated. Overweight and obesity at 2 years were defined using the UK-WHO age- and sex-specific BMI charts (25), where overweight was defined as a BMI > 91st percentile and obesity as a BMI > 98th percentile (26). Small-for-gestational age (SGA) and large-for-gestational age (LGA) infants were defined as a birth weight < 10th and > 90th percentile respectively using customised percentiles adjusted for maternal height, booking weight and ethnicity and for infant gestational age and sex (27). Fat mass (FM) and fat-free mass (FFM) (kg) were measured within 4 days of birth (mean (s.d.): 1.9 (1.0) days) and at 2 months (2.1 (0.3) months) in 221 infants by air displacement plethysmography using the PEA POD Infant Body Composition Tracking System (COSMED USA, Inc, Concord, CA, USA). To adjust body composition variables for body size, fat mass index (FMI) and fat-free mass index (FFMI) were calculated by dividing FM and FFM by length in metres squared (kg/m^2) respectively.

Sample collection and analysis

Umbilical cord venous blood samples collected at delivery and peripheral venous blood samples collected at 2 years were immediately stored at 5°C and then processed to serum within 3 h for storage in small aliquots (200 µL) at –80°C until analysis. Leptin concentrations were measured in duplicate at the Cork Centre for Vitamin D and Nutrition Research laboratory by a Quantikine enzyme-linked immunosorbant assay (ELISA) (DLP00, R&D Systems) using an automated processing system (DS2, DYNEX Technologies Ltd, Worthing, UK). The assay sensitivity was 7.8 pg/mL. The inter- and intra-assay coefficients of variation (CV) were 8.7 and 4.0%, respectively. Maternal leptin concentrations at 14–16 weeks gestation were measured previously by Luminex Sandwich Assay (Alere, San Diego, CA, USA), as described by Kenny *et al.* (23).

Outcome variables

As growth during a specific period is likely predicted by earlier growth, conditional models of weight gain were constructed using linear regression analysis. Conditional growth represents the variation in infant growth not explained by prior growth, providing uncorrelated measures (28). For example: conditional weight gain between birth and 2 months was calculated by saving the standardised residuals from the linear regression of weight SDS at 2 months on weight SDS at birth. Conditional weight gain between 2 and 6 months is given as the standardised residuals from the regression of weight SDS at 6 months on weight SDS at 2 months and at birth. This process was continued when calculating conditional weight gain between 6 and 12 months and between 12 and 24 months. Conditional change in FMI and FFMI (kg/m²) from birth to 2 months was also calculated by saving the standardised residuals from the regression of the measurement at 2 months on the measurement at birth.

Statistical analysis

Data were analysed using the statistical software package IBM SPSS for Windows version 21.0 (IBM released 2012). Most variables were nonparametric and are presented as medians or percentages. Characteristics were compared between groups using χ^2 or Mann–Whitney *U* tests, where appropriate. Spearman's correlation coefficients were calculated to examine relationships between cord blood leptin and measurements at birth and 2 years.

Unadjusted associations between umbilical cord blood leptin and conditional change in weight and

body composition during infancy were examined using linear regression. Multivariate models were adjusted for maternal and infant variables that were considered *a priori* as confounders in the main associations. These included maternal age at delivery, overweight/obesity at 15 weeks gestation (≥ 25 kg/m²), smoking during pregnancy, tertiary level education, family income and infant sex, gestational age, breastfeeding status and age at introduction to solids (weeks). In order to examine the association between relatively lower cord blood leptin concentrations and BMI SDS at 2 years, unadjusted trend *P* values across quartiles of cord blood leptin were calculated using linear regression, with the lowest quartile as a reference. Multivariate models were first adjusted for birth weight and then further adjusted for *a priori* maternal and infant confounders. All statistical tests were two-tailed and a value of *P* < 0.05 was considered statistically significant.

Results

Maternal and subject characteristics of those included in the current analysis, as well as a comparison with those not included in the analysis, are presented in Table 1. Compared with those not included in the analysis, the median maternal BMI in this subgroup was slightly higher (median (interquartile range, IQR): 24.5 (22.4, 27.2) vs 23.8 (21.9, 26.8) kg/m², *P* = 0.033), and a higher proportion of infants were predominantly breastfed at 2 months (33.4 vs 25.8%, *P* = 0.006). Females had higher leptin concentrations at birth than males (median (IQR): 12.8 (8.5, 19.6) vs 8.3 (5.3, 13.1) ng/mL) and at 2 years (2.4 (1.7, 3.1) vs 1.6 (1.2, 2.3) ng/mL), *P* < 0.001 for both. SGA infants had significantly lower cord leptin concentrations (median (IQR): 5.6 (3.4, 8.2) ng/mL) than average-for-gestational age (AGA) (10.3 (6.3, 17.1) ng/mL) and LGA infants (14.5 (10.5, 33.1) ng/mL), *P* < 0.001. At 2 years, there was no significant difference in leptin concentrations between the groups, with median (IQR) concentrations of 2.0 (1.2, 2.6), 2.0 (1.4, 2.7) and 2.0 (1.3, 2.6) ng/mL in SGA, AGA and LGA infants respectively, *P* = 0.68.

The median (IQR) maternal leptin concentration at 14–16 weeks was higher in mothers whose BMI was ≥ 30 kg/m² (*n* = 37) at 14–16 weeks gestation (11.8 (6.7, 17.1) ng/mL) compared with those with a BMI < 25 kg/m² (*n* = 179) (6.4 (5.5, 13.6) ng/mL), *P* = 0.007. Cord leptin concentrations were also higher in infants of obese mothers (12.0 (7.5, 23.0) ng/mL) compared with those with a BMI < 25 kg/m² (9.9 (5.8, 15.6) ng/mL), *P* = 0.025. Maternal and cord blood leptin concentrations were weakly correlated (*r* = 0.163, *P* = 0.003). There was no

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Table 1 Maternal and infant characteristics at birth and 2 years ($n=334$). Data are presented as % (n) or median (IQR).

	Not included in the analysis ($n=1620$)	Included in the analysis ($n=334$)	P-value
Maternal characteristics			
Caucasian	98.0 (1576)	99.1 (331)	0.255
Third-level education	84.3 (1354)	85.0 (284)	0.786
Smoked during pregnancy	13.2 (208)	13.3 (44)	1.000
Age at delivery (<25 years)	9.0 (146)	6.6 (22)	0.183
BMI at 14–16 weeks gestation (kg/m^2)	23.8 (21.9, 26.8)	24.6 (22.4, 27.2)	0.033
Leptin at 14–16 weeks gestation (ng/mL)	8.3 (5.5, 14.9)	7.7 (5.5, 14.8)	0.577
Infant characteristics			
Sex (male)	50.7 (822)	52.4 (175)	0.624
Gestational age (weeks)	40.1 (39.1, 41.0)	40.2 (39.4, 41.4)	0.004
Birth weight (kg)	3.50 (3.18, 3.81)	3.51 (3.29, 3.76)	0.111
Birth weight SDS	0.20 (−0.44, 0.84)	0.19 (−0.30, 0.70)	0.766
SGA (yes)	10.8 (119)	8.7 (29)	0.310
LGA (yes)	10.2 (112)	12.3 (41)	0.322
Predominantly breastfed 2 months	25.8 (405)	33.4 (111)	0.006
Predominantly breastfed 6 months	11.6 (172)	15.5 (51)	0.063
Cord blood leptin (ng/mL)	–	10.4 (6.3, 17.2)	–
Body composition			
Fat mass index at birth (kg/m^2)	1.40 (1.01, 1.86)	1.4 (1.08, 1.9)	0.298
Fat free mass index at birth (kg/m^2)	11.57 (11.03, 12.20)	11.61 (11.08, 12.20)	0.739
Fat mass index at 2 months (kg/m^2)	3.4 (2.9, 4.0)	3.5 (2.9, 4.1)	0.809
Fat free mass index at 2 months (kg/m^2)	12.4 (11.8, 13.0)	12.5 (11.9, 13.0)	0.539
Change in FMI from 0 to 2 months (kg/m^2)	2.07 (1.44, 2.61)	1.99 (1.31, 2.66)	0.505
Change in FFMI from 0 to 2 months (kg/m^2)	0.88 (0.28, 1.47)	0.77 (0.30, 1.42)	0.635
Change in weight SDS			
0–2 months	−0.21 (−0.70, 0.26)	−0.23 (−0.73, 0.32)	0.632
0–6 months	0.10 (−0.48, 0.70)	0.16 (−0.62, 0.82)	0.761
0–12 months	0.35 (−0.32, 1.02)	0.41 (−0.33, 1.19)	0.518
Child characteristics at 2 years			
Age at assessment (years)	2.1 (2.1, 2.2)	2.1 (2.1, 2.2)	0.002
BMI SDS	0.69 (0.12, 1.24)	0.68 (0.06, 1.30)	0.755
2 year leptin (ng/mL)	–	2.0 (1.4, 2.7)	–
Overweight	14.6 (162)	15.2 (50)	0.753
Obese	6.3 (70)	6.8 (22)	0.689

BMI, body mass index; IQR, inter-quartile range; LGA, large-for-gestational age; SDS, standard deviation score; SGA, small-for-gestational age.

correlation between maternal leptin concentrations and infant birth weight SDS ($r=0.073$, $P=0.181$), FMI at birth ($r=0.067$, $P=0.265$) or FFMI at birth ($r=0.043$, $P=0.476$).

Table 2 presents Spearman's correlation coefficients between cord leptin and various measurements at birth and 2 years. Cord leptin was positively correlated with weight and adiposity and showed weaker correlations with lean mass (FFM and FFMI) at birth. After adjustment for FM and FMI at birth respectively, cord leptin concentrations were no longer correlated with FFM and FFMI ($r=0.07$ and $r=0.05$, respectively, $P>0.05$ for both).

Cord blood leptin (ng/mL) was inversely associated with conditional weight gain between birth and 2 months (Table 3). There were no associations between cord blood leptin concentrations and conditional weight gain over subsequent age intervals in the first 2 years. Cord blood leptin was also inversely associated with conditional

Table 2 Correlations between cord blood leptin and measurements at birth and 2 years*.

	<i>r</i>	P-value
Weight and body composition at birth		
Birth weight SDS	0.47	<0.001
Birth length SDS	0.29	<0.001
FM (kg)	0.49	<0.001
FMI (kg/m^2)	0.48	<0.001
FFM (kg)	0.23	<0.001
FFMI (kg/m^2)	0.12	0.05
Anthropometry and leptin at 2 years		
Weight SDS	0.07	0.18
Length SDS	0.06	0.30
BMI SDS	0.02	0.79
Leptin	0.07	0.20

BMI, body mass index; FFM, fat free mass; FFMI, fat free mass index; FM, fat mass; FMI, fat mass index; SDS, standard deviation score.

*Spearman correlation coefficients.

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Table 3 Association between cord blood leptin (per ng/mL) and conditional weight gain in the first 2 year of life and conditional change in body composition in the first 2 months.

Variable	Unadjusted estimate (95% CI)	P-value	Adjusted estimate (95% CI)	P-value
Conditional weight gain				
0–2 months*	–0.023 (–0.033, –0.012)	<0.001	–0.024 (–0.035, –0.013)	<0.001
2–6 months [§]	0.002 (–0.008, 0.013)	0.673	0.002 (–0.009, 0.013)	0.738
6–12 months [§]	0.005 (–0.006, 0.017)	0.391	0.005 (–0.007, 0.018)	0.385
12–24 months [§]	0.001 (–0.011, 0.012)	0.880	0.000 (–0.013, 0.012)	0.956
Conditional change in body composition				
FMI 0–2 months*	–0.020 (–0.033, –0.007)	0.003	–0.021 (–0.034, –0.007)	0.003
FFMI 0–2 months*	–0.012 (–0.024, 0.001)	0.081	–0.004 (–0.017, 0.008)	0.484

95% CI, 95% confidence interval; FMI, fat mass index; FFMI, fat free mass index.

*Model adjusted for maternal age, maternal BMI >25 kg/m² at 15 weeks gestation, maternal tertiary level education, family income, maternal smoking during pregnancy and infant sex, gestational age, breastfeeding status at 2 months; [§]Model adjusted for maternal age, maternal BMI >25 kg/m² at 15 weeks gestation, maternal tertiary level education, family income, maternal smoking during pregnancy and infant sex, gestational age, breastfeeding status at 6 months and age (weeks) at introduction to solids.

change in FMI between birth and 2 months but was not associated with conditional change in FFMI.

Cord blood leptin concentrations were not correlated with weight, length or BMI SDS at 2 years or with 2-year leptin concentrations (Table 2). In the linear regression analysis, compared with the lowest quartile of cord blood leptin, there was no significant association between higher cord leptin concentrations and BMI SDS at 2 years in the unadjusted model or after adjustment for confounders including birth weight SDS (Table 4). Leptin concentrations at 2 years were correlated with BMI SDS at 2 years ($r=0.455$) and the median (IQR) 2-year leptin concentration was higher in those classified as overweight/obese compared with nonoverweight/obese 2 year olds (2.6 (2.0, 3.7) vs 1.8 (1.2, 2.6) ng/mL, $P<0.001$).

Discussion

We have shown that cord blood leptin is positively associated with fat mass at birth and that higher cord leptin concentrations are associated with slower conditional weight gain in early infancy, driven by lower changes in fat mass. To our knowledge, this is the first study to relate

umbilical cord blood leptin concentrations to changes in direct measures of body composition in infancy.

Consistent with findings from three other prospective studies (11, 12, 21), we found that cord blood leptin was inversely associated with weight gain in early infancy. These data suggest that unlike in adults and older children, where high leptin concentrations are indicative of leptin resistance (29), young infants are sensitive to the appetite- and weight-regulating effects of leptin. However, for the first time, we have also shown that cord blood leptin was inversely associated with changes in fat mass index (FMI), but not with changes in fat-free mass index (FFMI) in the early postnatal period. These data suggest that the influence of neonatal leptin concentrations on early postnatal weight gain is through the moderation of fat accretion.

Research into animal models has provided evidence for a number of potential mechanisms whereby lower cord leptin concentrations lead specifically to increases in fat mass. Leptin receptor expression in adipose tissue has been demonstrated in a number of species, including humans, supporting a role for leptin in adipocyte metabolism (31). Studies in rat models have shown that leptin influences adipocyte insulin sensitivity resulting in reduced glucose

Table 4 Associations between quartiles of umbilical cord blood leptin and BMI SDS at 2 years.

	Difference in mean BMI SDS at 2 years vs Q1				P-trend
	Q1	Q2	Q3	Q4	
Cord leptin, median (range) ng/mL	4.3 (0.6–<6.0)	8.1 (6.0–<10.1)	12.7 (10.2–<17.1)	24.4 (17.1–73.9)	
Model 1, unadjusted	0.000	–0.07 (–0.36, 0.21)	0.07 (–0.21, 0.35)	0.02 (–0.27, 0.30)	0.659
Model 2, adjusted for birth weight SDS	0.000	–0.19 (–0.46, 0.09)	–0.14 (–0.43, 0.15)	–0.27 (–0.57, 0.04)	0.137
Model 3, final model*	0.000	–0.22 (–0.51, 0.06)	–0.14 (–0.44, 0.16)	–0.27 (–0.59, 0.05)	0.258

SDS, standard deviation score; 95% CI, 95% confidence interval.

*Model adjusted for maternal age, maternal BMI >25 kg/m² at 15 weeks gestation, maternal tertiary level education, family income, maternal smoking during pregnancy and infant sex, birth weight SDS, gestational age, breastfeeding status at 6 months and age (weeks) at introduction to solids.

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uptake by adipocytes and decreased lipogenesis (30). We found that cord blood leptin concentrations were positively associated with weight and FMI at birth and were significantly lower in SGA infants, indicating that low cord blood leptin may reflect intrauterine growth restriction (IUGR). Attig *et al.* (31) have shown that IUGR piglets display greater increases in adiposity after weaning upon free access to food than normal-weight controls (29). The same authors have reported that the expression of leptin receptor (ObRb) among the hypothalamic nuclei differed between normal birth weight and IUGR piglets, possibly reflecting an immature stage of neuronal development. This altered pattern of expression may disrupt neuronal pathways through which leptin regulates feeding behaviour and adipocyte metabolism (31, 32). IUGR piglets were also shown to have altered adipocyte morphology and a high density of small white adipocytes at 14 days, indicating an increased capacity for lipid storage. Postnatal leptin administration to IUGR piglets starting at 2 days resulted in an adipocyte morphology similar to that of normal-weight controls, indicating that leptin treatment may correct a propensity toward excess fat deposition (31).

Two studies with repeat anthropometric measurements during infancy reported that inverse associations between cord blood leptin and weight gain persisted from birth into early childhood (11, 21). However, these studies did not report on associations between cord leptin and weight gain over intermediate age intervals during infancy, limiting the ability to identify independent critical periods. In the current study, we found no association between cord blood leptin and conditional weight gain between 2 and 6 months, 6 and 12 months or 12 months and 2 years, suggesting that cord blood leptin's influence on postnatal weight gain trajectory operates in the early postnatal period.

We found no significant association with BMI SDS at 2 years across quartiles of cord blood leptin. However, after adjustment for potential confounders including birth weight SDS, consistent inverse, but nonsignificant associations across quartiles of leptin, were observed. Two previous studies reported inverse associations between cord blood leptin and BMI in early childhood and have suggested that early-life leptin concentrations may play a role in the development of obesity (20, 21). Our ability to detect an inverse association may have been limited by our relatively small sample size.

Data on leptin concentrations throughout infancy and into childhood is limited. Unlike Mantzoros *et al.* (20), who reported that cord leptin was positively associated with leptin at 3 years, we found no association between cord and 2-year leptin concentrations. Our finding indicates that

leptin in early childhood may reflect current nutritional status rather than intrauterine exposures. This is supported by our observation that despite significantly lower cord leptin concentrations in SGA infants compared with AGA and LGA infants, there were no significant differences in 2-year leptin concentrations between the groups.

Reports on the association between maternal leptin concentrations in pregnancy and anthropometric measures at birth are conflicting (21, 33, 34), and differential effects of maternal leptin across pregnancy and between overweight/obese and normal weight mothers on fetal growth have been described (35, 36). We found a weak correlation between maternal and cord blood leptin concentrations but no correlation between maternal leptin in early pregnancy and weight and body composition measurements at birth. However, our ability to assess these relationships may have been limited due to the use of different assays to measure maternal and cord leptin concentrations and the lack of data on maternal concentrations beyond the first trimester. In agreement with previous reports, maternal obesity was associated with higher maternal (35, 37) and cord (34, 36, 38, 39) leptin concentrations. Maternal contributions to fetal leptin concentrations are believed to be minimal, with fetal leptin concentrations mainly derived from synthesis in fetal adipose tissue (40). Studies have shown that increased circulating maternal leptin concentrations and a high maternal BMI are associated with greater mobilisation of nutrients *in utero* and higher fetal plasma glucose and insulin concentrations, leading to increased fetal adiposity and leptin synthesis (41).

In the current study, those who were overweight/obese at 2 years had higher 2-year leptin concentrations than nonoverweight/obese children. Data from a number of studies suggest that a reversal in the association between leptin and growth occurs early in childhood (42, 43, 44). Among participants of Project Viva in the US, cord blood leptin was inversely associated with BMI SDS at 3 years, while higher 3-year leptin concentrations were associated with greater weight gain between 3 and 7 years and a higher BMI, waist circumference and fat mass at 7 years (44). Thus, the higher leptin concentrations observed in overweight/obese children at 2 years in the current study could potentially be a reflection of leptin resistance, which may lead to greater weight gain and adiposity in later childhood.

To our knowledge, this is the first study to relate cord leptin to changes in direct measures of body composition in early infancy. Other strengths of this study include its prospective design, the availability of data on a number of pre- and perinatal factors, including maternal leptin

concentrations in early pregnancy, and the multiple follow-up assessments during infancy. However, we acknowledge that there are a number of potential limitations. Our sample size was small relative to the initial cohort and only 66% of this subset had available measures of body composition in early infancy, representing the possibility of bias and/or imprecision. Despite this, the current study cohort did not differ significantly from the remainder of the cohort regarding exposure and outcome measures or major sociodemographic characteristics. Other study limitations include that maternal prepregnancy BMI was not available, that infant feeding was not quantified and that direct body composition measurements were not available beyond 2 months.

In conclusion, we have shown, in a well-characterised birth cohort, that umbilical cord blood leptin is positively associated with direct measures of adiposity at birth and inversely associated with conditional weight gain in the first 2 months of life, which is largely driven inverse associations with changes in adiposity. Fetal and early postnatal life have been identified as particularly sensitive periods of development, during which disturbances can result in long-term metabolic consequences, 'programming' later disease risk (45). Lower neonatal leptin may represent one of the mechanisms underlying the association between an altered intrauterine environment, rapid postnatal weight gain and subsequent obesity risk. As we examined conditional change in weight and body composition, the magnitude of the effect of cord blood leptin on weight gain and changes in adiposity in early infancy is difficult to interpret. Nevertheless, we have shown that higher cord leptin concentrations play a role in moderating fat accretion in early infancy. Longitudinal data on body composition beyond infancy would allow for the examination of whether this association with adiposity persists and for the determination of any clinical significance. Further investigation into the determinants and long-term consequences of neonatal and early-life leptin concentrations is required.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

M K and C ní C conceptualised and designed the study, completed the statistical analysis and drafted the manuscript. M K was responsible for

the final content. C ní C carried out the biochemical analysis and database construction. The Cork BASELINE Birth Cohort Study is a multidisciplinary collaboration led by D M M (Principal Investigator), M K, J O'B H, A D I and L C K. L C K is the Principal Investigator of SCOPE Ireland. All authors read and approved the manuscript before submission.

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