Childhood Obesity and Slipped Capital Femoral Epiphysis

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Abbreviations: SCFE is Slipped Capital Femoral Epiphysis, otherwise known as Slipped Upper Femoral Epiphysis.

Table of Contents Summary: A study providing the most robust evidence to suggest a causal association between Slipped Capital Femoral Epiphysis and childhood obesity.

What's Known on this Subject: An association between SCFE and childhood obesity has long been suggested, though there have been no robust attempts to explore this association. The current evidence for this is almost exclusively based on small low-quality case series from specialist centres.

What this study adds: Using 600,000 children with BMI collected routinely, and 4.25 million years of follow-up, this study provides the most robust evidence to support a causal association between obesity and SCFE - a strong association, a temporal relationship, and a marked dose-response.

Contributions

Daniel Perry conceived the study, sought permissions to access the data, performed the analysis, wrote the primary draft of the paper and contributed to development of the final manuscript.

David Metcalfe contributed to the analysis and contributed to the development of the final manuscript.

Steven Lane offered advice regarding the analysis and interpretation of data, and contributed to development of the final manuscript.

Steve Turner contributed to the design of the study, offered advice regarding the analysis and interpretation of data, and contributed to development of the final manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Abstract

Background.
Slipped Capital Femoral Epiphysis (SCFE) is believed to be associated with Childhood Obesity, although the strength of the association is unknown. There is little evidence to suggest if this association is causal.

Methods
We performed a cohort study using routine data from a nationwide childhood heath screening examination at primary school entry (5-6 years old) at schools in Scotland, linked to a nationwide admissions database. A subgroup of children also had BMI recorded at exit from primary school (11–12 years old).

Results
BMI was available for 597,017 children at 5-6 years old school, and 39,468 at 11-12 years old. There were 4.26 million child-years at risk for SCFE. Amongst children obese at 5-6 years old, 75% remained obese at 11-12 years old. There was a very strong biological-gradient between childhood BMI at 5-6 years old and SCFE, with the risk of disease increasing by 1.7 (95% CI 1.5-1.9) for each integer increase in z-score of BMI. There risk of SCFE was almost negligible amongst children with the lowest BMI. The severely obese at 5-6 years old had 5.9 (95% CI 3.9-9.0) times greater risk of SCFE compared to those with a normal BMI, and the severely obese at 11-12 years had 17.0 (95% CI 5.9-49.0) times the risk of SCFE.

Conclusion
High childhood BMI is very strongly associated with SCFE. The magnitude of the association, temporal relationship, dose-response, added to the plausible mechanism, offer the strongest evidence available to support a causal association.

Introduction

Childhood obesity is a global problem and a major cause of lifelong morbidity[3]. The WHO report on ending childhood obesity highlighted a lack of awareness of the consequences of childhood obesity[4]. Long-term outcomes of childhood obesity are well-described[5-8], however there is poor understanding of short-term outcomes that may cause early childhood disability. Slipped Capital Femoral Epiphysis (SCFE) is a disease of the growth plate (physis) that causes profound lifelong disability and is believed to be caused by obesity[9-14]. Although an association between SCFE and childhood obesity has been suggested[14], this has not yet been definitively demonstrated. Clarifying the relationship between SCFE and childhood obesity has been identified as a priority for the American Academy of Orthopedic Surgeons (AAOS)[15].

SCFE alters the shape of the hip resulting in bone impingement and is one of the most common reason for hip replacement surgery in adolescence and early adulthood[16]. It affects 1 in 1,300 individuals during childhood[17], typically requires urgent surgery, and often results in deformity. Early detection and surgery can minimize the severity of deformity, although the disease frequently goes undetected for many months, often because the pain poorly localizes to the thigh or knee creating confusion for children, parents, and clinicians alike[17,18]. Diagnostic delays worsen clinical outcomes and can have significant medico-legal consequences for a range of clinicians[18].

The current evidence for an association between SCFE and childhood obesity arises from observations of increasing SCFE incidence rates coupled with rising childhood obesity[10,11], and retrospective case series from specialist centres[12-14,19]. We sought to define the strength of this association using a nationwide population cohort study so

determine whether or not there is evidence for a causal relationship between obesity and SCFE.

Methods

Study Design, Setting and Population

This was a historic cohort study using linked healthcare datasets within Scotland. The cohort was formed from two sources of routine universal childhood height and weight measurements at primary school entry (5-6 years old).

Cohort 1 comprises the Study of Trends in Obesity in North East Scotland (STONES) collected from the Grampian region of Scotland, which represents approximately 10% of the Scottish population. Information was collected from 1970 onwards. The Scottish Community Health Index (CHI) number, which is a unique identity number amongst all Scottish residents, was collected for children born after 1992. Prior to 1992, children were matched to other datasets based upon initials, sex and date of birth. This population has been described previously[20].

Cohort 2 comprises the Child Health Systems Programme (CHSP-P1), which is a nationwide child health surveillance programme. CHSP-P1 began in 1995, and encompassed all of Scotland by 2003. The CHI number was collected throughout.

Both cohorts were linked to the Scottish Morbidity Record (SMR01) to December 2016. SMR01 is an episode-based record relating to inpatients and day cases discharged from all Scottish hospitals. SMR01 was computerised in 1968, and has been used for the financial management of hospitals since 1989. On-going data quality assessment

through periodic random sampling by NHS Scotland demonstrates high data quality with an accuracy of 89.0% (95%CI 87.9-90.1%) for the main conditions coded within SMR01[21].

Study Variables

Height and weight of children was routinely recorded at school entry (5-6 years old) to monitor obesity trends across Scotland. Measurements were carried out by school nurses, though no information was available on measurement equipment. Other variables were sex, exact age of entry into the cohort, year of cohort entry, and after 2001, an area-based quintile measure of socioeconomic status (Carstairs 2001).

For a sub-group of children, their height and weight was additionally recorded at exit from primary school (aged 11-12 years old) in a linked child health surveillance programme (CHSP-P7).

Outcome Measures

Within SMR01 we sought an electronic diagnostic record representing SCFE (ICD-10 M93.0* [Slipped upper femoral epiphysis] or ICD-9 732.2 [Unspecified slipped upper femoral epiphysis]). Cases were restricted to codes recorded at age >5 years old and <18 years old, i.e. the period 'at risk of SCFE'. Previous work in England using the SCFE ICD-10 code in linked-databases has demonstrated it to be specific for the identification of SCFE[17]. The first date of diagnostic code entry within the medical record was considered the index date. An individual could only contribute one SCFE diagnosis as laterality was not coded, so it would have been unclear whether additional

SCFE diagnosis codes truly represented a contralateral event, or a secondary admission related to the initial diagnosis (e.g. removal of metalwork).

Children contributed to follow-up until they (a) reached age 18 years old, (b) received a diagnosis of SCFE or (c) were censored in December 2016 when data were extracted.

Statistical Analyses

BMI was calculated and expressed as a z-score of the UK 1990 reference population (UK90), adjusted for age and sex[22]. The transformation of BMI data to z-scores was performed using the LMS method and the zanthro package within Stata 14.1[23]. Z-scores are a measure of how many standard deviations a score varies from the mean. There is debate around the clinical cutoff definitions for obesity in children, however to aid interpretation BMI was categorised according to cutoffs recognised by both UK90 and the Center for Disease Control and Prevention CDC[24-26] (underweight<5th percentile, normal weight 5th-85th percentile, overweight ≥85th percentile, obese ≥95th percentile). We further stratified obesity as mild/moderate obesity (≥95th-99th percentile), and severe (morbid) obesity (≥99th percentile). Z-scores were converted to the clinical cutoff BMIs to improve clinical relevance and interpretation (i.e. ≥95th centile equates to a z-score ≥1.645).

During data cleaning, any height or weight recorded as '0' was replaced with 'missing'. All data were explored graphically, which initially identified a decimal error in one year of source data for height/ weight, which was addressed. A height or weight outside ±5 SDs were excluded as that these were likely to be spurious (height n=311, weight

n=1,159), which has been the approach previously used in the interpretation of these datasets[20].

The analysis was conducted using Stata 14.1 (StataCorp, College Station, TX, USA). The incidence of SCFE was calculated and stratified according to BMI at primary school entry and exit (where available). Poisson confidence intervals were calculated for rate estimations.

A Cox proportional hazards regression model was fitted to estimate the SCFE hazard using the covariates age of cohort entry, sex, quintile of socioeconomic deprivation (e.g. from most affluent [first quintile] to least affluent [fifth quintile]), and z-score for BMI. The relationship between Schoenfeld residuals and event time was examined to formally test the proportional hazards assumption. Deprivation was considered within the analysis due to the known association between deprivation and obesity[20]. The measure of area deprivation used was the 2001 Carstairs score expressed as quintiles[27], and fitted as a categorical variable. Carstairs is an area-based measure of material deprivation routinely used by the Scottish Government that includes measures of unemployment, car ownership, overcrowding, and social class. Scores are assigned to postcode sectors, with the mean population in each postcode sector being 5,012 individuals. Quintile 1 represents the most affluent and quintile 5 the least.

The cumulative age to SCFE diagnosis was examined by separating data into $\geq 85^{th}$ percentile (i.e. overweight and obese children) and $<85^{th}$ percentile (i.e. underweight or normal). The categories were compared using log-rank tests for equality of survivor functions.

The study protocol, data request application and Stata code are available as supplementary material. Reporting is in line with the REporting of studies Conducted using Observational Routinely-collected Data (RECORD) statement. Raw data is not available to be shared owing to the terms of the data sharing agreement. The threshold for statistical significance was $p<0.05$.

Results

The cohort included routine health records of 615,950 children 5-6 year old children at school entry. BMI could be calculated in 597,017 (97%) children, of whom 11.9% were overweight and 9.2% obese. The mean age of cohort entry was 66.2 months (5 years and 6 months, IQR 63.0 to 72.0 months). Total follow-up amongst children for whom the BMI was known in the SCFE risk period (between 6 and 18 years old), was 4.26 million years. Mean follow-up was 7-years, 1-month.

A screening examination at exit from primary school (11-12 years old) was available amongst 39,468 of children from the initial cohort. BMI was available for 38,458 children at both school entry and exit. BMI was broadly consistent at both time points (Table 1). Of the 3,973 children obese ($\geq 95^{th}$ percentile) at 5-6 years old, 2,963 (75%) remained obese at 11-12 years old. Amongst those that were overweight (n=5,086) at 5-6 years old, 39% were obese at 11-12 years old. This was in contrast to those that were underweight ($<5^{th}$ percentile) at 5-6 years old (n = 973), of whom 2% were obese at 11-12 years old.

During the follow-up period 209 children received a diagnosis of SCFE. BMI was available for 195 of these children at 5-6 years, and was also available for 32 children at 11-12 years old. One case was excluded because weight was >5 standard deviations above the population mean and likely spurious. SCFE diagnoses were recorded in 117 males and 92 females (5:4 male:female).

Crude incidence of SCFE was 4.7 (95% CI 4.1-5.4) per 100,000 6-18 child years of risk, although the crude incidence rate is an underestimate as the cohort had an uneven distribution of follow-up. The cohort expanded in recent years, which resulted in disproportionately greater numbers of children with shorter follow-up. The age of SCFE onset is known to be non-uniform across childhood, with the peak age at diagnosis amongst 11-year-olds (incidence of 13.4 (95% CI 10.0-17.7) per 100,000 child years) (Online Table 1). The incidence adjusted to the age structure of the European Standard Population was 5.45 (95% CI 4.8-6.1) per 100,000 6-18 child years of risk[28].

There was a strong association between BMI at 5-6 years old and SCFE. The incidence rate ratio for SCFE increased by 1.7 (95% CI 1.5-1.9; $p<0.001$) for each integer increase in z-score of BMI (Figure 1). Of the children who developed SCFE, 59 (30%) were obese at 5-6 years old and 25 (13%) children were overweight. The incidence rate ratio for developing SCFE compared to normal weight children at 5-6 years old was 5.9 (95% CI 3.9-9.0) amongst severely obese children, 3.8 (95% CI 2.6-5.8) amongst mild or moderately obese children and 1.5 (95% CI 0.9-2.3) amongst overweight children (Table 2). Assuming that this association between SCFE and obesity was causal, the proportion of SCFE cases that would be eliminated if the BMI of the entire population

were to fit within the 5-85th BMI percentile range defining 'normal' (i.e. the attributable risk or excess risk, which is the difference in disease rates between an exposed population and an unexposed population) is 78% amongst obese children and 31% in overweight children.

Figure 1

Amongst the smaller subpopulation of children from whom BMI was available at exit from primary school (aged 11-12 years old), there were 32 children with SCFE. The magnitude of the association at 11-12 years old was even stronger (Table 2). The incidence of SCFE in the obese 11-12 year olds was 23.8 (95% CI 14.8-36.4) per 100,000 6 to 18 child years of risk, compared to 1.9 (95% CI 0.6-4.5) per 100,000 6 to 18 child years amongst those of normal weight (risk ratio 12.3 (95% CI 4.6-32.6)). The risk in the severely obese was greatest, with the risk of SCFE being 17.0 (95% CI 5.9-49.0) times greater in this group compared to those with normal BMI. Of these children with SCFE, 26 (aproximately 80%) were overweight or obese compared to 35.8% in whole population of 11-12 year olds.

The age of SCFE diagnosis was significantly lower amongst those overweight or obese. Overweight and obese children were diagnosed 1-year earlier than children normal or underweight ($p<0.002$) (Figure 2). The age of disease onset decreased by 3.3 months (95% CI 0.5-6.0, $p=0.02$) with each integer increase of BMI z-score.

Figure 2

Carstairs score was available for 495,954 children (of whom 130 were affected by SCFE) and the incidence of SCFE was lowest in the most affluent quintile (Online Table 2). Those in the three most deprived quintiles had a similar risk of SCFE.

The Cox proportional hazards model used the covariates age of cohort entry, sex, quintile of socioeconomic deprivation, and z-score for BMI. Only the z-score for BMI and deprivation score contributed significantly (Table 3).

Discussion

We identify a very strong association between childhood obesity and SCFE; with increasing childhood BMI both increasing the risk and reducing the age of disease-onset. Obesity was recorded before any child was affected, which indicates that the association was temporal. Even children of "normal" weight are at risk of SCFE, though notably less than those overweight or obese children. Children with the lowest BMI at 5-6 years old had an almost negligible lifetime risk of SCFE, those with a normal BMI had an approximate risk of 1:2500, those overweight had had an approximate risk of 1:1750, those with mild and moderate obesity had a risk of 1:650, and those with severe obesity had a lifetime risk of SCFE in the order of 1:450. Although there was less data available for children at 11-12 years old, obesity at this age had the strongest association with SCFE, with the lifetime risk amongst severely obese being 17.0 (95% CI 5.9-49.0) times greater than those with a normal BMI; equating to a lifetime risk of approximately 1:250. This study also supports longitudinal studies that have suggested obesity at primary school entry (kindergarten) is intimately associated with obesity later in childhood[29].

Mechanical studies have demonstrated that childhood obesity may generate forces sufficient to overcome the yield point of the physis[30]. The peak age of SCFE is around puberty and rapid growth of the bone is believed to lower the mechanical yield point for physeal injury. It appears that obesity around puberty, rather than earlier in childhood, is the most important time-point in the development of the disease. SCFE histologically occurs through the zone of hypertrophy which is the location at which the supporting matrix of the physis is particularly redundant[31]. There is therefore biological plausibility through a mechanical disease mechanism for obesity causing SCFE.

Prior case series from specialist centers have suggested an association between SCFE and obesity[12,13,19], although these studies suffered from referral bias and poor generalizability to the wider population. Furthermore, the temporal relationship between disease and obesity has been difficult to establish; i.e. did children become obese due to hip disease or did hip disease develop due to obesity? The only prior cohort study of SCFE used a healthcare cohort from family medicine[17], which found that pre-disease BMI was 1.43 (95% CI 1.20-1.68) standard deviations above the mean. However, this study did not standardize the timing of BMI measurement, was unable to determine a dose-response, had no controls, used a healthcare population, and was prone to bias because BMI was more likely to be recovered amongst unhealthy individuals.

The age and sex-distribution of SCFE in this study was consistent with prior studies[19,32], and incidence rates were comparable to those identified in England and Wales (incidence 4.8; 95% CI 4.4-5.2 cases per 100,000 0-16 year olds)[17] and in Scotland[10].

The relationship with socioeconomic deprivation has previously been proposed as a risk factor for SCFE[17], although worsening deprivation and increasing childhood obesity are known to be intrinsically linked in the UK[33]. Even after adjusting for obesity, socioeconomic deprivation remained an independent risk factor. However, the relationship between the two is so intertwined that they may be difficult to adequately separate, particularly using area-based measures of deprivation, which may introduce an ecological fallacy.

This study has many strengths compared to previous attempts to understand the association between obesity and SCFE, though there are still limitations. We were unable to quantify the effects of ethnicity as this was poorly recorded within the dataset. However, the population of Scotland in the 2011 census was 96.0% White[34], and so unless ethnicity exerted an overwhelming effect, it's availability would be unlikely to help discern small difference in disease vulnerability. No adjustment was made for co-morbid disease associations, however a previous cohort identified from health records failed to find any strong evidence for an association with other childhood diseases[17]. We did not account for children dying or leaving Scotland, although this is unlikely to introduce bias as this is a non-directional effect related to obesity. A small number of children for whom measurements were beyond 5 standard deviations from the mean were excluded to remove spurious data, but some genuinely extreme values of BMI may have been falsely excluded. We cannot be certain regarding the exact sensitivity and specificity of the diagnostic codes used, although previous work has suggested that they are reliable[17].

The reduced age-of-onset in obese children is a novel finding. It is conceivable that

diagnoses may be more readily made, and therefore made sooner, in obese children owing to a clinician's heightened awareness of disease in this group. However, SCFE generally causes marked pain or a limp and is diagnosed based on clear radiographic findings. It is therefore unlikely that obese children are over-diagnosed or non-obese children are under-diagnosed. Two biological explanations are that obesity may lower the age of puberty and advance skeletal maturation, which may therefore account for the earlier SCFE age-of-onset amongst obese children[35], and that a greater mechanical load may trigger earlier physeal failure in obese children.

A confounding relationship is an alternative explanation for the observed effect between obesity and SCFE, i.e. a factor that is independently associated with both obesity and physeal failure. Abnormalities in serum leptin has been suggested as a possible independent risk factor for SCFE, with the suggestion that this may be a confounder[36]. However, the positive association between leptin and obesity more likely suggests that leptin is a disease mediator, or simply a proxy measure of 'obesity exposure'[37].

We demonstrate that childhood obesity is a major risk factor for the development of SCFE. The temporal relationship, dose-response, and magnitude of the association build on the existing biological plausibility and findings of previous lower-quality studies to offer the strongest possible support to a causal relationship between childhood obesity and SCFE.

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Figure 1 – A bar chart to illustrate the incidence of a diagnostic record of SCFE by BMI z-score at 5-6 years old. Bars represent the annual incidence rate with 95% exact Poisson confidence intervals. The smooth line represents disease predicted incidence with a Poisson regression line.

Figure 2 - A cumulative age to diagnosis curve, stratified by BMI z-score at 5-6 years old. ≥85th percentile = overweight and obese children). <85th percentile = underweight or normal).

Table 1 - Age and sex adjusted z-score for BMI expressed in percentile cutoffs at 11-12 years old, based on adjusted z-score BMI cut-offs at 5-6 years old.

BMI percentile at 11-12 years old	**UK90/ CDC Classification**	**Number of children**	**Percentage**
Children UNDERWEIGHT at 5-6 Years old (<5th percentile)			
<5th percentile	Underweight	302	31%
5th to 85th percentile	Normal Weight	615	63%
85th to 95th percentile	Overweight	37	4%
≥95th percentile	Obese	19	2%
Children of NORMAL weight at 5-6 Years old (5th to 85th percentile)			
<5th percentile	Underweight	843	3%
5th to 85th percentile	Normal Weight	20,816	73%
85th to 95th percentile	Overweight	3,762	13%
≥95th percentile	Obese	3,005	11%
Children OVERWEIGHT at 5-6 Years old (85th to 95th percentile)			
<5th percentile	Underweight	8	0%
5th to 85th percentile	Normal Weight	1,772	35%
85th to 95th percentile	Overweight	1,329	26%
≥95th percentile	Obese	1,997	39%
Children OBESE at 5-6 Years old (>95th percentile)			
<5th percentile	Underweight	3	0%

5th to 85th percentile	Normal Weight	407	10%
85th to 95th percentile	Overweight	600	15%
≥95th percentile	Obese	2,963	75%

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Table 2 - The incidence of diagnosis of SCFE, stratified by BMI at 11-12 years old per 100,000 6 to 18 child years of exposure.

Age of measurement	z-score for BMI	Cases of SCFE	Years at Risk	Incidence of SCFE per 100,000 population (95% CI)	Incidence Rate Ratio (95% CI)
5-6 years old	Underweight (<5th percentile)	2	169839	1.2 (0.1–4.3)	0.4 (0.1–1.4)
	Normal (5th to 85th percentile)	108	3212182	3.4 (2.8-4.1)	1.0 (Ref)
	Overweight (85th to 95th percentile)	25	509586	4.9 (3.2-7.2)	1.5 (0.9–2.3)
	Obese (All) (≥95th percentile)	59	381109	15.5 (11.8-20.0)	4.6 (3.4 – 6.3)
	Mild/ Moderate Obesity (≥95th to 99th percentile)	32	244490	13.1 (9.0–18.5)	3.8 (2.6–5.8)
	Severe Obesity (≥99th percentile)	27	136619	19.8 (13.0-28.8)	5.9 (3.9–9.0)
11-12 years old	Underweight (<5th percentile)	1	12855	7.8 (0-43.3)	4.0 (0.5-34.4)
	Normal (5th to 85th percentile)	5	258453	1.9 (0.6-4.5)	1.0 (Ref)
	Overweight	5	62791	7.9 (2.6-18.5)	4.1 (1.2-14.2)

	(85th to 95th percentile)				
	Obese (All) (≥95th percentile)	21	88159	23.8 (14.8-36.4)	12.3 (4.5 – 41.8)
	Mild/ Moderate Obesity (≥95th to 99th percentile)	10	54757	18.3 (8.8–33.6)	9.4 (3.2-27.6)
	Severe Obesity (≥99th percentile)	11	33402	32.9 (16.3-58.5)	17.0 (5.9-49.0)

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Table 3 – Cox proportional hazards regression model demonstrating predictors of SCFE. The co-variables used in the final model were BMI z-score and quintiles of socioeconomic deprivation as other co-variables (cohort entry and sex) did not contribute to the model.

Descriptor		**Odds Ratio (95% CI)**	**P-value**
Z-score for BMI at 5-6 years old (per integer increase)		1.75 (1.51-2.02)	<0.001
Deprivation			
	1 - Most Affluent	1 (ref)	
	2	1.75 (0.85- 3.63)	0.13
	3	2.59 (1.31- 5.09)	0.006
	4	2.24 (1.13- 4.44)	0.021
	5 - Least Affluent	2.50 (1.23- 5.07)	0.012