Predictors of adults' body mass index and the association with index child's infant birth weight, in the Lifeways Cross-Generation Cohort Study of a thousand families in the Republic of Ireland

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The Lifeways study is novel in having information on three generations of the same families. It is well established that infant birth weight (IBW) predicts individuals' risk of adult chronic disease and more recently studies report cross-generation transmission of risk patterns. The aims of this analysis were to examine whether adults' birth weights were associated with measures of own health status or social position and to relate adults' birth weights to that of the index child's IBW. Finally, we assessed whether birth weight of either adults or children was associated with adult body mass index (BMI) of parents and grandparents. We included 1075 children whose IBW was recorded at recruitment from hospital records and 2546 adult cohort members followed from 2001 until 2014. At baseline, a sub-group of 920 adults had reported own birth weight (RBW). Results showed male adults' RBW were significantly higher than females' ($P = 0.001$). Mothers' RBW was significantly correlated with IBW ($r = 0.178$, $P < 0.001$). In mixed effects linear models with BMI as the outcome variable, of all adults, and in sub-groups of adults with RBW and of mothers only, the IBW was associated with adult BMI adjusting for other predictors. Adults' BMI was positively associated with age ($P = 0.013$), index child's IBW ($P = 0.001$), gender ($P < 0.001$) but not own RBW, adjusting for family identification number. When mothers were removed from the adult models however, IBW ceased to be associated with BMI, a final model showed RBW being associated with adult BMI ($P = 0.04$). There are cross-generational associations in the Lifeways cohort, the maternal association being stronger.

Introduction

There has been increasing interest in life-course and cross-generation transmission of risk in relation to adult chronic diseases since Barker *et al.* first renewed attention on the issue.[1–5] Much work in this area has focused on associations between infant birth weight (IBW) and subsequent adult health status and mortality,[2] birth weight being seen both as the completed outcome of a pregnancy, but also as a general proxy for early life experience linked to longer-term outcomes in adulthood. Two analyses for instance from the large Nurses' Health Study in the United States[3,4] contrast the influence of birth weight on long-term health outcomes such as diabetes and coronary heart disease. Birth weight was strongly inversely associated with type 2 diabetes in adulthood, after adjustment for adult body mass index (BMI). Higher BMI in adulthood was also a strong risk factor for coronary heart disease among women who were small at birth. Other studies have shown a positive association between birth weight and later life BMI.[6,7] A recent umbrella review of systematic reviews and meta-analyses on IBW and long-term health outcomes,[2] cautions on the consistency of the evidence base in relation to IBW in itself.

The Lifeways cross-generational cohort study was designed *a priori* to examine associations across generations and it affords the opportunity of relating birth weight in cohort members to measures of health status across the life course.[8–12] It is one of the very few studies with three generations followed prospectively. In previous published analyses we have shown that BMI in children at three age points is consistently associated with BMI in the adult maternal line, whereas height shows associations in both lineages.[10] We have also shown that family dietary patterns aggregate most strongly in the maternal line[11] and that maternal macronutrient intake in pregnancy is associated with children's BMI aged 5.[12] Our objectives in this current analysis were to identify whether patterns of association existed for birth weights across generations, employing index child's measured IBW and data on reported birth weights (RBW) of all adults in this cohort, linked to adults' current health and social status. We further sought to identify whether index child's IBW, as a proxy for intrauterine growth and development, was associated with adult cohort members' characteristics, including in particular with adult BMI, as a measure of potential morbidity in those adults.

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Methods

The Lifeways cross-generation cohort study was established in 2001 and its methodology has been described previously.[8,9] In brief, expectant mothers were recruited in two maternity hospitals in the East and West of Ireland during first hospital booking visit and at baseline completed a questionnaire. They were asked to include in the study their proband infant, the father if available and at least one of four potential grandparents. There are up to six adult lineages in the study, mothers, fathers, maternal grandmother (MGM), maternal grandfather (MGF), paternal grandmother, paternal grandfather (PGF) and a seventh lineage of index children from birth onwards. Families have been followed up since then, when index children were subsequently born, and were aged 3, aged 5 and aged 9. IBW and gestational age were recorded from hospital records for index children.

At baseline in a self-completed health status questionnaire in 2001–2003, adults RBW as well as social and lifestyle indicators such as whether they smoked or not, their level of education and their accommodation status. BMI in all adults was initially self-reported or measured at baseline. For mothers, BMI was again measured at a 5-year follow-up of the child, and for fathers it was self-reported. In 2011, a number of the East-based grandparents' BMI was measured at a 10-year follow-up cardiovascular examination. For the purpose of this analysis, where more than one reported BMI for adults was available, it was decided to take the most recent BMI reported or measured, with priority given to measured variables, as previously this has shown to be a more accurate record.[13]

The purpose of the first part of the analysis was to examine whether RBW in adults was associated with their adult lifestyle risk factors or measures of social status, using a categorical analysis. RBW was divided into three categories (low being <3 kg, normal 3 kg to ⩽ 4 kg and high as >4.0 kg). We took 3 kg as the cut-off for the lower birth weight category as that has been associated in a systematic review with subsequent development of type 2 diabetes.[14] We included measures of social position likely to relate to birth weight from the baseline adult questionnaire (e.g. education and accommodation status) and lifestyle (e.g. smoking and BMI) in the analysis, as well as sex. BMI was categorized into low/normal ($<25 \text{ kg/m}^2$), overweight ($25-⩽30 \text{ kg/m}^2$) and obese ($>30 \text{ kg/m}^2$). Smoking status was based on two categories: 'Have you ever smoked?' answering 'yes or no'. The education and accommodation variables were divided, respectively, into three groups; 'no schooling/completed primary school', 'completed secondary school' and 'completed third-level education'; those adults who lived in 'detached houses', were compared with those who lived in 'semi-detached/mid-terrace' housing and those who lived in 'apartments/flats/other'. χ^2 Tests were carried out as appropriate.

The second part of the analysis aimed to look at the relationship between birth weights of all family members, including adults and index children. The index child's IBW, taken from recorded hospital data was correlated separately to each individual adult RBW (e.g. infant v. mother, infant v. MGM). We employed Pearson's correlations and also applied a Bonferroni's correction to account for multiple testing.

The next part of the analysis examined adult BMI as an outcome variable relative to own RBW or IBW or both, in mixed models which also included adult respondents' age, up to seven family lineage groups and adult respondents' educational status. We treated adult BMI as an indicator of potential morbidity in adults and wished to see whether it related to own RBW or was associated with the index child's IBW as a measure of cross-generation association. We also wished to assess whether the mother's relationship with IBW contrasted with that of other adult cohort members. A number of multilevel mixed effects linear regression models were performed with family identification number, which is a common shared variable for all family members, as a random effect included in the models. The first model in all adults included IBW only, the second included IBW and also RBW for adults with available data and the third model was confined only to mothers, including their own RBW and IBW. The next model included just IBW and adults other than mothers. The final adjusted model looked at both IBW and RBW in adults, excluding mothers. Index child's gestational age was adjusted for in all models.

As BMI was not normally distributed, different ways of transforming the data were examined and the inverse BMI seemed to fit the data best. However, as the results using inverse BMI were very similar to the non-transformed BMI, it was decided to show the non-transformed BMI results for ease of interpretation. Numbers of adults differ for different analyses due to missing values for covariates. Only adults with a singleton child were included in the analyses. All analyses were performed using the STATA statistical software package (version 13). All P-values were based on two-sided tests and considered statistically significant if <0.05.

We performed an analysis to identify whether the sub-sample of adults with RBW data differed significantly from other sub-samples randomly drawn from the larger data set. All samples were similar in respect of mean age, mean BMI, mean waist circumference and educational level. Those with RBW tended to have less reported morbidity, more likely to be General Medical Services means-tested medical card eligible and ever smokers, but the differences were small.

Results

The descriptive data for all adults, 1328 parents and 1218 grandparents, included in the analysis are reported in Table 1. The mean self-RBW of all adults ($n = 920$ with data available) was 3.37 (S.D. = 0.70) kg. The index child's IBW ($n = 1075$ with data available) was 3.51 (S.D. = 0.58) kg and gestational age in weeks was 39.9 (S.D. 1.8), with data available for 959 children.

Table 2 shows patterns for RBW in adults split into three categories. Males reported significantly higher birth weights

Table 1. *Descriptive statistics of parents and grandparents in the Lifeways Cross-Generation Cohort Study* (n = 2546)

	Parents (men and women)				Grandparents (men and women)			
	n	%	Mean	S.D.	*n*	%	Mean	S.D.
Age (years)	1328		31.9	6.1	1218		60.5	9.6
Sex								
Male	489	30.5			653	40.7		
Female	1113	69.5			953	59.3		
Family lineage								
MGM	N/A				564	35.1		
MGF					381	23.7		
PGM					389	24.2		
PGF					272	16.9		
Reported birth weight (g)	761		3336	669	159		3498	976
Reported birth weight, categories								
<3.0 kg	194	25.5			37	23.3		
3.0 to ⩽ 4.0 kg	466	61.2			85	53.5		
>4.0 kg	101	13.3			37	23.3		
BMI (kg/m^2)	1329		24.8	4.5	1223		28.3	5.4
BMI categories								
Low/normal (<25 kg/m^2)	788	59.3			318	26.0		
Overweight (25– < 30 kg/m^2)	372	28.0			513	42.0		
Obese (⩾30 kg/m^2)	169	12.7			392	32.1		
Ever smoked								
Yes	853	60.1			580	48.8		
No	566	39.9			608	51.2		
Education								
No schooling/completed primary school	338	21.7			1059	70.6		
Completed secondary school	465	49.0			335	22.3		
Completed third level	457	29.3			106	7.1		
Accommodation								
Detached	544	38.4			312	45.8		
Semi-detached/terrace	780	55.1			341	50.1		
Apartment/flat/other	93	6.6			28	4.1		

MGM, maternal grandmother; MGF, maternal grandfather; PGM, paternal grandmother; PGF, paternal grandfather; BMI, body mass index.

than females (*P* = 0.006), a higher percentage of males are seen to be in the higher birth weight category, when compared with females. Table 2 also shows the relationship at uni-variate level between adult characteristics and self-RBW. RBW had no significant association with whether a person had ever smoked in their lifetime, as well as no significant relationship with BMI or accommodation. However, education showed a significant u-shaped association where adults who completed third-level education were relatively less likely to be in the low or high birth weight categories.

Table 3 shows the correlation matrix for IBW and adults' RBW. There was a significant association overall between maternal RBW and IBW and for both sexes of children. There was a borderline significant association between MGM's RBW and that of her daughter. The PGF also showed some inverse associations, but with very small numbers. When Bonferroni's corrections were applied, only the relationship between maternal RBW and IBW overall (*P* = 0.0002) and for male

IBW were significant (*P* = 0.0084). No other correlations were significant. Figure 1 presents the scattergram for maternal RBW and IBW.

The results of the multilevel models for adults' BMI are given in Table 4. This showed expected significant associations between both education status and lineage and BMI, but also that the IBW was significantly associated with adult BMI (*P* = 0.0042). In the multi-level mixed effects linear regression model which then included adults' RBW also (*n* = 728), age was significantly associated with adult BMI (0.030), as well as IBW (0.004). The older a person was and the higher the IBW, the higher the adult BMI. However adults' own RBW had no association with BMI. Mothers had significantly lower BMI relative to fathers (acting as the reference group).

In the next model, confined to maternal lineage only (*n* = 483), again the IBW was associated with maternal BMI, with an effect of maternal education also, mothers with

Table 2. *Univariate analysis of adults' reported birth weight* v. *adult risk factors in the Lifeways Cross-Generation Cohort Study (*n = *920)*

	Birth weight categories			
	Low [< 3.0 kg , n (%)[a]]	Medium [3.0 to ⩽ 4.0 kg, n (%)[a]]	High [> 4.0 kg, n (%)[a]]	χ^2 (P-value)
% Within birth weight range				
Ever smoked				1.66 (0.435)
Yes	129 (56.3)	316 (58.0)	87 (63.0)	
No	100 (43.7)	229 (42.0)	51 (37.0)	
Education status				12.60 (0.013)
No schooling/completed primary school	65 (28.6)	139 (25.6)	48 (35.3)	
Completed secondary school	113 (49.8)	239 (43.9)	61 (44.9)	
Completed third level	49 (21.6)	166 (30.5)	27 (19.9)	
Body mass index (kg/m^2)				9.03 (0.060)
Low/normal (<25 kg/m^2)	129 (60.3)	304 (59.1)	62 (49.6)	
Overweight (25 to <30 kg/m^2)	50 (23.4)	150 (29.2)	40 (32.0)	
Obese (⩾30 kg/m^2)	35 (16.4)	60 (11.7)	23 (18.4)	
% Within sex				
Sex				10.09 (0.006)
Male	31 (16.8)	118 (63.8)	36 (19.5)	
Female	200 (27.2)	433 (58.9)	102 (13.9)	

[a]Numbers do not add up to total number because of missing values for covariates

Table 3. *Correlations of family birth weights in the Lifeways Cross-Generation Cohort Study*

	Index child's IBW	Maternal BW	Paternal BW	MGM BW	MGF BW	PGM BW	PGF BW
Index child's IBW							
r	1	0.178	0.138	0.137	0.176	0.153	− 0.402
P-value		<0.001[a]	0.115	0.253	0.361	0.394	0.064
n	1075	613	131	71	29	33	22
Girls' IBW							
r	N/A	0.143	0.149	0.198	0.149	0.229	− 0.345
P-value		0.012	0.217	0.234	0.582	0.377	0.449
n		305	71	38	16	17	7
Boys' IBW							
r	N/A	0.201	0.095	0.092	0.192	0.134	− 0.530
P-value		<0.001[a]	0.470	0.612	0.530	0.622	0.042
n		308	60	33	13	16	15
Maternal BW							
r	N/A	1	0.174	0.256	0.124	− 0.022	0.581
P-value			0.112	0.079	0.591	0.937	0.037
n		1113	85	48	21	15	13

IBW, infant birth weight; BW, birth weight; MGM, maternal grandmother; MGF, maternal grandfather; PGM, paternal grandmother; PGF, paternal grandfather.

[a]Correlation coefficient remained significant after Bonferroni's correction was applied.

completed secondary education having relatively higher BMI than those with third-level education. When mothers were excluded from the overall model, a different pattern emerged. Lineage remained significantly associated with adult BMI, but IBW and education were no longer significantly associated with adult BMI. In the final model (Table 5), for adults other than mothers with available RBW, that variable was significantly associated with adult BMI, but IBW showed no association and there was an inverse association with accommodation and BMI, as a marker of social position.
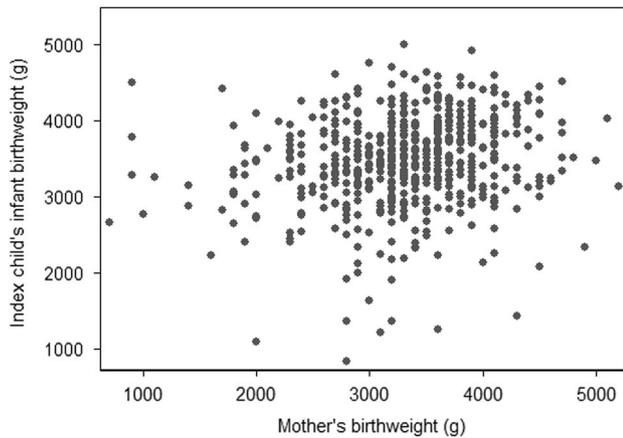
Fig. 1. Correlation between mother's birth weight and index child's infants birth weight in the Lifeways Cross-Generation Cohort Study (n = 613).

Discussion

There are very few cohort studies with examination data across three generations and seven lineages and this analysis appears to be novel in the literature in that it includes birth weights of both adult and children family members simultaneously in the models. Our analysis suggests there are patterns of association seen for birth weight across generations, in keeping with other studies.

It is increasingly well established that infants at the normal extremes of birth weight are more likely to develop adult chronic disease.[5,15,16] A number of cohort studies have shown familial associations also for parents and their children, some with contrasting patterns in maternal and paternal lineages.[16] The 1958 birth cohort in the United Kingdom is a rich data set which was able to prospectively assess birth weight in relation to own BMI at five different time points in the lifecourse from 7 to 33 years old and also had reported anthropometric information on both parents of participating children.[6] This analysis showed a direct association between IBW and own BMI in early life, becoming more j-shaped by the age of 33. The authors point out the usefulness of examining birth weight relative to genetic potential, in this case BMI of both parents and adult children. They concluded that maternal weight largely explained the association between own birth weight and adult BMI in the offspring.

We also wished to assess whether adult BMI, as a known proxy as well as a risk factor for adult chronic disease, was associated with either own RBW or index child's IBW in mixed models that also included age, lineage group and educational status. We examined a direct association between birth weights and BMI, as that association tends to be positive in other studies,[6,7] whilst being inverse for outcomes such as hypertension, diabetes and cardiovascular disease.[3,4,14]

Again, we found expected associations with gender and social position for RBW, suggesting the coherence of the data.

Having in effect adjusted for these associations, we find initially that child's IBW, but not adults' RBW, is significantly associated with the outcome of interest. IBW was consistently associated with adults' BMI, in the first three models. This analysis confirms other similar analyses which show that adults including parents and grandparents, do show an association with the birth weights of their offspring.[16–18] This is not to say there is necessarily a causal or temporal relationship, but rather that factors which may influence intrauterine growth or development may also be influencing the development of adult chronic disease in family members.

Very few human studies to date have examined transmission patterns across more than two generations.[17–21] The findings in these three generation study reports are conflicting. Some have only maternal lineage data and show an inverse association between grandchild's birth weight and grandparental cardiovascular disease[20] or diabetes.[21] Naess *et al.* in a large-scale study in Norway have shown inverse relationships between IBW and mortality in both grandparental lineages, suggesting that for cardiovascular outcomes, this association may be explained by the maternal characteristics, including smoking, but may reflect also transmitted intrauterine effects for diabetes.[18] None of these studies have RBW or measures such as BMI from grandparents as they are linkage in design, rather than prospectively followed families.

Our analysis further shows that it is the relationship between mother and infant that appears to be primarily driving the associations found. The only significant correlations for birth weight itself were between mother and child and when the mother is excluded from the adult analyses and considered separately, the patterns of association differ, IBW being no longer significantly associated with the remaining adults' BMI. Evidence is accumulating across the lifecourse for offspring outcomes related to pregnancy. Weight gain during pregnancy has been shown to influence neonatal fat mass.[22] A longer-term follow-up of the Aberdeen Children of the Nineteen Fifties study showed risk of cerebrovascular disease might be increased in adult offspring whose mothers gained weight during pregnancy but not for all-cause mortality or cardiovascular disease, though the offspring's own characteristics, including smoking and BMI, were strongly associated with cardiovascular outcomes.[23] Maternal obesity during pregnancy has been shown to be associated with cardiovascular events in adult offspring.[24] Wells has highlighted the significance of so-called maternal capital, whereby different components of the maternal phenotype developed over her own lifecourse can influence offspring development.[25]

Notwithstanding that consistent association it may partially reflect shared genetic traits. A recent Mendelian randomization analysis of Avon Longitudinal Study of Parents and Children data, replicated in the Generation R cohort, shows consistent associations between maternal and offspring BMI, attenuated significantly when robust genetic markers are adjusted for in the analysis.[26] A further Mendelian randomization analysis suggests maternal BMI is probably causally associated with higher IBW, consistent with the association we show in this analysis.[27]

Table 4. *Results of multilevel mixed effects linear regression models on adults' body mass index (BMI) in the Lifeways Cross-Generation Cohort Study*

Independent variables	All adults Model including IBW only (n = 2160)			All adults Model including IBW and adult's RBW (n = 728)			Mothers only Model including mother's RBW and IBW (n = 483)			All adults, excluding mothers Model including IBW only (n = 1319)		
	Adjusted β[a]	P-value	95% CI	Adjusted β[a]	P-value	95% CI	Adjusted β[a]	P-value	95% CI	Adjusted β[a]	P-value	95% CI
Age (years)	0.00340	0.813	−0.02493, 0.03176	0.05373	0.030	0.00516, 0.10231	0.02894	0.415	−0.04068, 0.09855	−0.02451	0.147	−0.05763, 0.00861
Adult's RBW (g)				0.00018	0.441	−0.00027, 0.00063	−0.00008	0.801	−0.00069, 0.00054			
Index child's IBW (g)	0.00050	0.042	0.00002, 0.00099	0.00105	0.004	0.00033, 0.00176	0.00116	0.007	0.00032, 0.00201	0.00032	0.329	−0.00032, 0.00095
Index child's gestational age (weeks)	0.01911	0.807	−0.13437, 0.88376	−0.08997	0.430	−0.31365, 0.13371	−0.08650	0.518	−0.34854, 0.17553	−0.00909	0.931	−0.21359, 0.19541
Education status												
Completed third level	Reference			Reference			Reference			Reference		
Completed secondary school	0.31361	0.281	−0.25654, 0.88376	1.48914	<0.001	0.73839, 2.23990	1.64379	<0.001	0.76328, 2.52430	−0.17348	0.719	−1.11732, 0.77037
No schooling/completed primary school	0.81300	0.012	0.17894, 1.44706	0.58900	0.215	−0.34216, 1.52017	0.35518	0.567	−0.76328, 1.57006	0.89777	0.054	−0.01705, 1.81259
Family lineage												
Father	Reference			Reference						Reference		
Mother	−2.52614	<0.001	−3.15104, −1.90124	−2.13897	<0.001	−3.01131, −1.26664	N/A			N/A		
MGM	0.98246	0.063	−0.05494, 2.01986	−0.02062	0.983	−1.87505, 1.83381				1.58022	0.008	0.41459, 2.74584
MGF	0.80533	0.177	−0.36503, 1.97569	0.44894	0.714	−1.95225, 2.85012				1.47266	0.028	0.16119, 2.78412
PGM	1.00399	0.087	−0.14647, 2.15444	−0.28205	0.812	−2.60144, 2.03735				1.69183	0.010	0.40016, 2.98351
PGF	1.31122	0.039	0.06872, 2.55372	1.73157	0.186	−0.83672, 4.29987				2.04597	0.004	0.65888, 3.43305
Constant	23.76924	<0.001	18.07643, 29.46205	22.94188	<0.001	14.5991, 31.28465	21.82199	<0.001	12.07144, 31.57255	26.70433	<0.001	19.11932, 34.28933
	ICC = 0.127			ICC = 0.128			N/A			ICC = 0.083		

IBW, infant birth weight; RBW, reported birth weight; CI, confidence interval; MGM, maternal grandmother; MGF, maternal grandfather; PGM, paternal grandmother; PGF, paternal grandfather; ICC, intraclass correlation coefficient.

[a]Results were adjusted for other variables listed in the table.

Table 5. *Results of multilevel mixed effects linear regression models on adults' body mass index (BMI) (excluding mothers) in the Lifeways Cross-Generation Cohort Study*

Independent variables	Full model (n = 242)			Final model (n = 277)		
	Adjusted β[a]	P-value	95% CI	Adjusted β[a]	P-value	95% CI
Age (years)	0.07807	0.023	0.01066, 0.14549	0.06098	<0.001	0.02806, 0.09389
Adult's RBW (g)	0.00052	0.129	−0.00015, 0.00118	0.00064	0.040	0.00003, 0.00124
Index child's IBW (g)	0.00099	0.131	−0.00030, 0.00228			
Index child's gestational age (weeks)	−0.11060	0.588	−0.51150, 0.29018			
Ever smoker						
No	Reference					
Yes	−1.08693	0.050	−2.17564, 0.00178			
Education status						
Completed third level	Reference					
Completed secondary school	0.99260	0.188	−0.48474, 2.46993			
No schooling/completed primary school	0.92327	0.223	−0.56048, 2.40701			
Accommodation						
Detached	Reference			Reference		
Semi-detached/terrace	−0.94205	0.104	−2.07921, 0.19511	−0.99360	0.068	−2.05964, 0.07244
Apartment/flat/other	−2.35689	0.052	−4.73297, 0.01919	−2.51437	0.025	−4.71704, −0.31171
Family lineage						
Father	Reference					
MGM	−1.12302	0.315	−3.31574, 1.06970			
MGF	−0.72285	0.622	−3.59453, 2.14883			
PGM	−1.15959	0.392	−3.81234, 1.49317			
PGF	1.00160	0.498	−1.89640, 3.89961			
Constant	23.51236	0.002	8.71029, 38.31442	22.94264	<0.001	20.1972, 25.68809
			ICC = 0.035			ICC = 0.033

CI, confidence interval; RBW, reported birth weight; IBW, infant birth weight; MGM, maternal grandmother; MGF, maternal grandfather; PGM, paternal grandmother; PGF, paternal grandfather.

[a]Results were adjusted for other variables listed in the table.

We have treated IBW as a co-variable rather than an outcome variable in this analysis. However there are several possible pathways to consider. In the maternal line, maternal BMI may causally predict higher IBW, that infant going on to higher childhood BMI.[15] The MGM may in turn be associated with both BMI of daughter and that of grandchild.[9,10] It is possible this path is mediated through IBW. Another explanation for the findings here is a clustering for risk of elevated BMI in families, with age, education and lineage, all playing a role both in determining IBW and adult BMI. The 1958 birth cohort also showed an association between babies' birth weight and parental birth weight and additionally an association between height of the MGM and social class of the MGF and birth weight, suggesting inter-generational influences in the maternal line.[28] A further very large linkage study from Norway also showed associations between parental birth weights and those of their offspring with the maternal association being stronger and suggesting that maternal genetic factors explained 22% of the variation in offspring birth weight.[29]

There are significant limitations to the Lifeways data, which may have influenced these findings. First, just over a third of adult respondents provided birth weight data and it is self-reported. There are differing views in the literature as to the reliability of such information[30] and grandparents were less likely to report their birth weight than parents. There is potential recall bias therefore to consider. As against that, in the reported data there were significant male/female differences and associations both with social position and infants' measured birth weights. It is plausible that many respondents to our adult questionnaire did not complete this question because they did not know what they weighed at birth, suggesting those who did respond had more accurate recall. For the RBW data for adults, the findings were coherent, in that males' birth weights were higher than those of females, as would be expected. There is a weak u-shaped association with education status, which is again an expected finding, as we know IBW in other studies is strongly associated with measures of social position, with both low and high birth weight associated with social disadvantage.[16,17]

How reliable is RBW in adults? Tehranifar *et al.*[30] found reasonable level of agreement between recorded and RBW in a small cohort of adult women, though with variation according to educational status. The Nurses' Health Study is an example of a very large cohort study employing RBW, which showed

clear associations with major health outcomes.[3,4] That study also reported validation of RBW in a sample of women as recalled by women themselves and their mothers against state birth records.[31] RBW and adult hypertension and obesity were assessed in a cohort of over 20,000 men in the Health Professionals Follow-up study.[7] A twin study relying on RBW showed an inverse association with adult blood pressure[32] and mean age of respondents in that study was 56 years old. In our study the grandparental generation were of a comparable age in that they averaged 60 years old and were free-living in the community, so were neither extremely elderly nor frail.

There are also important statistical power and sample size issues to acknowledge in the Lifeways cohort, as numbers were small and as yet major outcome events including mortality have been measured in the grandparents only.[33,34] This may have limited the expected associations seen in the literature for own birth weight and long-term outcomes.

This is not the first time we have shown lineage specific associations in this cohort however. In a previous analysis we showed a positive association between index child's IBW and all-cause mortality in the PGF but an inverse association with stroke and diabetes in the MGM.[33] Subsequently, Viljoen[34] expanded on that analysis, with larger numbers and further follow-up, showing the same pattern for the PGFs. We have also seen contrasting associations, in that BMI was more strongly associated with the maternal line in two separate analyses but the PGF is associated with his male grandson's BMI at the age of 9.[10] It is also biologically coherent that the maternal birth weight is correlated in this analysis with that of children of both sexes. Again, we have found maternal associations with offspring for diet, BMI and social position previously, so this analysis adds to those findings.[9–11]

In conclusion this study shows consistent associations between maternal RBW and that of offspring IBW. It also shows that there are patterns of association between birth weight and BMI across three generations of the same families, suggesting persistent common drivers for both outcomes, meriting further investigation.

Conflicts of Interest

None.

Ethical Standard

Ethical approval has been obtained for all stages of the study, including most recently by UCD Human Research Ethics Committee, LS-11-07.

References

1. Barker DJP, Osmond C, Winter PD, *et al*. Weight in infancy and death from ischaemic heart disease. *Lancet*. 1989; 334, 577–580.
2. Belbasis L, Savvidou MD, Kanu C, *et al*. Birthweight in relation to health and disease in later life: an umbrella review of systematic reviews and meta-analyses. *BMC Med*. 2016; 14, 147.
3. Rich-Edwards JW, Colditz GA, Stampfer MJ, *et al*. Birthweight and the risk for type 2 diabetes mellitus in adult women. *Ann Intern Med*. 1999; 130(Pt 1), 278–284.
4. Rich-Edwards JW, Kleinman K, Michels KB, *et al*. Longitudinal study of birthweight and adult body mass index in predicting risk of coronary heart disease and stroke in women. *BMJ*. 2005; 330, 1115.
5. Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. *Int J Epidemiol*. 2013; 42, 1215–1222.
6. Parsons TJ, Power C, Manor O. Fetal and early life growth and body mass index from birth to early adulthood in 1958 British cohort: longitudinal study. *BMJ*. 2001; 323, 1331–1335.
7. Curhan GC, Willett WC, Rimm EB, *et al*. Birthweight and adult hypertension, diabetes mellitus, and obesity in US men. *Circulation*. 1996; 94, 3246–3250.
8. O'Mahony D, Fallon UB, Hannon F, *et al*. Lifeways The Lifeways Cross-Generation Study: design, recruitment and data management considerations. *Ir Med J*. 2007; 100(Suppl.), 3–6.
9. Kelleher CC, Viljoen K, Khalil H, *et al*. Longitudinal follow-up of the relationship between dietary intake and growth and development in the Lifeways cross-generation cohort study 2001–2013. *Proc Nutr Soc*. 2014; 73, 118–131.
10. Kelly GE, Murrin C, Viljoen K, *et al*. Body mass Index is associated with the maternal lines but height is heritable across family lines in the Lifeways cross-generation cohort. *BMJ Open*. 2014; 4, e005732.
11. Shrivastava A, Murrin C, Sweeney MR, *et al*. Familial intergenerational and maternal aggregation patterns in nutrient intakes in the Lifeways Cross-Generation Cohort Study. *Public Health Nutr*. 2013; 16, 1476–1486.
12. Murrin C, Shrivastava A, Kelleher CC, *et al*. Maternal macronutrient intake during pregnancy and 5 years postpartum and associations with child weight status aged five. *Eur J Clin Nutr*. 2013; 67, 670–679.
13. Shiely F, Perry IJ, Lutomski J, *et al*. Temporal trends in misclassification patterns of measured and self-report based body mass index categories – findings from three population surveys in Ireland. *BMC Public Health*. 2010; 10, 560.
14. Whincup PH, Kaye SJ, Owen CG, *et al*. Birthweight and risk of type 2 diabetes: a systematic review. *JAMA*. 2008; 300, 2886–2897.
15. Cnattingius S, Villamor E, Lagerros YT, *et al*. High birthweight and obesity – a vicious circle across generations. Int J Obes (Lond). 2012; 36, 1320–1324.

16. Durmuş B, Arends LR, Ay L, *et al.* Parental anthropometrics, early growth and the risk of overweight in pre-school children: the Generation R Study. *Pediatr Obes.* 2013; 8, 339–350.

17. Manor O, Koupil I. Birthweight of infants and mortality in their parents and grandparents: the Uppsala Birth cohort Study. *Int J Epidemiol.* 2010; 39, 1264–1276.

18. Naess O, Stoltenberg C, Hoff DA, *et al.* Cardiovascular mortality in relation to birthweight of children and grandchildren in 500,000 Norwegian families. *Eur Heart J.* 2013; 34, 3427–3436.

19. Kwok MK, Leung GM, Lam TH, *et al.* Grandparental education, parental education and child height: evidence from Hong Kong's Children of 1997 birth cohort. *Ann Epidemiol.* 2013; 23, 475–484.

20. Smith GCS, Wood AM, White IR, *et al.* Birthweight and risk of cardiovascular disease in the maternal grandparents. *Am J Epidemiol.* 2010; 171, 736–744.

21. McCarron P, Davey Smith G, Hattersley AT, *et al.* Type 2 diabetes in grandparents and birthweight in offspring and grandchildren in the ALSPAC study. *J Epidemiol Community Health.* 2004; 58, 517–522.

22. Crozier SR, Inskip HM, Godfrey KM, *et al.* Weight gain in pregnancy and childhood body composition: findings from the Southampton Women's Survey. *Am J Clin Nutr.* 2010; 91, 1745–1751.

23. Bhattacharya S, McNeill G, Raja EA, *et al.* Maternal gestational weight gain and offspring's risk of cardiovascular disease and mortality. *Heart.* 2016; 102, 1456–1463.

24. Reynolds RM, Allan KM, Raja EA, *et al.* Maternal obesity during pregnancy and premature mortality from cardiovascular event in adult offspring: follow-up of 1 323 275 person years. *BMJ.* 2013; 347, f4539.

25. Wells JC. Worldwide variability in growth and its association with health: incorporating body composition, developmental plasticity, and intergenerational effects. *Am J Hum Biol.* 2017; Jan 22. https://doi.org/10.1002/ajhb.22954 [Epub ahead of print].

26. Richmond RC, Timpson NJ, Felix JF, *et al.* Using genetic variation to explore the causal effect of maternal pregnancy adiposity on future offspring adiposity: a Mendelian Randomisation Study. *PLoS Med.* 2017; 14, e1002221.

27. Tyrrell J, Richmond RC, Palmer TM, *et al.* Early Growth Genetics (EGG) Consortium. Genetic evidence for causal relationships between maternal obesity-related traits and birthweight. *JAMA.* 2016; 315, 1129–1140, Erratum in *JAMA.* 2016;315:1661.

28. Lunde A, Melve KK, Gjessing HK, *et al.* Genetic and environmental influences on birth weight, birth length, head circumference, and gestational age by use of population-based parent-offspring data. *Am J Epidemiol.* 2007; 165, 734–741.

29. Emanuel I, Filakti H, Alberman E, *et al.* Intergenerational studies of human birthweight from the 1958 birth cohort. 1. Evidence for a multigenerational effect. *Br J Obstet Gynaecol.* 1992; 99, 67–74.

30. Tehranifar P, Liao Y, Flom JD, *et al.* Validity of self-reported birthweight by adult women: sociodemographic influences and implications for life-course studies. *Am J Epidemiol.* 2009; 170, 910–917.

31. Troy LM, Michels KB, Hunter DJ, *et al.* Self-reported birthweight and history of having been breastfed among younger women: an assessment of validity. *Int J Epidemiol.* 1996; 25, 122–127.

32. Poulter NR, Chang CL, MacGregor AJ, *et al.* Association between birthweight and adult blood pressure in twins: historical cohort study. *BMJ..* 1999; 319, 1330–1333.

33. Shrivastava A, Murrin C, O'Brien J, *et al.* Grandparental morbidity and mortality patterns are associated with infant birthweight in the Lifeways cross-generation cohort study 2001–2010. *J Dev Orig Health Dis.* 2012; 3, 458–468.

34. Viljoen K. Longitudinal follow-up of morbidity, healthcare utilisation and mortality patterns in the Lifeways cross-generation cohort study. Ph.D. Thesis, Health Sciences Library (vol. 1766), 2014. University College Dublin: Dublin.