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Longitudinal follow-up of the relationship between dietary intake and growth and development in the Lifeways cross-generation cohort study 2001–2013

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In this paper we will review evidence on the early life and familial influences on childhood growth and development, with particular reference to the Lifeways cross-generation cohort study in the Republic of Ireland. The Lifeways cross-generation cohort study was established in 2001–2013 through two maternity hospitals in the Republic of Ireland and was one of many new cohort studies established worldwide in the millennium period. Mothers were recruited at first booking visit, completing a self-administered questionnaire, which included a 147 item semi-quantitative FFQ. Longitudinal follow-up is ongoing in 2013, with linkage data to hospital and general practice records and examination of children when aged 5 and 9 years. The study is one of very few containing data on grandparents of both lineages with at least one grandparent recruited at baseline. There have been consistent associations between parental and grandparental health status characteristics and children's outcomes, including infant birth-weight, BMI when child was aged 5 years and childhood wheeze or asthma when child was aged 3 and aged 5 years. In conclusion, empirical evidence to date shows consistent familial and cross-generational patterns, particularly in the maternal line.

Diet: Pregnancy: Children: Parents: Grandparents

As the global obesity epidemic continues to pose a major public health challenge, it has become increasingly important to understand how risk for adult chronic disease is transmitted across generations and through the life course of individuals[1–11]. In the present paper, we will review briefly recent evidence, with particular reference to the Lifeways cross-generation cohort study in the Republic of Ireland. This linkage cohort study was one of several established globally in the millennium period[12] and has followed index children since recruitment during pregnancy in 2001–2013 and also their mothers, fathers and at least one grandparent. The design and data management considerations have been described previously and the original mothers were found to be comparable in demographic terms with women of the same age in the contemporary Survey of Lifestyles, Attitudes and Nutrition (SLAN)[13,14]. The study objectives were to document health status, diet and lifestyle in the family members and to establish patterns and links across generations. The study continues to follow participants up to 2013 and the data collected in each sweep are summarised in Table 1.

In the initial 5 years follow-up, primary care utilisation patterns were documented and the study examined how indicators of social position, particularly means-tested eligibility to free healthcare, influenced health status of family members. In the Republic of Ireland, there is a two-tiered means-tested health care system,

Abbreviations: GMS, general medical services; OR, odds ratios.

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Table 1. Summary of data collection sweeps to date in the Lifeways cross-generation cohort study

Year	Data collected	Family members	Families
2001–2003	Self-administered health and lifestyle questionnaire including semi-quantitative FFQ	Mothers (1126), fathers (334) and four lineage grandparents (713). MGM 286 MGF 165 PGM 164 PGF 98	1128
2002–2004	Hospital clinical linkage records	Mothers (1092), infants (1103)	1100
2002–2003	Standardised cardiovascular examination	Grandparents (982). MGM 379 MGF 228 PGM 226 PGF 149	517
2005	GP records	Children (703) aged 3 and all adults (1630) Mothers 708 Fathers 189 MGM 292 MGF 159 PGM 168 PGF 114	827
2007	Health Service Executive immunisation records	Children (749)	749
2007–2008	Self-administered health and lifestyle questionnaire including semi-quantitative FFQ and examination of weight, height and waist circumference	Children (570) aged 5 and mothers (563) Father measures (78)	656
2011–2013	Death records from General Registry Office	Grandparents (1784) MGM 542 MGF 465 PGM 407 PGF 370	724
2011–2012	Self-administered brief postal health and lifestyle questionnaire	All adults (1587) Mothers 460 Fathers 277 MGM 288 MGF 209 PGM 203 PGF 150	593
2012	Examination weight, height and waist circumference, saliva and hair samples in GP and blood sample for lipoprotein profile	Sub-sample of Children (301) aged 9 And one parent Mother 263 Father 5	296
2013	Standardised cardiovascular examination and saliva and hair samples	East coast Grandparents (140 – but will increase) MGM 52 MGF 34 PGM 29 PGF 25	85
2013	GP family practitioner records	1426 forms to 528 GP	Pending

MGM, maternal grandmother; MGF, maternal grandfather; PGM, paternal grandmother; PGF, paternal grandfather; GP, general practice.

and access to free primary and community care including general practice is available to those below a certain income level, so-called general medical services (GMS) eligibility. This has been found to be a robust indicator of both social disadvantage and various health outcomes[15].

A life-course approach to diet, growth and development

In social epidemiology, a comprehensive account of influences across the life course must be undertaken in order to understand why outcomes such as CVD, cancers or diabetes might develop in adulthood[16]. Such an approach takes account of the immediate proximal pathophysiological processes leading to a specific disease outcome, and more recently how genetic, genomic or nutrigenomic factors acting at different time points might be affecting the outcome in question, which we discuss later [4,17–24]. However, there are also contextual factors to be considered, such as individual lifestyle choices or health behaviours predisposing to risk factor development, and in turn how so-called meso-level situations

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such as the work environment, occupation or social class determine those health choices at different life stages, all of these being underpinned by the wider sociopolitical structure[16]. This level of understanding is required if changes are to be wrought by public policy strategies. Study designs to take account of these factors may be longitudinal but also have design challenges to record what is measurable at the level of the individual cohort member and how best to record and examine ecological level factors such as a region or area, or group characteristics such as family membership.

The seminal influence of Barker[1,3,5,6] in reframing our understanding of early life influences on adult chronic disease has created a paradigm shift in our understanding of these processes over the past three decades. In the original Hertfordshire retrospective cohort study, where current health outcomes were linked to original infant anthropometric records, Barker *et al.* showed the graduated inverse relationship between both birth-weight and weight in infancy and death for CHD at all ages in 10 636 men[1]. As they pointed out, there are various reasons for babies to be small at birth and in infancy, including low birth-weight, short stature, placental insufficiencies and failure to thrive[3]. Since then many studies have considered cumulative, trajectory and critical period influences on longer term outcomes. It is now well understood that there are two processes at the extremes of birth-weight, whereby larger babies are at greater risk of subsequent diabetes and obesity, in turn related to maternal weight and height[8,25] and lower birth-weight babies subjected to degrees of intrauterine growth retardation are also susceptible to later adult chronic disease[1,5,7,10]. The developmental plasticity hypothesis, whereby there is a critical period during which a system is plastic, followed by loss of plasticity and a fixed functional capacity, is now well accepted as a biological phenomenon, and pregnancy, during which the intrauterine development of all children occurs, is one such critical period shared by all individuals[5,10,11].

Barker has since extended this concept to define what he calls 100 years of nutritional flow[6]. The 1000 d from conception to toddlerhood not only include maternal influences such as her nutritional supply to the fetus during pregnancy and early childhood feeding practices, but also the quality, size and shape of the placenta are increasingly understood to play a role in successful fetal and early childhood growth and development milestones and subsequent long-term health outcomes. The maternal grandmother is especially influential as it is she who makes the grandchild's egg for subsequent fertilisation by the ovulating mother. In this sense, the developmental investment in the index child dates across generations and an ageing adult owes his health status to his own constitutional and environmental exposures but also to that of his parents and grandparents. There is also the genetic influence of both parents and all grandparents, the X-linked effects of the mother, the Y-linked effects of the paternal line, and notably through the maternal line, the mitochondrial DNA transmission[26,27]. Recent studies have shown an association between variants in the *ADCY5* gene and birth-weight and up to seven loci identified which account for a similar proportion of the variance in infant birth-weight as smoking[19]. This may predispose individuals both to relatively lower birth-weight and a propensity to adult chronic disease.

Cross-generational evidence

In recent years, a number of studies have been published showing the relationship between infant birth-weight and subsequent maternal and paternal morbidity and mortality[28–31]. Generally such an association has been shown for lower birth-weight, particularly for mothers. Many studies have attempted to examine how children's growth trajectories relate to their parents' anthropometric characteristics[9,11]. Prospects for understanding the genetic, epigenetic or nutrigenomic mechanisms have recently been reviewed[23]. These authors define epigenetics as the regulatory processes that control the transcription of information encoded in the DNA sequence into RNA before their transcription into proteins. The tissue specificity of epigenetic patterns is a well-established phenomenon and not all studies report expected associations[21], even though in principle nutrigenomic effects may be important as for instance DNA methylation which occurs *in utero* depends on the availability of several nutrients including methionine, vitamins B_6, B_{12} and folate[17].

A further use of genetic markers is in so-called Mendelian randomisation, whereby an individual receives at random a specific allele from its parent, this process being unlikely to be confounded by any subsequent behavioural characteristic of the individual. It is then possible to adjust for the known influence of this marker on an apparent prospective association between a risk factor and the disease-specific outcome of interest, using genotype as an instrumental variable. This has been shown for the *FTO* gene in Danish adults in relation to the association of obesity with IHD[32] and to attenuate greatly the apparently strong association between maternal BMI and offspring adiposity[33]. These studies have attempted to address biased or confounded associations in that parents may share genetic or environmental characteristics, but not the direct health behaviours of their offspring[34].

Several animal studies have provided evidence for transgenerational effects of intrauterine exposure[18,22,35,36]. Female rats, exposed to protein restriction during pregnancy and lactation, were found to have offspring that delivered a progeny with altered growth and metabolism[35]. A similar protein restriction trial in pregnant rats reported that second-generation offspring had raised blood pressure and endothelial dysfunction which was passed through the maternal line[36]. In contrast, Harrison and Langley-Evans[18] reported that protein restriction during pregnancy results in a phenotype of raised blood pressure and reduced nephron number passed through maternal and paternal lines. More recently, Ponzio *et al.*[22] have demonstrated that phenotypes resulting from maternal protein restriction are evident in a second and third generation of animals.

Studies of body composition and diet in human subjects have either been limited to one generation or have used proxy markers for diet intake across one or more generations, such as those of the Overkalix studies[26,37] and the Dutch Winter Hunger study[20]. By contrast with parental data studies[28–31,38,39] there are relatively fewer data on how grandparental characteristics affect their grandchildren's growth and development; all such studies have either been retrospective or data linkage in design and none to date had dietary intake data across generations. To date there are just four well-characterised human studies with three generations[40–43]. Manor and Koupil[40] showed a U-shaped association between grandchild's birth-weight and circulatory disease mortality in maternal grandmothers only for infants born prior to 1977. There was a U-shaped association for maternal grandfathers' overall and circulatory disease mortality and for paternal grandfathers there was an inverse association between grandchild's birth-weight and overall mortality. McCarron *et al.*[41] found that the grandchildren of maternal grandparents with reported type 2 diabetes were more likely to be in the top tertile of birth-weight. There was evidence for an inverted U-shaped association between birth-weight of grandchildren and diabetes in paternal grandmothers. Smith *et al.*[42] have shown an inverse relationship between maternal grandparents' risk of IHD or cerebrovascular disease and infant birth-weight and did not have data on paternal lineages. In a very large linkage study in Norway, inverse relationships were shown according to both maternal and paternal lineages and cardiovascular outcomes in grandparents; adjusting for maternal smoking accounted for much of the effect on cardiovascular mortality. For grandparental diabetes mortality, U-shaped associations were seen with grandchild birth-weight for the maternal grandmother and inverse associations for all other grandparents[43].

Prospective studies with information on diet and parental BMI

In an exploration of the literature, we attempted to identify cohort studies that included a measure of nutritional status (BMI or diet assessment) across two or three generations[44–106]. Prospective or cohort studies that include specifically information on maternal diet or BMI and that of other family members in relation to index children are summarised in Table 2. As Poston has pointed out, many of these are relatively recently established[25]. The studies vary in their objectives; several look at offspring size as the outcome of interest; others include diet and body size as factors associated with child and adult morbidities. Maternal pre or postnatal BMI is the variable most frequently reported (63 %) by these studies followed by paternal postnatal BMI (41 %; Table 2). Diet is less frequently reported with only one-third collecting information on prenatal maternal diet; prenatal paternal diet has only been collected by eight studies.

The 1958 birth cohort has described the relationship between birth-weight of the grandchild and the influence of height by the grandparents[57]. Only one other study by Davis *et al.*[51], has described a measure of BMI for grandparents. This study is limited, however, by the fact that grand maternal and grand paternal body composition was aggregated in the reported analysis. To our knowledge, no other studies have reported data available on either the BMI or diet of the proband child and their individual maternal and paternal grandparents. This makes the Lifeways cross-generation cohort study a highly unusual dataset in the literature, in that it contains information on health status, dietary intakes and adult chronic disease outcomes in the grandparental generation related to the health status of their grandchildren[13,14].

Findings to date in the Lifeways study: pregnancy and early years

The Lifeways cross-generation cohort study was established in 2001–2013 through two maternity hospitals in the Republic of Ireland and was one of many new cohort studies established worldwide in the millennium period[12,13,14]. Mothers were recruited at first booking visit, completing a self-administered questionnaire which included a 147 item validated semi-quantitative FFQ. Longitudinal follow-up is ongoing in 2013, with linkage data to hospital and general practice records and examination of children when aged on average 5 and 9 years. The study is one of very few containing data on grandparents of both lineages, with at least one grandparent recruited at baseline. A summary of publications related to diet and cross-generation transmission to date for the Lifeways cohort study is given in Table 3[107–121]. These analyses in this cohort have been consistent in showing an influence on health outcomes at different time points of lifestyle factors including diet and of cross-generation and familial associations. This is arguably remarkable given that it is not a large cohort study, although characterised in some detail and with linkage to health records.

We have previously shown a social gradient in relation to baseline dietary intake at recruitment for all adult family members, in that those eligible for GMS had lower intakes of vitamin C and higher total fat intakes, having adjusted for other risk factors[110]. Both age and cohort group were important factors, as might be expected, since the parental and grandparental dietary patterns might be likely to differ and sex differences are also apparent, with higher mean energy intakes in males compared with females. Social gradients at the level of food groups have been reported in the Surveys of Lifestyles, Attitudes and Nutrition at each of the three time points 1998, 2002 and 2007[122,123], so the Lifeways study corroborates that observation at the level of selected nutrient intakes.

The pregnancy outcomes were also examined in relation to indicators of maternal social position and health status[107–109]. Determinants of mothers' self-rated health during pregnancy showed a strongly socially graduated pattern and mothers whose own parents were educated

to third level had better self-rated health than those whose parents left education early[107]. Younger and less socially advantaged mothers tended to have lower birth-weight babies[108]. The dietary patterns of mothers during pregnancy were socially graduated, as was smoking status[109]. Predictors of pre-term delivery and occupational predictors of pregnancy outcomes were reported in this cohort[111–112]. Mothers required to do shiftwork tended to have a higher risk of pre-term delivery, adjusted for other factors[111] and this cohort was included in a subsequent meta-analysis, which showed a small effect of shiftwork on risk for this outcome[124].

While many studies report a social gradient to pregnancy outcomes, a few attempts to comprehensively explain the degree to which known health status and lifestyle variables explain that gradient have been made. In the Lifeways study low maternal educational level was associated with an increased risk of this clinical outcome of preterm delivery (hazard ratio 2·14, 95 % CI 1·04, 4·38) and notably the explanatory combination of a material factor such as rented or crowded home, and behavioural factors such as smoking, alcohol consumption and high saturated fat intake during pregnancy reduced the hazard ratio for low education level by 42 %[112]. We looked at predictors of low birth-weight of 3 kg or less both in this cohort and in another cohort of disadvantaged Traveller infants, a nomadic disadvantaged group in Ireland and found that maternal smoking and alcohol consumption were important predictors of this outcome, but when these factors were taken account of the birth-weight differential according to social class persisted. We used this cut-off point, as opposed to the clinical cut-off of 2.5 kg, as epidemiological studies show this is associated with later risk of adult chronic disease, providing empirical evidence in an Irish context for findings reported in other cohorts internationally[113].

Follow-up when children averaged age 5 years

A number of analyses have been undertaken across the generations of participating families related to the wave when children now averaged age 5 years[116–118]. Although the responses were received for just 669 of 1126 women originally recruited and not all of these had complete examination data, there was no significant difference in baseline maternal BMI in this sweep's participants compared with that of non-participants, although these mothers were older on average than non-participants. We applied mixed effect models to take account of family relatedness, which enables correlation between family members to be modelled and also to take account of incomplete or variable numbers of family participants. Each family could contain up to seven possible members; in the child the height and weight were measured but for other adult family members the data were self-reported. We found consistent correlations for height between family members in both paternal and maternal lines, but the patterns for BMI were significant only for the maternal line. In these statistical models, education level, and also self-rated health and fruit and vegetable consumption patterns were accounted for because they each showed a social gradient and a relationship with BMI in previous analyses, with a strong significant family effect seen across the generations in the maternal line[116].

The reported evidence in the general literature on the relative influence of paternal and maternal lines on children's BMI is mixed[9,38,39,68,125,126]. The Growing Up in Ireland study found that measured parental weight status was correlated with childhood obesity at age 9 years[38]. While the Avon Longitudinal Study of Parents and Children study for instance showed no distinction in strength of association between maternal and paternal lines[39], the Generation R cohort study also showed a strong maternal pattern, although there was a paternal influence as well[9].

Familial aggregation patterns in dietary intake were also assessed in the Lifeways study. Nuclear family effects were found, with the maternal association being stronger than the paternal association and the maternal grandmothers showed an association both with their own daughters' diet and with that of their index grandchild's diet at age 5 years. The mother's current diet tended to be more strongly associated with that of her child than her pregnancy consumption, although in the case of non-breastfeeding mothers, dietary fat intake during pregnancy was more strongly associated[117]. Brion *et al.*[46], employing Avon Longitudinal Study of Parents and Children data, found a similar association with regard to prenatal maternal fat intake.

Maternal dietary intake at both time points was also examined in relation to child's BMI at age 5 years. A social gradient in relation to maternal fruit and vegetable intake was found during pregnancy and also when the child averaged age 5 years. Total energy intake in mothers was greater during pregnancy. Increased odds of overweight or obesity were found in mothers with higher intakes of sugar during pregnancy and higher fat intakes when the child was aged 5 years. Mothers with persistently high intakes of SFA and those who had lowered their sugar consumption since pregnancy were more likely to have overweight or obese children and we discuss the possible biological plausibility of these findings in that paper[118]. Again, cohort data on this issue are rare. The Southampton women's survey[127] reported that after adjustment for maternal factors including height and duration of breastfeeding maternal *n*-6 PUFA intake positively predicted fat mass in children aged 4 and 6 years.

Dietary patterns and risk of childhood wheezing or asthma

A specific health outcome of interest that can already be examined in the children themselves is childhood wheeze or asthma, which is strongly suspected to have a dietary basis. The Lifeways study was one of the first to show that general practitioner-reported wheeze or asthma

Table 2. Prospective studies with information on either diet or parental BMI, or both

				Prenatal*						Postnatal					
				Mother		Father		Grandparent		Mother		Father		Grandparent	
Reference	Country	Sample size	Year established	BMI	Diet	BMI	Diet	BMI	Diet	BMI	Diet	BMI	Diet	BMI	Diet
Alves *et al.*[44]	Portugal	8647	2005	x	x					x	x	x			
Bergmann *et al.*[45]	Germany	7609	1990							x		x			
Brion *et al.*[46]	UK	14000	1990	x	x	x	x			x	x	x	x		
Burke *et al.*[47]	Australia	2087	1989							x					
Brunekreef *et al.*[48]	Netherlands	3963	1996		x					x	x	x			
Chatzi[49]	Greece	1590	2007	x	x	x				x	x	x	x		
Dabelea *et al.*[50]	USA	52	1965†							x		x			
Davis *et al.*[51]	USA	2591	2003							x		x		x	
Dejmek *et al.*[52]	Czech Republic	7577	1994							x					
Devereux *et al.*[53]	UK	1400	1997	x	x										
Drouillet *et al.*[54]	France	1900	2003	x	x	x				x					
Dubois *et al.*[55]	Canada	1450	1998							x		x			
Eggesbo *et al.*[56]	Norway	2500	2003	x	x					x					
Emanuel *et al.*[57]	UK	3076	1958							x					
Gorden-Larsen *et al.*[58]	USA	14706	1995							x					
Gracie *et al.*[59]	Canada	3388	2008	x	x										
Grandjean *et al.*[60]	Faroe Islands	1022	1986		x					x	x	x			
Guldner *et al.*[61]	France	4000	2002	x	x										
Guxens *et al.*[62]	Spain	3768	1997	x	x	x				x	x				
Grazuleviciene *et al.*[63]	Lithuania	4405	2007	x											
Hawkes *et al.*[64]	Ireland	2185	2008	x											
Hawkins *et al.*[65]	UK	13113	2000	x											
Hill *et al.*[66]	Wales	420	2009		x		x								
Hryhorczuk *et al.*[67]	Ukraine	4510	1992	x	x		x								
Hui *et al.*[68]	Hong Kong	8327	1997							x		x			
Hunt *et al.*[69]	Canada	521	1981							x		x			
Inskip *et al.*[70]	UK	3159	1998	x	x										
Jaddoe *et al.*[71]	Netherlands	10000	2002		x										
Jedrychowski *et al.*[72]	Poland	432	2000	x	x										
Kaplowitz *et al.*[73]	UK	224	1986							x		x			
Karvonen *et al.*[74]	Finland	442	2002	x	x	x						x			
Katier *et al.*[75]	Netherlands	2500	2003	x	x	x	x								

Table 2. (*Cont.*)

Reference	Country	Sample size	Year established	Prenatal*						Postnatal					
				Mother		Father		Grandparent		Mother		Father		Grandparent	
				BMI	Diet	BMI	Diet	BMI	Diet	BMI	Diet	BMI	Diet	BMI	Diet
Kroke *et al.*[76]	Germany	1300	1985							x	x	x	x		
Kummeling *et al.*[77]	Netherlands	2843	2000	x	x					x	x	x			
L'Abee *et al.*[78]	Netherlands	2997	2006	x		x				x		x			
Laitinen *et al.*[79]	Finland	8767	1966	x						x					
Lagstrom *et al.*[80]	Finland	1827	2007	x	x	x	x			x	x	x	x		
Li *et al.*[81]	UK	3076	1958							x					
Ludvigsson *et al.*[82]	Sweden	17 000	1997							x		x			
Magnus *et al.*[83]	Norway	108 500	1999	x	x	x	x			x					
Mizutani[84]	Japan	1417	1987	x	x					x					
Moschonis *et al.*[85]	Greece	2374	2003							x		x			
Nohr *et al.*[86]	Denmark	100 000	1995	x											
O'Callaghan *et al.*[87]	Australia	4062	1981	x						x		x			
Oken *et al.*[88]	USA	1044	1999	x	x							x			
Park *et al.*[89]	Slovakia	1134	2002	x	x										
Parkinson *et al.*[90]	UK	1029	1999							x	x	x			
Pirkola *et al.*[91]	Finland	4168	1986	x											
Polanska *et al.*[92]	Poland	1800	2007	x	x										
Porta *et al.*[93]	Italy	708	2003		x										
Porta *et al.*[94]	Italy	654	2005							x	x				
Quante *et al.*[95]	Germany	2000	2011	x	x	x				x					
Richiardi *et al.*[96]	Italy	7500	2005	x	x					x	x				
Schaefer-Graf *et al.*[97]	Germany	324	1995†							x		x			
Sekine *et al.*[98]	Japan	8941	1992							x		x			
Skalkidou *et al.*[99]	Sweden	580	2009	x						x					
Tsuchiya *et al.*[100]	Japan	1260	2007	x						x					
van Eijsden *et al.*[101]	The Netherlands	6161	2003	x	x					x		x			
Vandentorren *et al.*[102]	France	20 000	2011	x	x		x								
Vecchi Brumatti *et al.*[103]	Italy	900	2007							x	x	x			
West *et al.*[104]	UK	14 000	2007	x	x	x				x	x				
Wilhelm *et al.*[105]	Germany	234	2000								x				
Wickman *et al.*[106]	Sweden	4089	1994	x											
	Denmark	1650	2010‡	x	x	x									
	Italy	2000	2011‡	x	x	x				x	x	x			
	Netherlands	150 000	2011‡	x	x										
	Netherlands	250	2010‡	x	x	x	x								

* Prenatal BMI may be estimated before pregnancy or measured during pregnancy.
† Cohorts of children born to mothers with gestational diabetes mellitus or previous macrosomia.
‡ Cohorts currently recruiting or have recently completed recruitment.

Table 3. Cross-generational or longitudinal Influences on health outcomes in the Lifeways cohort study 2001–2013

	Authors and date	Outcome of interest	Summary of findings
1	Segonds-Pichon *et al.*[107]	Maternal self-rated health in pregnancy	Strong social gradient and an association with grandparental educational status
2	Murrin *et al.*[108]	Maternal dietary intake during pregnancy	Strong social gradient for food consumption patterns
3	Murrin *et al.*[109]	Infant birth-weight	Associations between both maternal and maternal grandmother's BMI and infant's birth-weight
4	Kelleher *et al.*[110]	Dietary patterns of all adults at baseline	Age, gender and GMS eligibility associated with both total fat intake and total vitamin c intake
5	Niedhammer *et al.*[111]	Infant birth-weight <3 kg or <2·5 kg	U-shaped relationship to maternal alcohol intake and inverse relationship to maternal smoking patterns
6	Niedhammer *et al.*[112]	Pre-term delivery of infants	Association with low educational level, 42 % of which is explained by material and lifestyle factors, including smoking, alcohol consumption and high saturated fat intake during pregnancy
7	Hamid *et al.*[113]	Predictors of birth-weight <3 kg in All Ireland Traveller Health Study and Lifeways cohorts	Strong social gradient observed, partially but not fully explained by maternal smoking status
8	Fitzsimon *et al.*[114]	General practitioner-reported wheeze child aged 3 years	Models adjusting for demographic factors show positive associated with spreadable fat intake and inverse association with fruit & vegetable and oily fish intake
9	Viljoen *et al.*[115]	Parent-reported asthma, child aged 5 years	Strong social pattern and inverse association with maternal vegetable intake during pregnancy
10	Murrin *et al.*[116]	BMI and height in three generations, child aged 5 years	Consistent familial associations for height in both maternal and paternal lines, but associations for BMI only significant in maternal line
11	Shrivastava *et al.*[117]	Familial aggregation patterns for dietary nutrient intakes, child aged 5 years	Consistent nuclear familial patterns seen and association with maternal grandmother's dietary intake
12	Murrin *et al.*[118]	Maternal macronutrient intake during pregnancy and 5 years postpartum and child weight status aged 5 years	Maternal prenatal sugar and SFA intake at both time points associated with offspring adiposity
13	Khalil *et al.*[119]	Maternal BMI, child aged 9 years	Significant association between overweight and obese maternal status and both current and future self-reported financial situation
14	Shrivastava *et al.*[120]	Grandparental morbidity and mortality to 2011 and infant birth-weight	Contrasting associations seen with inverse association between maternal grandmothers' risk of stroke or diabetes and infant birth-weight, but positive associations in paternal families for CVD risk factors and mortality
15	Viljoen *et al.*[121]	Grandparental mortality to 2012 and infant birth-weight	Positive association between infant birth-weight and paternal grandfather's mortality patterns

GMS, General medical services.

when the child averaged 3 years was inversely associated with maternal fruit and vegetable and fish consumption during pregnancy[114]. In Table 4, we show predictors of reported asthma for children at both time points when they were aged on average 3 and 5 years, replicating the original analysis at the new time point. Various biological, lifestyle and socioeconomic determinants of both child and maternal association that were significant predictors of asthma at the uni-variate level were included as covariates in multivariate models[115]. Separate logistic regression models were constructed to examine the effect of food group intake relative to asthma status at each phase of follow-up. Models were adjusted for combinations of birth-weight, sex, region, maternal age, maternal socioeconomic status (measured by education or GMS eligibility), parity, marital status and smoking in pregnancy. Oily fish intake proved to be protective of asthma at both year 3 (odds ratios (OR) = 0·52, 95 % CI 0·30, 0·92) and year 5 (OR = 0·51, 95 % CI 0·28, 0·92). Similarly, vegetable intake in the upper quartile proved protective at year 3 (OR = 0·42, 95 % CI 0·19, 0·93) and year 5 (OR = 0·43, 95 % CI 0·18, 0·99). This shows that mothers of asthmatic children tended to be younger, more disadvantaged and to have a lower oily fish, fruit and vegetable intake during pregnancy. Conversely, high intake of added or spreadable fats were related to asthma at year 3 follow-up (OR = 2·46, 95 % CI 1·34, 4·51). These data are quite consistent over the two time points and notably it is the baseline maternal dietary intake, rather than characteristics at aged 5 years, which show the main effects. The mechanisms through which this may operate are not as yet understood but may be nutrigenomic in origin and several other investigators have examined this question[128]. The Lifeways dataset has recently formed part of a pooled analysis as part of the CHICOS (Developing a Research strategy for Child Cohorts in Europe) consortium funded by the FP7 programme to elucidate these pathways further[12]; one analysis looked at the influence of maternal fish intake on birth outcomes[129] and another on how birth outcomes might predict risk of childhood asthma[130].

Table 4. Predictors of General Practitioner-reported wheeze (10·4 % of *n* 614) in children aged 3 years and of maternal reported asthma (14·3 % of *n* 511) in children aged 5 years in the Lifeways Cohort Study

Baseline predictors at age 3 years		Baseline predictors at age 5 years	
Maternal determinants		Maternal determinants	
Lifestyle		Lifestyle	
Oily fish – use *v.* non-use	OR = 0·52**†	Oily fish – use *v.* non-use	OR = 0·51**†
Vegetables – Q4 *v.* Q1	OR = 0·42**†	Vegetables – Q4 *v.* Q1	OR = 0·43*†
Fresh fruit – Q4 *v.* Q1	OR = 0·49*†	Fresh fruit – Q4 *v.* Q1	OR = 1·22†
Added/spreadable fats – Q4 *v.* Q1	OR = 2·46**†	Added/spreadable fats – use *v.* non-use	OR = 1·24†
Smoking in pregnancy – yes *v.* no	OR = 1·21	Smoking in pregnancy – yes *v.* no	OR = 1·62
Breastfeeding – ever *v.* never	OR = 0·62	Breastfeeding – ever *v.* never	OR = 0·84
Socioeconomic		Socioeconomic	
Education – 3rd level *v.* prim/sec school	OR = 0·69	Education – 3rd level *v.* prim/sec school	OR = 0·64
GMS eligible – yes *v.* no	OR = 2·26**	GMS eligible – yes *v.* no	No association
Marital status – lone *v.* cohabiting	OR = 1·84**	Marital status – lone *v.* cohabiting	OR = 1·24
Biological		Biological	
Age – continuous in years	OR = 0·99	Age – continuous in years	OR = 0·98
Parity – multip *v.* nullip	OR = 0·91	Parity – multip *v.* nullip	OR = 0·96
Baby's determinants		Baby's determinants	
Birth-weight – continuous in gram	OR = 1·00	Birth-weight – continuous in gram	OR = 1·00
Gestational age – continuous in weeks	OR = 0·92	Gestational age – continuous in weeks	OR = 0·98
Gender – female *v.* male	OR = 0·39**	Gender – female *v.* male	OR = 0·71
Region of birth – East *v.* West	OR = 2·03**	Region of birth – East *v.* West	OR = 1·23

GMS, General medical services; OR, odds ratio; prim, primary; sec, secondary; multip, multipara; nullip, nullipara.
* $P < 0·05$ ** $P = 0·05–0·09$
† Adjusted OR are reported for nutritional variables; all other values are from the univariate analysis.

Longitudinal follow-up when children were aged 9 years

Because these analyses to date showed such patterns of association across the generations, it was decided to follow-up adults and children again and between 2011 and 2013 further follow-up has taken place of the families. This included a short self-administered health questionnaire for all adults, with 1587 respondents in 593 families, 53·9 % of the original birth cohort families. A note search was undertaken initially in 2011 for grandparent deaths in the General Registry Office. Grandparental morbidity and mortality patterns were then related also to infant birth-weight. We related also the grandparents' blood pressure and lipoprotein profile at baseline recruitment stage to their grandchildren's birth-weight, the first such report to date and examined indicators of morbidity, stroke and diabetes based on self-report from the baseline questionnaire and general practice records for the grandparents at follow-up when the children averaged age 3 years. Maternal grandmothers' likelihood of both stroke and diabetes were inversely related to infant birth-weight and an inverse or U-shaped association was seen for maternal grandparents' mortality patterns, although not statistically significant. Conversely, the patterns for paternal grandparents and birth-weight were positive[120] and paternal grandfathers who had now died were more likely to have had higher birth-weight grandchildren, adjusted for grandchildren's gestational age, gender, mothers' age, height, parity, educational status, smoking in pregnancy and grandparents' age, smoking and educational status. Given the novelty of these findings, and the possibility that some form of participant self-selection had influenced the association, we extended the General Registry Office note search in 2012 to all grandparents for whom we had any contact details and not just those who had been examined or completed a questionnaire at baseline. Preliminary analysis of these data reconfirm a positive association between higher birth-weight and paternal grandfathers' mortality[121]. Our findings in relation to the maternal line were therefore broadly consistent with most other published studies[42,43]. Although the Norwegian linkage study shows

Table 5. Anthropometric measurements of Lifeways cross-generation cohort study children at birth, at age 5 and at age 9 years

	Mean	SD	Minimum	Maximum	Range
Measurements at birth (*n* 921)					
Weight (g)	3485·05	586	1090·0	5360·0	4270·0
Length (cm)	50·57	2·83	36·00	62·00	26·00
PI (kg/m^3)	26·86	3·35	16·1	61·2	45·1
Measurements at age 5 (*n* 568)					
Weight (kg)	20·92	3·04	13·3	34·6	21·3
Height (cm)	112·04	4·97	97·1	126·8	29·7
BMI (kg/m^2)	16·62	1·74	12·5	24·4	11·9
Measurements at age 9 (*n* 292)					
Weight (kg)	34·95	7·61	22·0	68·3	46·3
Height (cm)	138·50	6·78	119·1	158·3	39·2
BMI (kg/m^2)	18·13	3·25	11·9	38·4	26·5

a contrasting pattern to ours in relation to the paternal lineage[43], in that both paternal and maternal grandparental cardiovascular mortality patterns were inversely associated with birth-weight, there was an important effect for maternal smoking on that relationship and secular influences on lifestyle may be explaining the differences in patterns in the cohorts to date. There are very few evidenced studies published on this issue, which merits further research and investigation.

During 2012 we conducted examinations through their general practitioners of height and weight of children and their mothers and took salivary and hair samples for future genotyping, 301 were successfully completed and seventy-six of these mainly Dublin-based children also had blood samples taken for lipoprotein profile. Anthropometric measurements at birth, when children were aged 5 and 9 years are summarised in Table 5. We assessed the representativeness of the children who participated in the 2012 follow-up and had valid height and weight measurements. We compared these children with our original baseline cohort in terms of mothers' age, baseline BMI, education level and medical card holder status[119]. A greater proportion of children at follow-up had mothers who did not hold a medical card (90·3 *v.* 79·2 %, $P<0·001$) and achieved a tertiary level of education (60·3 *v.* 45·4 %, $P<0·001$). Mothers were also slightly older than the cohort at baseline (mean age 32·0 years *v.* 29·0 years, $P<0·001$) but did not differ significantly in BMI. The east coast grandparents are undergoing a cardiovascular risk profile assessment in 2013, including also salivary and hair samples and morbidity follow-up of grandparents through general practitioners is ongoing in 2013. In the next stage of this study, a detailed analysis of these biological outcomes will be undertaken, related to the information gathered in previous sweeps of the study.

Conclusions

In the present review, we establish that there is renewed and increasing interest in the associations between intrauterine and early childhood development and health outcomes in later life and the possible explanatory mechanisms, particularly in relation to dietary intake. There are contrasting mechanisms for lower birth-weight and higher birth-weight infants, often within the normal clinical range for this parameter. Empirical studies have focused in recent years on possible genetic and epigenetic mechanisms. Although some authors maintain that studies showing observational associations across generations are subject to significant bias, which may be addressed by more robust, un-confounded genetic associations across generations, the evidence base is at an early stage. Human cross-generation studies of parents and children are increasingly common but three-generation studies are rare. The Lifeways cohort study is unusual in that it contains information on three generations of family members and dietary information on all active cohort members including adults and children. Empirical evidence to date shows consistent familial and cross-generational patterns, particularly in the maternal line. The latest sweep includes biological information on children for the first time, including samples for genetic profiling.

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Conflicts of Interest

None.

Authorship

All authors are members of the present Lifeways study team and contributed to the drafting and scientific content of this paper. C. K. has been principal investigator of the study team since its establishment and has overseen all sweeps and data analyses to date. C. M. and A. S. received the PhD degrees for their work on the 2007 sweep when children averaged age 5 years, K. V., H. K. and R. S. are presently completing their PhD degrees on the 2011–2013 sweep. J. O'B. is data manager for the study.

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