BMA

Life course and developmental origins of adult health and disease

Professor Christine Power
and Professor Diana Kuh

British Medical Association
bma.org.uk

About the authors

Professor Christine Power

Professor Chris Power is based at the UCL Great Ormond Street Institute of Child Health within the Population, Policy and Practice programme. Chris is a life-course epidemiologist whose research focuses on the early life origins of social inequalities in health, early life adversities and their long-term outcomes, as well as influences on growth, obesity and development at different life stages. She contributed to the establishment and development of life-course epidemiology, which examines social, psychological and biological influences onwards from the earliest stages of life on later health outcomes. She has published extensively using longitudinal data from the 1958 British birth cohort, and has contributed to biomedical data creation of this study in mid-adulthood. She works with several national and international collaborations, such as the *Public Health Research Consortium* and the Research Network on *Later-Life Interventions to Reverse Effects of Early Life Adversity.*

Professor Diana Kuh

Diana Kuh is Professor of Life Course Epidemiology, Director of the MRC Unit for Lifelong Health and Ageing at UCL, and Director of the MRC National Survey of Health and Development (NSHD). NSHD is the oldest of the British birth cohort studies that has followed up over 5000 individuals since their birth in March 1946, and has developed into an integrated and interdisciplinary life course study of ageing. Diana helped to create and advance the field of life course epidemiology which studies how biological, psychological and social factors at different stages of life, independently, cumulatively or interactively affect adult health, ageing and chronic disease risk. In a broad range of more than 400 publications she has shown the importance of childhood physical and cognitive development and lifetime socioeconomic factors, lifestyle and prior health experience on later adiposity, cardiovascular, reproductive and musculoskeletal function, quality of life and survival. Her latest co-edited book *A life course approach to healthy ageing* was published by Oxford University Press in 2014.

Developmental Origins of Health and Disease and life course research benefitted hugely from the inspirational work of the late Professors Barker and Hertzman. We are indebted to them both for their tremendous insights, imagination, enthusiasm and seminal contributions to the field.

Life course and developmental origins of adult health and disease

This update builds on the original chapter by Professor David Barker on the Fetal Origins of Adult Disease (FOAD), showing how this research area has broadened and deepened over the last few years. To set these advances into their wider historical context we note that the idea that early life experience could have long-term influence on adult health and survival had been a key element in the national debate about population health and industrial efficiency in the first half of the twentieth century which led to systems and policies for monitoring and improving child health. In the post-war period, with child health improving, research attention had turned to adult lifestyles as the main risk factors for chronic diseases, although empirical evidence about the importance of early life for later health continued to slowly accrue. However, the research undertaken by Professor Barker and his team from the mid-1980s which widened into the Developmental Origins of Health and Disease (DOHaD), was a major catalyst for an explosion of interdisciplinary life course research that continues in the second decade of the twenty-first century.

Life course research, of which DOHaD is an integral part, has provided evidence that what happens in utero, in childhood and adolescence, and across generations, affects adult health, disease and ageing. The health outcomes studied now extend beyond the original focus on cardiometabolic disease to encompass more chronic diseases and the natural history of physiological functions. Studying function at the individual or multi-system level, at the body organ or system level, or at the molecular and cellular level facilitates the investigation of

health across life, before disease is manifest. It has led to a greater focus on the links between development and ageing, the progressive impairment of function post maturity.[1] Identifying potential sensitive periods when rapid change occurs in lifetime functional trajectories, the drivers that shape these trajectories, and how they in turn shape disease risk can help design the timing and type of effective primary interventions. It is increasingly recognised that long-term health consequences flow from normal variations across the range of physiological processes, not just at the pathological level; and that long-term health consequences of some early insults may occur when there is 'mismatch' between the pre-natal and post-natal environment.[2] It is also increasingly recognised that sensitive developmental periods occur not just in fetal life but during infancy, childhood and adolescence.

Since the original publication, the early physical and social exposures that impair or promote lifelong health are being better characterised and their differential effects studied. Three examples must suffice. First, the early FOAD focus on poor maternal and fetal nutrition[3] has been extended to include fetal exposures such as defective placentation, maternal glucose intolerance or hypertension, and psychological stress, and also to encompass environmental chemical exposures at any stage of development that may have long-term effects.[4,5] Second, research increasingly distinguishes the effects of the prenatal, prepubertal, and pubertal stages of the growth trajectory on a range of health outcomes (see illustrative examples).[6,7] And third, research is characterising how various material and psychosocial adversities in early life have differential impacts on later life health (see illustrative example).[8] What is clear is that while poverty, neglect and abuse have many powerful negative lifelong consequences, effects are generally graded across the social distribution. This is important given the growing social inequalities in child health in the UK, and the UK's poor rankings on child wellbeing and on inequality compared to 29 other rich countries.[9,10]

The life course approach studies the pathways that link physical and social exposures from early life onwards to later health outcomes. For some researchers, understanding the biological mechanisms is now the prime concern. Evolutionary biology has come to provide a broad interpretative framework for understanding why adaptations made by the fetus or infant during critical periods of growth and development increase the chances of survival in the short term and reproductive success, but may have negative long-term effects on health; developmental biology is increasing our knowledge of this developmental plasticity, including transgenerational mechanisms;[11] and the emerging field of epigenetics is showing that the early environment alters gene expression in ways that may have lifelong consequences.[12] Epigenetic mechanisms may be one way in which early social adversities 'get under the skin' and become biologically embedded:[13,14,15,16] other potential key mediators include inflammation, neuroendocrine processes (particularly of the HPA axis), and neural structure and function.[17]
-Other researchers focus on behavioural, psychosocial or socioeconomic pathways whereby exposures in childhood and adolescence lead to cumulative long-term damage to health, or where a chain of risk is established where one adverse experience makes subsequent adverse experiences more likely. In addition, increasing attention is being given to understanding the nature of physiological, psychological or social resilience that helps to maintain health and function in those who experience a poor start to life.

Given these advances in life course research, we focus this update on three areas of importance for adult health, namely body size and composition, cardiometabolic function, and physical and mental capacities, where there is growing evidence that early life plays an important role. As an exhaustive review is beyond the scope of this update, we draw mainly on our own research in the two oldest British birth cohort studies - the MRC National Survey of Health and Development (NSHD) started in 1946, and the National Child Development Study (NCDS) started in 1958.[18]

Developmental origins of body size and composition

Body size and composition are a focus of concern because of the health burden associated with obesity and low muscle mass, together with the increasing trend in obesity prevalence over a relatively short period: in England, prevalence among adults has risen from approximately 16% to 24% in women and from 13% to 26% in men over the period 1993 to 2013.[19] Children are also now more likely to be overweight or obese than previous generations and to have an earlier age of onset.[20] Yet importantly in terms of developmental origins, most of today's middle-aged and older adults were not overweight in their childhood but many have gained weight over the course of their adult lives. This trajectory of adiposity gain has implications for cardiometabolic function (see below) and is a focus of recent research. Tracking the lives of individuals over decades the UK cohorts indicate several of the developmental factors that influence life course body size.

Early life: Growing evidence on early life determinants implicates factors representing poor nutrition and growth in the development of adult adiposity in the UK. For example, early life socio-economic disadvantage, a marker for poor nutrition and living conditions, has been associated with more rapid gain in BMI from child to adulthood[21,22] and within adulthood.[23] In childhood, the social gap in adiposity has widened in recent decades, as early life disadvantage has become associated with higher BMI.[24] Low birthweight and factors linked to poor fetal growth such as maternal smoking in pregnancy have also been linked to rapid BMI gain or obesity in adulthood.[21-25] Despite mounting evidence for an effect of maternal smoking in pregnancy on offspring adiposity gain, so far the underlying explanations are unknown. Yet findings for early life disadvantage, low birthweight and maternal smoking in pregnancy are consistent with a developmental origins approach whereby trajectories of BMI are set in train in response to environmental influences early in development. Research is underway on potential mechanisms linking early life influences to later adiposity (e.g. via gut microbiota[26] or epigenetic mechanisms).

Intergenerational: Children of overweight or obese parents are at greater risk of obesity than children of normal weight parents and this effect persists throughout their life, i.e. from the early years to adulthood. This well-established intergenerational association is partly due to genetic factors, although genetic contributions may not be fixed over the life course or over time. For example, obesity susceptibility gene variants were shown to mainly affect weight gain in childhood rather than gain at later stages of life.[27] Studies comparing different generations show stronger parent-child obesity associations in more recent than older generations in the UK[24] and new evidence on increased effects of genetic susceptibility for later born generations suggests that genetic factors have interacted with environmental changes during development related to era of birth.[28] However, intergenerational associations may also be due to intrauterine over-nutrition with greater nutrient transfer from obese mothers to the growing fetus, potentially leading to permanent changes in appetite, metabolism, and other functions. An example of supporting evidence for such effects is provided by studies showing that significant weight loss associated with surgery in severely obese mothers was accompanied by reduced prevalence of obesity in their children.[29] But it is uncertain whether the intrauterine environment affects adiposity of offspring at less severe levels of maternal obesity.[30] Debate is ongoing on the public health impact of dramatic increases in maternal obesity (prevalence in women of child-bearing age, 16-44 years in England rose from approximately 12% in 1993 to 20% in 2013)[19-31] on adiposity levels of future generations. Given the secular trends, younger generations will be more exposed to over-nutrition prenatally than their predecessors. In terms of underlying mechanisms, research in animals, and increasingly in humans, suggests that intrauterine environment (e.g. associated with maternal under-nutrition, obesity and gestational diabetes) and postnatal adversity factors may affect later adiposity via epigenetic alterations.[32,33] The mechanisms whereby the intrauterine environment promotes adiposity in offspring throughout life is an active area of current research.

Accumulating lifetime factors: Several factors in childhood, adolescence and adulthood have been related to adiposity gain and development of obesity. For example, individuals maltreated in childhood have an increased risk of obesity in adulthood across several population samples.[34] In particular, childhood physical abuse has been related to an increased rate of gain in BMI through to mid-life[8], although causality and underlying mechanisms are not yet known. Other adversities, such as sleep deprivation in childhood and at later life-stages, are implicated in recent studies of adiposity,[35,36] whilst health behaviours at different life-stages, including frequent television viewing, low activity levels and fast-food consumption, have also been associated with adiposity gain or obesity.[37,38,39] Some studies suggest that, in turn, obesity leads to less physical activity.[40]

There is growing evidence to suggest that risk of later obesity increases with accumulation (i.e. higher number) of early and lifetime factors.[41,42] Faster weight gain in childhood predicts later obesity and earlier timing of menarche[43,44] and tracking of obesity from child to adulthood is known to be strong.[45] This strong tracking highlights the importance of delaying obesity onset, particularly as those with early onset have a higher BMI and waist circumference than those with later onset.[46]

Increasingly, life course studies are investigating childhood influences on direct measures of body composition in adulthood; this includes fat and lean mass which BMI does not distinguish, and bone size, strength and density. For example, in the NSHD, higher birth weight and prepubertal weight gain were associated with greater appendicular lean mass,[7] and bone strength[6] in early old age; whereas greater weight gain in childhood and adolescence was associated with higher fat mass, fat to lean ratio and android to gynoid ratio (i.e. an 'apple-shaped' body). Faster gain in BMI from puberty onwards was associated with lower muscle quality (derived from dividing the maximum grip strength by upper body appendicular lean mass).[47] Those living in less favourable socioeconomic circumstances across life tended to have more fat and less muscle in early old age, and had a higher android to gynoid ratio; the effects of childhood socioeconomic position were partly attributed to earlier differences in pre-adulthood weight gain.[48] These different patterns of body composition, the reduction in muscle mass and increase in fat mass with age are particularly important for cardiometabolic function and physical capacity and their change with age.

Developmental origins of cardiometabolic function

Much research since the FOAD hypothesis continues to focus on cardiometabolic outcomes, particularly using markers of function such as blood pressure, lipids, and indicators for diabetes (glucose and insulin) that can be investigated throughout life. Commonly studied developmental factors include body size and socioeconomic position at different life stages, both of which have been interpreted as markers for nutrition or more general living conditions. Research on these factors has in part sought to further test the FOAD hypothesis, although its main purpose has been to consider whether growth and social conditions at specific life stages have a predominating influence on cardiometabolic function.

Body size and trajectories over the life course: The effects of poor fetal growth, as indexed by low birthweight, have been confirmed in systematic reviews and meta-analyses showing associations with higher blood pressure in adulthood,[49] type 2 diabetes risk,[50] and weakly, with adverse lipid profile.[51] Relatedly, systematic review and meta-analysis of preterm birth show associations for blood pressure and LDL cholesterol but not for BMI, fasting insulin or glucose.[52] How such indicators of poor fetal growth combine with the strong effects of current body size in adulthood has been a focus of recent research, with attention on lifetime growth trajectories, mainly for adiposity.

The long follow-up of the older UK cohorts has been invaluable in showing the child to adult weight/ BMI trajectories related to adult cardiometabolic disease risk[18] and its change with age.[53] These cohorts suggest that for specific biomarkers it matters how an individual arrives at the BMI they have in adulthood, i.e., their BMI trajectory. Whilst others show that fast weight gain in infancy predicts higher adult blood pressure,[54] the birth cohorts show that it is not just weight gain in infancy that is detrimentally associated with adult cardiometabolic

risk factors such as blood pressure, but also excessive gain across childhood, adolescence and adulthood.[55] Individuals who were thinner in childhood/ adolescence appear to be more vulnerable than others to the effects of gains in BMI for blood pressure[56] and lipids.[57] Excessive BMI gain is also associated with elevated glucose levels or risk of type 2 diabetes[46,58] but in this instance, effects are stronger for those who were heavier rather than thinner in childhood.[46] Recent research in Britain and elsewhere, suggests that individuals with a high BMI in both child and adulthood have the highest risk of type 2 diabetes[46,59] most probably due to their high adiposity level in adulthood. Additionally, a high BMI in childhood but not in adulthood does not appear to increase the risk of type 2 diabetes,[46,58,59] a finding that is consistent with the lowered risk of diabetes associated with weight loss e.g. following surgical or lifestyle intervention. The impact of secular trends (such as earlier age of obesity onset) on cardiometabolic function is not yet clear, although some insights are available. For example, a recent comparative study of the cohorts born in 1946 and 1958 suggested that the effects of rate of BMI gain on adult blood pressure had not diminished over time, but were stronger in the younger generation.[55]

Studies of obese mothers, for whom there is an increased risk of insulin resistance and gestational diabetes during pregnancy, suggest that their children may be at risk of metabolic disease later in life.[60] Intrauterine mechanisms are implicated, for example, by comparison of offspring born before and after surgery for severe obesity. Those born after maternal weight loss following surgery show improved cardiometabolic function (lower fasting insulin, glucose and triglycerides and higher HDLc) at age 2–26 years.[29] More evidence to confirm such effects, their applicability to less severe obesity and on mechanisms is warranted.

Socio-economic conditions over the life course: The UK birth cohorts demonstrate life-long associations between early socio-economic conditions and later measures of cardiometabolic function, separate from (and accumulating with) the well-known associations with adult social position. Early socio-economic disadvantage predicts a poorer cardiometabolic profile in adulthood, across several measures including blood pressure, inflammatory and endothelial markers, metabolic syndrome.[18] Physiological effects of early disadvantage are recognised internationally[61] as affecting future inequalities in cardiometabolic outcomes. In addition, there is growing evidence for links between other childhood adversities such as maltreatment and adult cardiometabolic function,[62,63] and research to unravel possible explanations is currently underway.

Developmental origins of adult mental and physical capacities

It has been long-established that the early environment, from the intrauterine period through to early adult life, along with genetic inheritance, powerfully shapes cognitive, emotional and physical development. Recent research often involves imaging markers of function and structure;[64,65] for example, an MRI study showing how birthweight and other neonatal characteristics shape brain development.[66] Positive environmental stimuli are required for children to meet their full developmental potential; material and psychosocial adversities can impair or delay development. In turn, indicators of developmental and educational attainment, along with environmental and genetic factors, are associated with adult mental (cognitive and emotional) and physical capacities.[67,68,69,70,71] The evidence base is being strengthened by studies that better characterise the timing, type and severity of early adversities, developmental trajectories, and the range of adult outcomes and their change over time (see illustrative examples).[72,73] Interestingly, the key mediators of biological embedding of early adversity noted above, namely inflammation, neuroendocrine processes and neural structure and function, are also seen as key biological mechanisms, along with changing body composition, of later life functional decline and the emergence of frailty.[74]

Increasingly, functional ageing is assessed using tests of strength, physical performance (such as walking speed, chair rising, standing balance) and cognitive performance (such as verbal memory and processing speed). Maintaining function is associated with continued independent living, whereas reduced levels of performance predict subsequent morbidity and mortality.[75] There is strong evidence from systematic reviews that disadvantaged

childhood socioeconomic conditions are associated with poorer walking speed and chair rise time right across life.[76] NSHD findings show striking similarities in childhood relative social inequalities of a range of tests of physical and cognitive performance in men and women in their early sixties; various pathways across life were implicated, including both physical growth and neurocognitive development.[77]

For example, there is strong evidence that lower birth weight is associated with lower grip strength across life, independent of later body size.[78] NSHD findings show that prepubertal height and weight gain were also positively associated with midlife strength and physical performance, but weight gain from puberty onwards had adverse effects on performance,[70] except for grip strength in men which was probably due to pubertal muscle development.[69] Neurodevelopmental indicators, such as infant motor milestones, childhood cognitive ability and adolescent motor co-ordination are also related to adult physical inactivity,[79,80] physical and mental performance,[68;70] and brain structure.[81,82]

Concluding remarks

In 1976, the Court Report on child health services emphasised 'the extent to which experience in childhood determines the adult outcome' noting that during growth, the child is 'literally being created by the slowly forming imprint of experience, the essential tension between the biological and the social, hereditary and environmental influences'.[83] It argued that 'the effects of early disadvantage can be much diluted by the environmental circumstances the child encounters during the middle and later years of childhood; and that it is especially worth making this corrective effort because early disadvantage leads to later disadvantage, so that, unless there is an intervention, there develops a compounding of the difficulties. It is this chain of events that is influential rather than the critical effects of particular circumstances in early life considered in their own right'. Forty years later, Dame Sally Davies in the Annual Report of the Chief Medical Officer for England 2012, entitled 'Our children deserve better: prevention pays' acknowledged the 'growing knowledge of the complex interplay between psychosocial events and biological factors, and we now understand that events that occur as a fetus and in early life play a fundamental part in later life, and indeed in the lives of future generations….The evidence base for the life course approach is strong. What happens early in life (indeed in fetal life) affects health and wellbeing in later life'.[84] Professor Barker's research suggested that some insults in the prenatal and early postnatal period could be critical and difficult to modify. This key question on whether early damage to health can be lessened or eliminated is a challenge for current research that raises further questions on how difficult it is to achieve, and on the most effective type and timing of interventions.[85] However, the ultimate goal to achieve individual well-being and societal wealth, is to provide safe and secure environments in which each generation can have a healthy start to life.

Recommendations

The following four main recommendations require action beyond individual behaviour that is at national level, to address the broader social and economic drivers influencing early environments and possible remedial actions.

1. There is strong and growing evidence that many aspects of adult health have their origins in prenatal and child development. Thus, societal efforts to support the maximisation of physical, cognitive and emotional development of children are a high priority to promote health at later life stages, including independence and functioning in old age. These efforts are needed for all children, and in particular for the most vulnerable. Foremost, strategies should be devised to **prevent all forms of early adversity**, including deprivation or trauma. For example, by providing:

   – support to all new parents during pregnancy, childbirth and infancy to enable parents to give their children the best start to life. This includes material and emotional security and access to effective health visiting
   – support for families to provide stimulating environments that maximise all aspects of child development, e.g. through the Sure Start programme
   – effective regulation of, and protection from, hazards in the physical environment that are known to disrupt child development with long-term health consequences
   – extra support for vulnerable families where the physical, cognitive or emotional development of children is delayed
   – effective protection for children from abusive or neglectful parents and other adults

2. Life course research reveals that factors at different life stages combine (interact and/ or accumulate) to influence later health outcomes. This suggests that, in many instances, it is **never too late** to lessen the health burden associated with a poor start in life. Interventions to reduce the short-term and lifelong impact of early life adversities need to be developed, evaluated and implemented. For example, by providing:

   – safety nets for adolescents and young adults who make choices that harm their health, enabling them to return to a healthy trajectory
   – effective services that reduce the chance of smoking initiation, and cut down alcohol consumption, and offer effective ways of ceasing smoking and alcohol abuse
   – effective services to support young adults during the transition from education to work and in leaving the parental home
   – effective contraception services for young women and men and pre-pregnancy advice so that every baby is wanted

3. Key to healthy adult cardiometabolic and other functional outcomes is to prevent or **delay onset of obesity**, particularly in childhood and adolescence, and adiposity gain at any life-stage. Action is needed to weaken the parent to child intergenerational obesity link, to reduce continuity (i.e. tracking) of obesity from child to adulthood and to prevent excess adiposity gain. For example, by:

   – optimising the chance of good nutrition by ensuring local availability of food outlets that facilitate good nutritional choices, and offering advice to parents, children and young adults
   – optimising the chance of healthy exercise by ensuring local availability of open spaces, public facilities and transport options that facilitate good exercise choices, and offering advice to parents, children and young adults for initiating and maintaining exercise habits

4. **Social inequalities in adult health and function have their origins in socially patterned exposures and experiences during development.** Policies and interventions that focus on reducing these social differences are needed to address inequalities in adult health as well as improving population health overall.

References

1 Kuh D, Cooper R, Hardy R et al (2014) *A Life Course Approach to Healthy Ageing (First edition)*. Oxford: Oxford University Press.

2 Hanson MA, Gluckman PD (2014) Early developmental conditioning of later health and disease: physiology or pathophysiology? *Physiological Reviews* **94**:1027-1076.

3 Barker DJ, Gluckman PD, Godfrey KM et al (1993) Fetal nutrition and cardiovascular disease in adult life. *Lancet* **341**:938-941.

4 Balbus JM, Barouki R, Birnbaum LS et al (2013) Early-life prevention of non-communicable diseases. *Lancet* **381**:3-4.

5 Grandjean P, Barouki R, Bellinger DC et al (2015) Life-Long Implications of Developmental Exposure to Environmental Stressors: New Perspectives. *Journal of Endocrinology* **156**:3408-3415.

6 Kuh D, Wills AK, Shah I et al (2014) Growth from birth to adulthood and bone phenotype in early old age: a British birth cohort study. *Journal of Bone and Mineral Research* **29**:123-133.

7 Bann D, Wills A, Cooper R et al (2014) Birth weight and growth from infancy to late adolescence in relation to fat and lean mass in early old age: findings from the MRC National Survey of Health and Development. *International Journal of Obesity* **38**:69-75.

8 Power C, Pinto Pereira SM, Li L (2015) Childhood maltreatment and BMI trajectories to mid-adult life: follow-up to age 50y in a British birth cohort. *PLoS One* **10**:e0119985.

9 UNICEF, Adamson P (2010) *Report Card 9: The Children Left Behind: A league table of inequality in child well-being in the world's rich countries*. Florence: UNICEF Innocenti Research Centre.

10 UNICEF (2013) *Report Card 11: Child well-being in rich countries*. Florence: UNICEF Innocenti Research Centre.

11 Aiken CE, Ozanne SE (2014) Transgenerational developmental programming. *Human Reproduction Update* **20**:63-75.

12 (2015) *Special Issue: Epigenetics* 1083-1463.

13 Hertzman C (1999) The biological embedding of early experience and its effects on health in adulthood. *Annals of the New York Academy of Sciences* **896**:85-95.

14 Hertzman C, Boyce T (2010) How experience gets under the skin to create gradients in developmental health. *Annual Review of Public Health* **31**:329-347.

15 Suderman M, Pappas JJ, Borghol N et al (2015) Lymphoblastoid cell lines reveal associations of adult DNA methylation with childhood and current adversity that are distinct from whole blood associations. *International Journal of Epidemiology* **44**:1331-1340.

16 Suderman M, Borghol N, Pappas JJ et al (2014) Childhood abuse is associated with methylation of multiple loci in adult DNA. *BMC Medical Genomics* **7**:13.

17 Rutter M (2012) Achievements and challenges in the biology of environmental effects. *Proceedings of the National Academy of Sciences of the United States of America* **109 Suppl 2**:17149-17153.

18 Power C, Kuh D, Morton S (2013) From developmental origins of adult disease to life course research on adult disease and aging: Insights from birth cohort studies. *Annual Review of Public Health* **34**:7-28.

19 Moody A (2015) *Health Survey for England 2013, Volume 1, Chapter 10: Adult anthropometric measures, overweight and obesity*. England: Health and Social Care Information Centre.

20 Johnson W, Li L, Kuh D et al (2015) How Has the Age-Related Process of Overweight or Obesity Development Changed over Time? Co-ordinated Analyses of Individual Participant Data from Five United Kingdom Birth Cohorts. *PLoS Medicine* **12**:e1001828.

21 Parsons T (2005) *Childhood predictors of BMI trajectories; Childhood Obesity: Contemporary Issues*. United States: CRC Taylor & Francis.

22 Power C, Graham H, Due P et al (2005) The contribution of childhood and adult socioeconomic position to adult obesity and smoking behaviour: an international comparison. *International Journal of Epidemiology* **34**:335-344.

23 Strand BH, Murray ET, Guralnik J et al (2012) Childhood social class and adult adiposity and blood-pressure trajectories 36-53 years: gender-specific results from a British birth cohort. *Journal of Epidemiology & Community Health* **66**:512-518.

24 Pinot de Moira A, Power C, Li L (2010) Changing influences on childhood obesity: a study of 2 generations of the 1958 British birth cohort. *American Journal of Epidemiology* **171**:1289-1298.

25 Monasta L, Batty GD, Cattaneo A et al (2010) Early-life determinants of overweight and obesity: a review of systematic reviews. *Obesity Reviews* **11**:695-708.

26 Dogra S, Sakwinska O, Soh SE et al (2015) Rate of establishing the gut microbiota in infancy has consequences for future health. *Gut Microbes* **6**:321-325.

27 Elks CE, Loos RJ, Hardy R et al (2012) Adult obesity susceptibility variants are associated with greater childhood weight gain and a faster tempo of growth: the 1946 British Birth Cohort Study. *American Journal of Clinical Nutrition* **95**:1150-1156.

28 Rosenquist JN, Lehrer SF, O'Malley AJ et al (2015) Cohort of birth modifies the association between FTO genotype and BMI. *Proceedings of the National Academy of Sciences of the United States of America* **112**:354-359.

29 Smith J, Cianflone K, Biron S et al (2009) Effects of maternal surgical weight loss in mothers on intergenerational transmission of obesity. *Journal of Clinical Endocrinology and Metabolism* **94**:4275-4283.

30 Lawlor DA (2013) The Society for Social Medicine John Pemberton Lecture 2011: Developmental overnutrition--an old hypothesis with new importance? *International Journal of Epidemiology* **42**:7-29.

31 Health & Social Care Information Centre (2013) *Health Survey for England 2013.* England: Health & Social Care Information Centre.

32 Godfrey KM, Costello PM, Lillycrop KA (2015) The developmental environment, epigenetic biomarkers and long-term health. *Journal of Developmental Origins of Health and Disease* **6**:399-406.

33 Sharp GC, Lawlor DA, Richmond RC et al (2015) Maternal pre-pregnancy BMI and gestational weight gain, offspring DNA methylation and later offspring adiposity: findings from the Avon Longitudinal Study of Parents and Children. *International Journal of Epidemiology* **44**:1288-1304.

34 Danese A, Tan M (2014) Childhood maltreatment and obesity: systematic review and meta-analysis. *Molecular Psychiatry* **19**:544-554.

35 Nielsen LS, Danielsen KV, Sorensen TI (2011) Short sleep duration as a possible cause of obesity: critical analysis of the epidemiological evidence. *Obesity Reviews* **12**:78-92.

36 McEwen BS, Karatsoreos IN (2015) Sleep Deprivation and Circadian Disruption: Stress, Allostasis, and Allostatic Load. *Journal of Clinical Sleep Medicine* **10**:1-10.

37 Hancox RJ, Milne BJ, Poulton R (2004) Association between child and adolescent television viewing and adult health: a longitudinal birth cohort study. *Lancet* **364**:257-262.

38 Parsons TJ, Manor O, Power C (2008) Television viewing and obesity: a prospective study in the 1958 British birth cohort. *European Journal of Clinical Nutrition* **62**:1355-1363.

39 Viner RM, Cole TJ (2006) Who changes body mass between adolescence and adulthood? Factors predicting change in BMI between 16 year and 30 years in the 1970 British Birth Cohort. *International Journal of Obesity* **30**:1368-1374.

40 Richmond RC, Davey SG, Ness AR et al (2014) Assessing causality in the association between child adiposity and physical activity levels: a Mendelian randomization analysis. *PLoS Medicine* **11**:e1001618.

41 Gillman MW, Ludwig DS (2013) How early should obesity prevention start? *New England Journal of Medicine* **369**:2173-2175.

42 Robinson SM, Crozier SR, Harvey NC et al (2015) Modifiable early-life risk factors for childhood adiposity and overweight: an analysis of their combined impact and potential for prevention. *American Journal of Clinical Nutrition* **101**:368-375.

43 Druet C, Stettler N, Sharp S et al (2012) Prediction of childhood obesity by infancy weight gain: an individual-level meta-analysis. *Paediatric and Perinatal Epidemiology* **26**:19-26.

44 Ong KK, Emmett P, Northstone K et al (2009) Infancy weight gain predicts childhood body fat and age at menarche in girls. Journal of Clinical Endocrinology and Metabolism **94**:1527-1532.

45 Power C, Pouliou T, Li L et al (2011) Parental and offspring adiposity associations: insights from the 1958 British birth cohort. Annals of Human Biology **38**:390-399.

46 Power C, Thomas C (2011) Changes in BMI, duration of overweight and obesity, and glucose metabolism: 45 years of follow-up of a birth cohort. *Diabetes Care* **34**:1986-1991.

47 Cooper R, Hardy R, Bann D et al (2014) Body mass index from age 15 years onwards and muscle mass, strength, and quality in early old age: findings from the MRC National Survey of Health and Development. *Journals of Gerontology Series A Biolological Sciences & Medical Sciences* **69**:1253-1259.

48 Bann D, Cooper R, Wills AK et al (2014) Socioeconomic position across life and body composition in early old age: findings from a British birth cohort study. *Journal of Epidemiology & Community Health* **68**:516-523.

49 Huxley R, Neil A, Collins R (2002) Unravelling the fetal origins hypothesis: Is there really an inverse association between birthweight and subsequent blood pressure? *Lancet* **360**:659-665.

50 Whincup PH, Kaye SJ, Owen CG et al (2008) Birth weight and risk of type 2 diabetes: A systematic review. *The Journal of the American Medical Association* **300**:2886-2897.

51 Huxley R, Owen CG, Whincup PH et al (2004) Birth weight and subsequent cholesterol levels: Exploration of the "fetal origins" hypothesis. *The Journal of the American Medical Association* **292**:2755-2764.

52 Parkinson JR, Hyde MJ, Gale C et al (2013) Preterm birth and the metabolic syndrome in adult life: a systematic review and meta-analysis. Journal of *Pediatrics* **131**:e1240-e1263.

53 Wills AK, Lawlor DA, Muniz-Terrera G et al (2012) Population heterogeneity in trajectories of midlife blood pressure. *International Journal of Epidemiology* **23**:203-211.

54 Jarvelin MR, Sovio U, King V et al (2004) Early life factors and blood pressure at age 31 years in the 1966 northern Finland birth cohort. *Hypertension* **44**:838-846.

55 Li L, Hardy R, Kuh D et al (2015) Life-course body mass index trajectories and blood pressure in mid life in two British birth cohorts: stronger associations in the later-born generation. *International Journal of Epidemiology* **44**:1018-1026.

56 Li L, Law C, Power C (2007) Body mass index throughout the life-course and blood pressure in mid-adult life: a birth cohort study. *Journal of Hypertension* **25**:1215-1223.

57 Pinto Pereira SM, Power C (2013) Life course body mass index, birthweight and lipid levels in mid-adulthood: a nationwide birth cohort study. *European Heart Journal* **34**:1215-1224.

58 Owen CG, Kapetanakis VV, Rudnicka AR et al (2015) Body mass index in early and middle adult life: prospective associations with myocardial infarction, stroke and diabetes over a 30-year period: the British Regional Heart Study. *BMJ Open* **5**:e008105.

59 Juonala M, Magnussen CG, Berenson GS et al (2011) Childhood Adiposity, Adult Adiposity, and Cardiovascular Risk Factors. *New England Journal of Medicine* **365**:1876-1885.

60 Nicholas LM, Morrison JL, Rattanatray L et al (2015) The early origins of obesity and insulin resistance: timing, programming and mechanisms. *International Journal of Obesity* **40(2):**229-38.

61 Havranek EP, Mujahid MS, Barr DA et al (2015) Social Determinants of Risk and Outcomes for Cardiovascular Disease: A Scientific Statement from the American Heart Association. *Circulation* **132**:873-898.

62 Thomas C, Hypponen E, Power C (2008) Obesity and type 2 diabetes risk in midadult life: the role of childhood adversity. *Pediatrics* **121**:e1240-e1249.

63 Norman RE, Byambaa M, De R et al (2012) The long-term health consequences of child physical abuse, emotional abuse, and neglect: a systematic review and meta-analysis. *PLoS Medicine* **9**:e1001349.

64 Kim P, Evans GW, Angstadt M et al (2013) Effects of childhood poverty and chronic stress on emotion regulatory brain function in adulthood. *Proceedings of the National Academy of Sciences of the United States of America* **110**:18442-18447.

65 Noble KG, Houston SM, Brito NH et al (2015) Family income, parental education and brain structure in children and adolescents. *Nature Neuroscience* **18**:773-778.

66 Walhovd KB, Fjell AM, Brown TT et al (2012) Long-term influence of normal variation in neonatal characteristics on human brain development. *Proceedings of the National Academy of Sciences of the United States of America* **109**:20089-20094.

67 Richards M, Power C, Sacker A (2009) Paths to literacy and numeracy problems: evidence from two British birth cohorts. *Journal of Epidemiology & Community Health* **63**:239-244.

68 Richards M, Shipley B, Fuhrer R et al (2004) Cognitive ability in childhood and cognitive decline in mid-life: longitudinal birth cohort study. *BMJ* **328**:552.

69 Kuh D, Hardy R, Butterworth S et al (2006) Developmental origins of midlife grip strength: findings from a birth cohort study. *Journals of Gerontology Series A Biolological Sciences & Medical Sciences* **61**:702-706.

70 Kuh D, Hardy R, Butterworth S et al (2006) Developmental origins of midlife physical performance: evidence from a British birth cohort. *American Journal of Epidemiology* **164**:110-121.

71 Clark C, Caldwell T, Power C et al (2010) Does the influence of childhood adversity on psychopathology persist across the lifecourse? A 45-year prospective epidemiologic study. *Annals of Epidemiology* **20**:385-394.

72 Geoffroy MC, Gunnell D, Power C (2014) Prenatal and childhood antecedents of suicide: 50-year follow-up of the 1958 British Birth Cohort study. *Psychological Medicine* **44**:1245-1256.

73 Geoffroy MC, Pinto Pereira SM, Li L et al (2016) Childhood maltreatment and child-to-adulthood cognition and mental health in a prospective birth cohort. *Journal of the American Academy of Child and Adolescent Psychiatry* **55**:33-40.

74 Ferrucci L, Studenski S (2012) *Clinical problems in aging; Harrison's principles of internal medicine*. New York: McGraw-Hill 570-585.

75 Cooper R, Kuh D, Hardy R (2010) Objectively measured physical capability levels and mortality: systematic review and meta-analysis. *BMJ* **341**:c4467.

76 Birnie K, Cooper R, Martin RM et al (2011) Childhood socioeconomic position and objectively measured physical capability levels in adulthood: a systematic review and meta-analysis. *PLoS One* **6**:e15564.

77 Hurst L, Stafford M, Cooper R et al (2013) Lifetime socioeconomic inequalities in physical and cognitive aging. *American Journal of Public Health* **103**:1641-1648.

78 Dodds R, Denison HJ, Ntani G et al (2012) Birth weight and muscle strength: A systematic review and meta-analysis. *The Journal of Nutrition, Health and Ageing* **16**:609-615.

79 Pinto Pereira SM, Li L, Power C (2014) Early-life predictors of leisure-time physical inactivity in midadulthood: findings from a prospective British birth cohort. *American Journal of Epidemiology* **180**:1098-1108.

80 Pinto Pereira SM, Li L, Power C (2015) Early Life Factors and Adult Leisure Time Physical Inactivity Stability and Change. *Medicine & Science in Sports Exercise* **47**:1841-1848.

81 Ridler K, Veijola JM, Tanskanen P et al (2006) Fronto-cerebellar systems are associated with infant motor and adult executive functions in healthy adults but not in schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America* **103**:15651-15656.

82 Booth T, Bastin ME, Penke L et al (2013) Brain white matter tract integrity and cognitive abilities in community-dwelling older people: the Lothian Birth Cohort, 1936. *Neuropsychology* **27**:595-607.

83 Committee on Child Health Services (1976) *Fit for Future: Report of the Committee on Child Health Services (Court Report)*. Great Britain: Committee on Child Health Services.

84 Department of Health (2012) *Chief Medical Officer's annual report 2012: Our Children Deserve Better: Prevention Pays.* England: Department of Health.

85 National Institute on Aging: Network on Reversibility Meeting (14 October to 15 October 2013) https://www.nia.nih.gov/about/events/2014/network-reversibility-meeting.

British Medical Association
BMA House, Tavistock Square, London
WC1H 9JP
bma.org.uk

BMA 20160685