# NETWORK ON REVERSIBILITY

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## WORKSHOP SUMMARY

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### Executive summary

Early-life adversity can have significant impact on later-life health and wellbeing. Prenatal and childhood exposure to a range of adversities can set in train processes that affect both physical and mental health in adulthood. Since September 2012, the US–UK Network on Reversibility has been holding a series of interdisciplinary workshops to explore the potential of ‘reversibility’ strategies to counter the impact of early-life adversity. The Network’s third workshop was held in London, UK, in partnership with the Economic and Social Research Council (ESRC), with a focus on pathways and potential intervention strategies.

Adversity can take make forms, spanning inadequate maternal nutrition, neglect or physical or sexual abuse, and low socioeconomic status. Similarly, the impact of early-life adversity is highly diverse, affecting economic and social status, and many aspects of physical and mental health. Many of the diseases of adulthood have their roots in early experience.

The long-lasting impact of early-life adversity encourages a ‘life-course’ perspective on health and wellbeing. One implication of this model is that health interventions should consider not just proximal causes of disease but also earlier-life factors that have contributed to disease susceptibility.

Reversibility is one possible route to this end. It is based on the idea that some of the biological and psychological effects of early-life adversity can be reversed, alleviating the vulnerabilities leading to adverse health and social outcomes. Natural windows of opportunity may exist when human biology renders individuals more open to reversal strategies, or it may be possible to create such windows artificially. Moreover, it may be possible to delineate differences among individuals that enhance or diminish their lifelong vulnerability to early adversity as well as their responsiveness to preventive interventions.

This model depends on a sound understanding of the biological, psychological and social pathways that lead from adversity to adult outcome. Although undoubtedly complex, progress is being made in identifying and disentangling these pathways.

Insights into life-course effects have come from several sources, particularly birth cohorts, which provide longitudinal data across both social and medical domains. Intervention studies such as randomised controlled trials provide useful data on the malleability of outcomes. Experimental animal studies allow for more controlled investigation of early-life effects and more searching investigation of mechanisms of risk persistence.

Birth cohorts such as the UK’s 1958 cohort have been invaluable in establishing the life-course concept. Cross-cohort comparisons can also provide insight into the effects of social or other changes over time. Adult cohorts, such as the Midlife US (MIDUS) study, can also provide useful data. MIDUS has the advantage of deep metabolic phenotyping data, as well as neurobiological and cognitive profiling of some participants.

Pooling of data in meta-analyses can strengthen associations between early-life adversity and outcomes, while comparisons across studies can also be informative. For example, a meta-analysis has confirmed that maltreatment leads to obesity, and sheds light on a possible pathway through depression.

Early adversity acts at a number of levels (genetic, epigenetic, cellular, organ system, psychological and social) and through multiple biological systems (immune, endocrine, neuroendocrine and neural). It remains a major challenge to track the impact of adversity on these systems, and in particular to establish chains of causality potentially spanning several decades. Nevertheless, progress is being made in linking adversity to epigenetic modulation of gene expression, telomere biology, long-lasting changes in brain function and to sustained changes in personality.

The nature of adversity is also not well understood. Work is underway to clarify which forms of adversity are of most long-term significance and when, in the life course, adversity is most harmful – recognising that adversities often co-occur and can continue for extended periods.

A key question is how much of adult ill-health or poor social outcomes can be attributed to early-life adversity. Research on the Dunedin birth cohort supports the Pareto principle, that 20 per cent of the highest risk participants typically make up 80 per cent of adults with costly impairments in medical and mental health. Furthermore, around 80 per cent of these high-cost individuals can be predicted on the basis of early-life adversity scores.

Adult outcomes are strongly influenced by brain function and behaviour, which are moulded in early life. The mechanisms of brain plasticity are gradually being unravelled, raising hopes that it may be feasible to reverse maladaptive neural programming. It may, for example, be possible to open up windows pharmacologically using drugs such as fluoxetine, to enhance the impact of cognitive or other therapies.

Severe maltreatment has a lasting effect on the early brain, greatly increasing the risk of later-life psychopathologies. Exposure to abuse is associated with changes in the brain indicative of heightened threat awareness. This may be advantageous in a threatening environment, but is harmful over the longer term. Longitudinal studies may reveal ‘resilience factors’ that enable children to avoid the harmful downstream effects of abuse.

The 1958 birth cohort has shed light on the impact of early life on early adulthood, but also the extent to which early-adulthood factors influence later life. Multiple adversities influence early adulthood social status, but early-adult factors are themselves strong predictors of later-life status. Nevertheless, there is some ‘churn’ between categories, raising hopes that it may be possible to promote social mobility.

Pregnancy is a critical time in the life course. Through prenatal programming, pregnancy has a life-long impact on infant health, while early parenting is also an important influence on child development. Furthermore, pregnancy is a time of profound biological change, which may create a window for interventions for both mothers and their babies. Interventions to support women in pregnancy could benefit offspring, but also later pregnancies. Pregnancy as a focal point could also help to address the intergenerational transmission of adversity, as mothers’ maternal practices are strongly influenced by their own experience.

Nutrition is a critical aspect of pregnancy, with obesity and excessive weight gain a growing problem in western (and westernising) populations. As well as excess calorie intake, poor diets may lead to micronutrient deficiencies. Large-scale complex interventions are being organised to improve maternal diet.

One potential pathway from early-life adversity to adult outcomes is through changes in the length of telomeres, the structures that cap chromosomes. Early-life adversity is associated with accelerated telomere shortening, a biomarker of cellular ageing, although it is not clear if telomere shortening contributes directly to poor health or is a byproduct of more fundamental disease processes. In later life, a bidirectional relationship may exist – cellular stresses may drive telomere shortening, which may in turn contribute additional cellular stresses.

Inflammation is a further potential pathway for long-term harm. Inflammation is of short-term benefit, but chronic activation is associated with a range of disease processes – affecting both physical and mental health. Early-life adversity is associated with chronically raised levels of various inflammatory mediators.

New longitudinal studies would be both expensive and take time to generate results, so there is considerable interest in following up past interventions or expanding ongoing studies. However, adult interventions were typically not set up to address early-life adversity, and follow up would present practical challenges.

Considering intervention strategies, starting with all ‘at risk’ individuals might be too inclusive, but does provide opportunities to identify resilience factors limiting the impact of adversity. Understanding these factors could suggest targets for intervention, which could be assessed in trials. It might also be beneficial to adapt therapies to individuals, to reflect their personality type or neurocognitive capabilities.

A recurrent question is the potential differences between prospectively gathered and retrospectively reported measures of maltreatment in childhood. An analysis from the Dunedin birth cohort suggests only moderate agreement between prospectively and retrospectively gathered data, but the longer-term impact of both is similar.

Not all individuals exposed to adversity suffer ill-effects, due at least in part to their genetic make up. Genetic factors may confer on some individuals an ‘inherited sensitivity’ to adverse environments. However, in some circumstances, genetic make-up may increase sensitivity not just to adversity but also to positive environments – ‘differential susceptibility’. This raises hopes that those most vulnerable to adversity might also benefit most from interventions.

There remains a need to clarify further the pathways from early-life adversity to adult outcomes. More analysis of birth cohort data could shed light on these pathways, particularly with integration of biomarker analysis (telomeres, epigenetic markers, inflammatory mediators, brain imaging) and through cross-cohort comparisons. The potential to embed randomised controlled trials within cohorts needs to be considered, alongside studies of the impact of natural economic or other events.

Biological biomarkers are potentially powerful tools to identify those at risk of poor outcomes and to track the impact of interventions. However, more quantitative work is needed to assess their predictive power, while their relationship with downstream mediators (e.g. brain structure and function, neurocognitive phenotypes) needs clarification.

Opportunities may exist to extract additional data from ongoing studies, or to follow up or re-analyse data from past studies from a life-course perspective. Animal models continue to provide a complementary line of research, offering opportunities to test hypotheses and gather additional biological information.

An important issue to consider is the timing of interventions. The life-course approach emphasises the importance of trajectories, and suggests that early intervention has the potential to have greatest impact. There are, however, examples of successful adult interventions. Moreover, early-life interventions will never achieve 100 per cent success so a need will remain for adult interventions.

### MONDAY 14 OCTOBER

### MORNING SESSION: THE TOPOGRAPHY OF ADVERSITY AND PATHWAYS TO ADULT HEALTH

### Prenatal influences linked to adult health through gene expression mechanisms

As Keith Godfrey emphasised, the effects of early-life adversity are extremely broad. Just about every organ system is affected, with profound implications for physical and mental health. The initial effects may be subtle, and not immediately indicative of harm, but their long-term impact can be profound.

Many effects arise in the prenatal period, for example through programming of fetal physiology. Some effects of *in utero* adversity may be detrimental to a newborn, but some may have adaptive advantage – fetal programming may be a way to prepare offspring for a difficult nutritional environment. Problems may then arise when there is a mismatch between anticipated and actual environment, with a potential advantage becoming a liability.

Several studies have provided important clues to possible pathways mediating links between mothers’ behaviour, fetal traits, and offspring physiology and behaviour. Experimental studies have drawn attention to the importance of factors such as maternal nutrition, obesity and stress as critical factors affecting fetal growth and physiology.

One sign of a stressed pregnancy is a low-birth-weight baby. Low birth weight is a significant risk factor for adult disease, and is associated with a range of adverse neuroendocrinological responses (such as high stress hormone levels) and anxiety-related behaviour. It should be emphasised, however, that low birth weight is only a crude proxy measure for maternal influences that have long-term effects, and many such influences can have lasting consequences without necessarily affecting the infant’s size at birth.

Stress responses in offspring can also be influenced by maternal diet. Research on an Aberdeen cohort, for example, found that a high-protein diet given to mothers during pregnancy led to significantly elevated stress hormone responses in offspring at age 30[[1]](#footnote-1). It is likely that digestion of the red meat that women were advised to eat led to increased metabolic stress on the developing fetus, reprogramming its hypothalamic–pituitary–adrenal (HPA) axis and increasing stress sensitivity in offspring.

Low birth weight is also associated with temperament and behaviour problems in children. Pathway analysis suggests that this effect is mediated largely through differences in effortful control[[2]](#footnote-2). Magnetic resonance imaging (MRI) of adolescent offspring revealed a neuroanatomical correlate of this effect – reduced caudate size.

Evidence is accumulating that prenatal influences may be mediated by epigenetic changes – chemical modifications of DNA (e.g. methylation) or histones (e.g. acetylation) that alter gene expression. For example, Karen Lillycrop and colleagues found that, in the offspring of rats fed a high-protein diet, key metabolic genes showed significant changes in DNA methylation and expression levels, with corresponding changes in metabolic activity[[3]](#footnote-3) [[4]](#footnote-4).

Notably, these experimental changes could be blocked by supplementation of the maternal diet with folic acid. Folic acid could also reverse the effects of the high-protein diet when given to the offspring during post-natal life – but only during specific periods such as puberty. Such findings hint at the possibility of ‘windows’ when individuals might be receptive to epigenetic reprogramming.

It is tempting to speculate that the pubertal window, a second period of sensitivity to both adversity and intervention, may reflect the action of sex steroids, opening up chromatin structure to DNA-modifying enzymes. Although this approach has reprogramming potential, modifying chromatin conformation would open up the potential for both positive and negative environmental influences. Use of folic acid in this context also needs to be treated with caution, as it has many other effects.

Epigenetic effects can clearly have a significant impact on disease. In type 2 diabetes, for example, differential methylation has been identified at sites in the genome implicated in disease by genome-wide association studies. The effects of differential methylation at sites such as *FTO* are at least as large as those of coding genetic variants[[5]](#footnote-5).

Studying epigenetic effects remains technically challenging, particularly in large-scale high-throughput studies. Use of mass-produced arrays such as the 450k Illumina array has advantages in terms of rapid data collection, but also limitations – developed for cancer, it surveys less than 2 per cent of genomic CpG sites and not necessarily those of most interest to metabolic disease or behaviour.

Using an alternative, unbiased approach based on methyl-binding domain arrays and BATMAN software for analysis[[6]](#footnote-6), Godfrey and colleagues have attempted to identify methylation effects in gene networks associated with clusters of phenotypic traits, such as neuropsychological function, body composition and allergy, in well-characterised cohorts of children. In terms of cognitive function, this approach has implicated a network of genes associated with dienchephalon development, an association confirmed in two populations.

A similar approach has been used to identify differential methylation in networks potentially involved in childhood adiposity. *In vitro* studies have provided supportive evidence, showing that such methylation changes affect transcription factor binding and gene expression in metabolically relevant pathways. Such studies raise the possibility of identifying mechanistic links between adversity and outcomes at age 6.

There has also been interest in the possible impact of ‘genomic imprinting’ on fetal programming. At certain genomic sites, epigenetic modifications lead to differences in fetal gene expression depending on whether an allele is derived from the mother or from the father. Critically, several imprinted genes regulate growth of the fetus. These effects can be mediated through the placenta, which not only acts as the interface between fetus and mother but also has an endocrine function, inducing changes in maternal physiology and behaviour.

Although genomically imprinted genes have not to date been found to have a role in fetal programming, Rosalind John (Cardiff) has discovered that epigenetic effects at sites of genomic imprinting can lead to subtle changes in gene expression that influence birth weight. Such findings could reopen interest in genomic imprinting as a mediator of fetal programming. They also suggest a more bidirectional set of programming interactions between fetus (or placenta) and mother – the fetus/placenta influencing maternal behaviour before and after birth (which could in turn influence offspring development postnatally).

### The topography of adversity: Questions to consider

Jeanne Brooks-Gunn drew attention to a number of key issues that it would be helpful to address in order to understand the pathways linking early-life adversity to poor later-life health and social outcomes. A better understanding of such issues would also inform the development of interventions, particularly those targeting early-life stages.

One important issue is whether attention should focus on the most severe forms of adversity or more widely distributed but less extreme hardship. Child abuse and severe neglect receive much attention, and can have a significant impact on individuals affected, but should more attention be given to factors such as maternal depression or the impact of chaotic or turbulent households, which also have long-term impact and affect much larger numbers?

Indeed, it may be helpful to think more deeply about the nature of ‘adversity’. Poverty, for example, is an important long-term influence, but precisely which aspects of poverty are most significant? Furthermore, factors affecting child development often co-occur, so disentangling their effects may be difficult. A related but potentially important factor is the ‘weighting’ given to different forms of exposure: should all be viewed equally and simply summed to provide measures of exposure, or should some form of weighting be used? How can different forms of adversity be compared?

Another potentially important issue is the timing of adversity – does the age at which adversity is experienced have long-term significance? Few studies have addressed whether the age at which abuse or neglect occurs has an impact on long-term outcomes. Brooks-Gunn’s own analysis suggests that abuse experienced earlier in life does appear to have greater impact. A significant issue for such studies in that adversity is typically persistent, spanning time windows. Ultimately, though, it may be possible to discern whether there are periods when individuals are particularly vulnerable to adversity.

The importance of context also needs to be considered. For example, some studies have shown that the trajectory of changes in IQ and language skills after adversity vary according to whether families are living in poverty or not.

In terms of pathways, a critical issue is how individual lives unfold between the experience of adversity and the measured outcome in adulthood. These pathways are not yet well understood; cohort studies may provide a way in which they can be visualised. In particular, the impact of adolescence is rarely considered, yet the behaviours established in this critical period may be influenced by past adversity and, in turn, shape future risk behaviours. Life-long studies may help to pick out the mediating factors on the path from adversity to outcome, as well as possible external modulators that influence these trajectories, for better or worse.

It may also be helpful to consider the limitations of interventions. In a large randomised controlled trial of a highly intensive intervention of low-birth-weight infants, for example, effects on IQ and language development showed a distinct pattern. Infants with zero or one risk factors showed no benefits, being minimally disadvantaged. A treatment effect was seen in those with two or more risk factors, but even this intense programme could not help those at the extreme end of the risk scale.

Approaches exist to take a more person-oriented approach, such as classification trees, factor analysis and Boolean analysis, to identify factors that correlate with poor outcomes. Such analyses can reveal common factors, but run the risk of missing the specific elements that influence individual life history. Understanding how individual risk factors sum and interact with one another is a considerable methodological challenge.

### Pooling data on pathways across studies: The power of meta-analysis

Information on the impact of early-life adversity has traditionally come from two sources – studies in humans and in experimental animal systems. The latter have the advantage that the environment can be rigorously controlled and experimental subjects can be randomly assigned to treatment and control groups. Considering the impact of early-life adversity, for example, studies with non-human primates have clearly shown that early-life stress (peer-rearing rather than maternal care) leads to later-life obesity[[7]](#footnote-7).

For practical and ethical reasons, such studies are not possible in humans. Furthermore, it is unclear if the experimental conditions modelled in animals exert the same effects of more complex psychosocial experiences in humans. Some insight has come from ‘natural experiments’ – where a population or particular individuals have been exposed to adversity such as famine. These cases hint at cause and effect, but they are rare, usually lack a control group, and the circumstances are often unusual, raising questions about generalisability. Longitudinal cohort studies can provide information about natural populations, often over long periods. They identify associations, however, making it harder to draw conclusions about causality.

A recurrent theme is that human studies will inevitably have limitations. Nevertheless, they provide a valuable source of information. By shedding light on possible pathways, they generate leads that can be systematically assessed in experimental animal studies.

One way to address the drawbacks of individual studies is to apply statistical approaches such as meta-analysis – pooling of data from multiple studies. Andrea Danese drew attention to one particular analysis, of papers examining the links between early adversity – childhood maltreatment – and later-life obesity[[8]](#footnote-8).

This analysis collated information on 41 studies encompassing some 190 000 participants. In sum, the data confirmed an association between childhood mistreatment and adult obesity, with an average odds ratio of 1.36. Although not huge, the effect is significant and important at a population level because of the high prevalence of maltreatment: prevention or effective treatment of seven cases of childhood maltreatment could avoid one case of obesity in adulthood.

A risk in data pooling is that one large or anomalous study can skew findings. By systemically removing individual studies from the analysis, Danese was able to show that no one study had a strong biasing effect. A further risk is publication bias – studies finding no effect may be less likely to be published. Through modelling of the distribution of study findings, allowance can be made for the likely ‘missing’ false negatives. Such an adjustment led to a small shift in the odds ratio, to 1.21, which remains significant.

Furthermore, meta-analytic techniques can be used to extract additional value from data, exploiting the inevitable heterogeneity of multiple independent studies. Hence data could be grouped according to whether they were obtained prospectively or retrospectively, or from survey data or official records. Different types of adversity could be compared, as could different measures of outcome (BMI, waist size etc.). In general, such analyses mirrored patterns seen with the pooled data.

Meta-analyses also enable the possible effects of confounding or mediating factors to be examined, by pooling of studies that either did or did not make adjustments to take account of factors such as childhood or adulthood socioeconomic status or adult smoking. Such adjustments had little impact, with one striking exception – adult depression. Studies adjusting for adult depression showed markedly smaller effects, implying that depression and obesity sit on the same casual pathway. Depression could therefore be a mediator of obesity, but the reverse relationship (or reciprocal interactions) cannot be ruled out.

Potentially, meta-analyses could offer insight into the impact of different adversity factors or the timing of adversity. Fostering of children could act as a proxy measure of the cessation of maltreatment, for example, providing a way to examine the impact of adversity at different ages, potentially drawing on data already being collected in fostering interventions. Differing US and UK practice on adoption – adoption at birth is more common in the USA – might also provide a basis for interesting comparisons.

### Delineating pathways using extended longitudinal studies

Cohorts starting at birth: Longitudinal cohort studies have proven hugely influential in establishing the life-course perspective on adult health. Studies of birth or other long-term cohorts have clearly established that events throughout the life course – prenatal, childhood or later – have a significant impact on adult health.

A framework for this perspective, developed by Chris Power and colleagues, stresses the fact that multiple factors act on development pathways at stages throughout life[[9]](#footnote-9). It also emphasises the importance of trajectories – adult function will depend on peak function, typically achieved in early adulthood, and the subsequent rate of decline. Childhood factors can influence both the height of this peak and the rate of decline; adult factors can clearly affect only the latter.

Another important implication of this model is that it is not just outcome that matters – the route by which that outcome is achieved is also critical. The health risks of adult obesity are different for those who were obese in childhood and those who were not.

Longitudinal data can shed important light on developmental pathways, the factors that shape them, and the implications of differences between them. Although many adversities are shared, there are nonetheless groups affected only by one, allowing for more nuanced associations to be made between adversity and outcome.

Hence, analysis of data from the UK 1958 birth cohort has revealed that childhood neglect affects height, reduced stature being a well-established risk factor for cardiovascular disease[[10]](#footnote-10). The effect of childhood neglect is different from that of childhood abuse, which shows no association with height. The findings begin to suggest possible mechanisms – neglect might be associated with poor nutrition while abuse is not. More fine-grained analysis may enable the effects of childhood adversity at different ages to be studied.

Similarly, the data can be used to look at how different forms of childhood adversity lead to different outcomes. Neglect and sexual abuse, for example, differ in their impact on cognitive development and emotional wellbeing in adulthood. Neglect typically affects both aspects of development, while abuse has a much stronger impact on emotional development.

Moreover, how these impacts shift between adolescence and adulthood may shed light on important moderating factors. It would be particularly interesting to know whether the mitigation of effects is seen across the whole population or is confined to certain subgroups (and, if the latter, what distinguished these individuals from their more badly affected peers).

A remarkable demonstration of the hidden power of the life-course perspective comes from studies of suicide risk[[11]](#footnote-11). Suicide prevention has focused very heavily on proximal risks – life traumas increasing the risk of suicide. Yet cohort studies have shown that factors such as low birth weight, birth order and young maternal age and early emotional adversities influence suicide risk. Other work is raising the possibility that those who attempt suicide show distinctive cognitive abnormalities, the roots of which could conceivably lie in early-life exposures.

Cohorts starting at midlife*:* Other cohorts may capture information that could be analysed to shed light on causal pathways, mediating mechanisms and modulatory influences. One is the MIDUS (Mid-Life in the US) study[[12]](#footnote-12), described by Teresa Seeman.

Established in 1995/96, MIDUS aims to examine the long-term psychosocial factors influencing mid- and later-life health and wellbeing, and explore the possible neurobiological mechanisms mediating these effects. As well as mediating factors and modulating influences, the study may also reveal protective factors mitigating the impact of early-life adversity.

MIDUS began as a national representative sample of 6325 US residents aged 25 to 75, initially interviewed by phone. The study was expanded in 2005, to add direct contact and collection of biological material. As well as repeating the initial question, MIDUS2 has introduced a number of substudies, including a ‘daily diary’ study, phone-based cognitive assessments, and intensive physiological typing of 1200 participants. A subset of these subjects also undergo neurological assessment, including EEG and structural and functional MRI.

As well as this unusually deep physiological and neurobiological phenotyping, MIDUS also includes significant numbers of monozygotic and dizygotic twins as well as sibs. It has gathered data (retrospectively) on childhood adversity, categorised as socioeconomic (family education, relative income, parents on welfare) or socioemotional (parental death or divorce, abuse).

Both early socioeconomic and socioemotional adversity are associated with worse adult allostatic load (a measure of dysregulation across multiple metabolic systems). Adjustments for adult education eliminate the former association, suggesting it may be mediating the impact of early socioeconomic adversity. The impact of early adversity is significant – for adults with all early risk factors, it is equivalent to ten years of ageing.

Adjusting for adult health behaviours such as smoking or physical activity removes 60 per cent of the association for socioeconomic adversity and 40 per cent of the association for socioemotional adversity. Hence the data are capturing some of the routes by which early adversity impacts on metabolic health in later life. Data have not yet been stratified by participant age, but this may provide a way to examine whether the effects of adversity become stronger (or dissipate) in later life.

In terms of moderation, work with Greg Miller has shown that maternal nurturing can offset some of the negative effects of low socioeconomic status[[13]](#footnote-13). Among those exposed to a high socioeconomic status environment when young, levels of maternal nurturing had no subsequent impact on a measure of metabolic health. However, high levels of maternal nurturing lessened the detrimental effect of low socioeconomic status on metabolic health.

A similar effect has been seen in the CARDIA study, where the detrimental effects of childhood abuse are moderated by having a nurturing parent. (It is likely that the abusive and nurturing parents are different.)

Work led by Edith Chen, by contrast, has revealed adult factors that may mitigate the impact of early adversity[[14]](#footnote-14). Key psychological traits – being likely to learn from a bad experience, or to look for ways to solve a problem, as well as good emotion regulation and a strong future orientation, collectively referred to as ‘shift and persist’ – are associated with better overall biological risk profiles in adulthood after adversity. Again, this effect is seen only in those from a low socioeconomic status background. Potentially, the brain imaging data being collected in MIDUS could cast light on the neurobiological basis of these psychological differences.

### Approaches to estimating attributable risk

While the impact of early adversity on later life is now well recognised, it is less easy to quantify its impact on adult outcomes. To address this issue, Terrie Moffitt has used data from the Dunedin Multidisciplinary Health and Development Study[[15]](#footnote-15) to quantify links between childhood adversity and a range of adult social and health outcomes.

Launched in the 1970s, the Dunedin Study recruited around 1000 infants, 95 per cent of whom are still participating as adults. Moffitt has examined whether the cohort data support the ‘Pareto principle’, or the 80:20 rule, which suggests that 80 per cent of a given outcome relate to the actions of 20 per cent of the population. The principle has been found to hold in a wide variety of situations.

Across a range of measures, the Dunedin data are consistent with the Pareto principle. For welfare support, pack-years of cigarette smoking, and childhood years spent without a father, 20 per cent of the population account for 80 per cent of the total impact.

In a minority of cases, the rule breaks down. For example, just 3 per cent of women and 9 per cent of men account for 80 per cent of serious court convictions, suggesting that a small minority of participants are responsible for the bulk of serious criminal activity. By contrast, for insurance claims, the equivalent figure is 40 per cent, implying that this socially acceptable practice is much more widely spread across the population.

Hence, for individual measures, there does appear to be a ‘high-cost’ group responsible for a disproportionate percentage of social costs. A key question is whether it is the same people appearing in each high-cost category. Two-by-two comparisons indicate that the number of individuals in two high-cost categories is markedly greater than would be predicted were the two outcomes independent of one another. Similar patterns are apparent when multiple outcomes are compared. Hence the same individuals are tending to fall into more than one high-cost category.

The Dunedin data also suggest that childhood adversity – such as low socioeconomic status, low IQ and low self-control – has a significant impact on the likelihood of ending up in a high-cost category. The effect size is relatively small, typically accounting for around a third to a half of a standard deviation. However, when outcomes are considered collectively rather than individually, the impact of early adversity becomes more apparent: individuals in five high-cost groups were disproportionately from a disadvantaged background (0.8 standard deviation).

Indeed, these three childhood risk factors correctly predicted around 80 per cent of the individuals in three or more high-cost groups. Hence, across multiple outcomes, analysis of childhood risks was able to identify 80 per cent of the individuals responsible for 80 per cent of health and social care costs. Notably, around 30 per cent of individuals in this category were maltreated when young.

The Dunedin Study also included assessments – language and IQ tests, neurological assessment, motor coordination and staff evaluation of temperament – that have been combined into a measure of ‘brain integrity’ at age 3. Individuals in three or more high-cost groups as adults had on average half a standard deviation worse score on this measure.

### MONDAY 14 OCTOBER

### AFTERNOON SESSION: STRATEGIES FOR DEVELOPING INTERVENTIONS

### The timing of intervention: opening and closing critical periods

Many of the long-term effects of early adversity are mediated through changes in the brain, affecting mental health or behaviours influencing health or social function. It is therefore of great interest to know whether neural mechanisms exist in adulthood that could be exploited to reverse these effects. Indeed, suggested Bruce McEwen, various lines of evidence suggest that there is ‘plasticity’ in the adult brain, and that mechanisms of plasticity can be manipulated, either in naturally occurring or artificially induced ‘critical periods’.

There are several ways in which the brain can embed long-term changes to stimuli, including changes in dendrite size, synapse loss or formation, and new neuron formation (rare in adulthood but seen in some areas such as the dentate gyrus and olfactory bulb). Chronic stress can lead to profound changes in brain function by affecting these processes, which may be adaptive in the short term but harmful to physical and mental health in the long term.

A key role in stress responses is played by adrenal steroid hormones, glucocorticoids, which show complex biological interactions with neurons. As well as their classic action through nuclear receptors, they can also affect calcium buffering in mitochondria, act on cell surface receptors, and affect the release of both excitatory and inhibitory neurotransmitters. Hence they have the potential to affect neuron biology in multiple ways, depending on cellular context.

Evidence that reversal may be possible has come from studies showing that the selective serotonin reuptake inhibitor (SSRI) fluoxetine can impact on plasticity, enabling the effects of monocular deprivation to be reversed[[16]](#footnote-16). This principle has been applied in humans – the FLAME trial, for example, showed that fluoxetine could enhance recovery of motor function in stroke patients[[17]](#footnote-17).

Interestingly, similar effects can be achieved with caloric restriction[[18]](#footnote-18), work that has highlighted the potential involvement of glucocorticoids in plasticity. Conor Liston and colleagues have shown in living mice that glucocorticoids are critical players in synapse turnover[[19]](#footnote-19). Furthermore, synaptic plasticity is responsive to the natural circadian rhythms in glucocorticoid production[[20]](#footnote-20).

Such results hint at the possibility that SSRIs could be used to open up a plasticity window during which interventions could undo some of the harmful impacts of past adversity. Combined pharmacological and psychotherapeutic interventions could be conceived for depression[[21]](#footnote-21), but the same principle could be applied to other neurocognitive traits.

Another potential target is brain-derived neurotrophic factor (BDNF), a pro-plasticity factor that declines during ageing. Glucocorticoids are known to interfere with BDNF signalling, but can have both negative and positive effects on neuron survival – the latter potentially being mediated through direct interactions with the BDNF receptor, TrkB[[22]](#footnote-22).

Takao Hensch and Parizad Bilimoria have also discussed the potential to reactivate plasticity windows in adulthood[[23]](#footnote-23). They draw attention to the importance of inhibitory neurons, and the balance between inhibitory and excitatory neural signalling in establishing critical periods in development. Potentially manipulating such systems in adulthood could be a strategy to reopen windows and reprogramme brain function. As well as pharmacological interventions such as SSRIs, digestion of extracellular matrix structures in neural tissue can also boost plasticity[[24]](#footnote-24). Moreover, non-invasive approaches such as exercise and environmental stimuli may be able to act through these pathways.

A great many genetic and cellular factors will influence inhibitory–excitatory balance and plasticity. Although potential targets, interventions in such a complex and partially understood system would need to be undertaken with great care. Indeed, while promoting plasticity may be desirable, excess plasticity could have a catastrophic effect on learning and memory. Opening up plasticity also runs the risk of unintended consequences, as disadvantageous changes could also become locked in.

Other issues also need to be considered, including notable sex differences in brain structure and function (even if differences are less apparent at the behavioural or outcome level) and the brain remodelling effects of sex hormones.

Nevertheless, ‘top-down’ strategies exploiting these mechanisms may be beneficial. Regular physical activity clearly affects adult brain biology, as does psychotherapy and forms of social and personal support or providing meaning or goals to life. Interesting opportunities exist to combine these with pharmacological interventions that enhance plasticity[[25]](#footnote-25), or to exploit a better understanding of biological mechanisms in other ways – for example, might the circadian rhythms in glucocorticoid levels influence the effectiveness of psychotherapy given at different times of day?

### Extreme adversity: impact on neural function and implications for intervention

Childhood maltreatment has a profound impact on later life, not least in predisposing to increased risk for psychiatric disorders, including anxiety, depression and post-traumatic stress disorder (PTSD). Yet, as pointed out by Eamonn McCrory and Essi Viding, relatively little is known about the neurobiological mechanisms that may underlie such vulnerability.

McCrory and Viding described work on maltreated children, aged 10–14, recruited through UK social services who were carefully matched with a control group of peers who had not experienced maltreatment. Using structural and functional imaging, they have attempted to identify neural correlates of abuse that may act as risk factors or biomarkers of later psychopathology, and potentially also provide clues to causal mechanisms. Importantly, the children they studied were typically not presenting with a psychiatric disorder, allowing the possibility of disentangling the impact of abuse and concurrent psychopathology such as PTSD that has characterised many previous children who have been studied after a history of maltreatment.

Structural MRI revealed reduced grey matter volume in two brain regions – the orbitofrontal cortex, an area implicated in emotion regulation, and the middle temporal gyrus[[26]](#footnote-26), a region associated with autobiographical memory. Abnormalities in these regions have been implicated in depression and PTSD in adulthood. No volumetric differences were found in the amygdala or hippocampus.

Investigating differences in cortical thickness, gyrification and surface area provided a potentially more sensitive view of brain differences[[27]](#footnote-27). This study revealed reduced thickness in an extended right hemisphere cluster, encompassing the orbitofrontal cortex and ventral anterior cingulate, as well as reduced gyrification in the lingual gyrus. Volumetric differences in these regions have been seen in adult patients, suggesting that the changes in children may be precursors of more extensive deficits in adulthood.

Functional imaging provides additional insight into how the brain is actually responding to social stimuli. In a simple gender decision task that varied the emotion of the task faces, relative to their peers maltreated children showed increased reactivity in the amygdala and the anterior insula to faces expressing anger, implying an increased responsiveness to threat[[28]](#footnote-28). Strikingly, changes in these same brain areas have been documented in soldiers undergoing fMRI before and after combat duty[[29]](#footnote-29).

Together, these findings suggest that the brains of maltreated children are not ‘damaged’ but have undergone adaptive changes to facilitate hypervigilance to threat in a hostile environment. However, increased neural reactivity in the amygdala and anterior insula has been associated with anxiety disorders in adults. Therefore, this pattern of neural activation may represent a marker of neural vulnerability to mental health disorders in later life.

The use of a backward-masked dot-probe paradigm – where participants had no conscious awareness of having seen a face – revealed that heightened threat awareness occurs entirely outside conscious awareness[[30]](#footnote-30). Specifically, compared to controls children who had experienced maltreatment showed higher amygdala activation to angry faces that were pre-attentively processed. Surprisingly, they also showed higher amygdala activation to happy faces, suggested increased sensitivity to heightened affect in general at this early stage of processing, or greater responsivity to reward-related (as well as threat-related) facial cues.

McCrory and Viding have begun a longer-term study with a similar group of children. This longitudinal design of this study will investigate brain changes during the critical period of adolescence, and assess whether early neurocognitive correlates of maltreatment truly represent markers that are predictive of later brain changes or patterns of psychological functioning. There will be some attempt to consider resilience factors, and in particular the experience of social support, as modulators that may reduce vulnerability in some children.

McCrory and Viding considered the relevance of this research to intervention. Specifically, it was noted that these findings indicated that children presented with putative patterns of neurocognitive vulnerability in the absence of concurrent psychopathology. This raised the question whether in a longitudinal study it would be possible to identify possible neurocognitive risk markers that be used in as screen for psychiatric risk and indicate the need for a ‘preventative intervention’ that could be seen as boosting or augmenting resilience, and reducing the likelihood of future mental ill-health. (This was discussed more fully later in the day; see below.)

There was a brief discussion whether brain changes could be seen as ‘damage’ or in the context of adaptation. Godfrey noted that, in a Singapore birth cohort, maternal depression has been found to have an impact on white matter tracts in the amygdala of offspring[[31]](#footnote-31). This could be interpreted as ‘damage’, but equally the resultant changes to amygdala function could, in certain environments, be advantageous – the consequences of brain changes could be seen as positive or negative depending on the particular demands of the environmental context.

### Continuous variation of adversity in population-based samples: pathways and interventions

While the ‘clinical’ cohorts studied by McCrory and Viding provide insight into the impact of extreme childhood disadvantage, population cohorts can shed light on the outcomes of much larger numbers exposed to less severe hardship. John Hobcraft examined some of the lessons to be learned from the 1958 cohort and comparisons with other UK population cohorts, such as the 1970 cohort.

One advantage of long-running cohorts is that the effects of childhood adversity can be examined at different ages. Moreover, results of particular surveys act as ‘stepping stones’, providing outcome measures for earlier ages but also antecedents of outcomes at later ages.

The 1958 cohort data provide abundant evidence that multiple measures of childhood adversity have an impact on multiple social outcomes in late adolescence/early adulthood (ages 16–23) – including lack of qualifications, being unemployed, not in education or training, having an early birth or leaving home due to family friction. A similar pattern is seen at ages 23 and 33, with many early measures influencing the likelihood of living in social housing, receiving benefits, low income, low social class and high malaise (a likely forerunner of depression).

There are few gender differences in the legacies of childhood adversity, although some effects, such as low parental interest in education and disruptive behaviour, have a disproportionate effect on females. Notably, the most powerful influence, even at ages 23 and 33, is childhood cognitive test score. Cross-generational effects are also apparent in, for example, social housing, social class and partnership breakdown[[32]](#footnote-32).

Comparisons between the 1958 and 1970 cohorts revealed significant differences in outcome by gender and by cohort[[33]](#footnote-33). These differences do not seem to relate to childhood factors, and may reflect wider social issues or parenting traits that are not captured in the cohort surveys.

A further interesting question is how the traits seen at ages 16–23 relate to those at ages 23 and 33. The data point to a high degree of continuity, and a high likelihood that those experiencing disadvantage at age 16–23 will continue to be disadvantaged a decade later. However, data on movement in and out of categories suggests that there is some degree of ‘churn’ or social mobility – 50–66 per cent of people manage to exit a disadvantaged category.

Currently, little is known about the factors that predict upward social mobility. Deeper analysis of cohort data may be able to shed light on this area. Some thought has been given to ‘turning points’ – key events in an individual’s life that reset a social trajectory – though it is debatable whether one-off events are really so influential or hold general lessons.

Various efforts have been made to model approaches to interventions to support social mobility. John Hills, for example, developed a ‘Four Ps’ model[[34]](#footnote-34) (see Table), while Michael Rutter posited a psychological approach based on promoting resilience[[35]](#footnote-35). Hobcraft has integrated these approaches into a conceptual framework that could support the classification of interventions or development of new social mobility strategies (see Figure). Given the multiple disadvantages of the most at-risk (‘high-cost’) families, tackling individual factors – ‘sticking plaster’ solutions – is unlikely to be as effective as multifaceted interventions.

|  |  |
| --- | --- |
| Focus of intervention | Intervention to change |
| Risk of event | Effects of event |
| Entry into adverse state | **Prevention** | **Protections** |
| Exit from adverse state | **Promotion** | **Propulsion** |



### Multi-generational interventions: pregnancy as a critical period for both mother and child

Primiparous motherhood as a potential critical period: animal models: The transition to motherhood, reviewed by Frances Champagne, may provide a window of opportunity when naturally occurring neural plasticity could be exploited.

Significant hormonal changes occur during the female life course, most notably at puberty and menopause but also around the time of pregnancy. The placenta acts as a temporary endocrine gland, coordinating the needs of the fetus and the mother. One role of reproductive hormones is to adapt the brain for pregnancy, childbirth and lactation, promoting changes in physiology and behaviour. These effects are both short term, acting over the course of a pregnancy, but also long term, leading to significant differences in later pregnancies.

Hormonal–neural cross-talk in pregnancy has been extensively studied in animal systems. One key set of changes affects the hypothalamic oxytocin system[[36]](#footnote-36). Oxytocin is required to drive smooth muscle contraction, most notably during childbirth but also to expel milk during lactation. Outside pregnancy, oxytocin release by hypothalamic neurons is uncoordinated and insufficient to activate peripheral receptors and trigger uterine contractions or milk ejection. Pregnancy, however, is marked by significant changes in neural architecture. Glial cells lessen their contact with oxytocin-containing neurons, which come into closer contact and become connected (and electrically coupled) through gap junctions. In addition, upregulation of inhibitory GABA-ergic synapses prevents the release of oxytocin, leading to the build up of intracellular stores. When the neurons do finally fire, they do so in synchrony and release a surge of oxytocin sufficient to trigger uterine contraction.

In rodents, other brain changes include the formation of new brain cells, induced by prolactin in the subventricular zone late in pregnancy[[37]](#footnote-37). These new cells extend projections to the olfactory bulb, and appear to be involved in modulating the olfactory system of mothers so that their offspring are less aversive and thus promotes maternal care.

The brain therefore undergoes significant changes during pregnancy[[38]](#footnote-38). These feed through into many behavioural traits and neurocognitive function (including enhanced cognition and memory).

But the brain does not revert to its pre-pregnancy ground state after birth[[39]](#footnote-39). Oxytocin release, for example, is greater in mothers that have given birth before, and multiparous mothers are smarter than those that have experienced a single birth. Notably, the cognitive benefits are to a degree shared by foster mothers who have not themselves given birth, suggesting that interaction with offspring can trigger hormonal changes in females independently of childbirth itself.

Following the hormonal turmoil of pregnancy, the post-partum period is a time of vulnerability. Hormonal fluxes, acting in concert with life history, genetic factors and current adversity, lead to a heightened risk of mood disorders.

Furthermore, pregnancy is a key period in which intergenerational effects can be transferred. Low levels of maternal care experienced by a female, for example, reduce brain plasticity and lower sensitivity to oestrogen, in turn affecting the maternal care she delivers. Hence interventions might not only benefit a mother and immediate offspring but also future generations.

While much work has been done with experimental animals, the findings are consistent with what is known of human reproduction. For example, in rodents, low levels of licking and grooming by mothers leads to accelerated sexual development of offspring and a reduction in maternal care behaviours. Similarly in humans, low parental care is associated with earlier sexual behaviour.

The results also suggest that the wellbeing of mothers may have been neglected, with intervention programmes typically focusing almost exclusively on the development of offspring. Focusing on mothers, for example by alleviating stress in pregnancy or providing support during the difficult period after birth, could help to break the cycle whereby an ‘unhealthy’ pregnancy predisposes to further unhealthy pregnancies in succeeding generations.

Moreover, there may be opportunities to gather more information about the impact of existing intervention programmes on mothers and later offspring. For example, in the Nurse Family Partnerships, nurses visited disadvantaged pregnant women either during pregnancy or after birth, a difference that might have affected later outcomes.

*Motherhood as a potential critical period: human intervention studies:* The UK Government’s Foresight report on obesity[[40]](#footnote-40) concluded that population interventions to prevent obesity were likely to be successful only at birth or during early childhood. Keith Godfrey, however, drew attention to more recent evidence that pregnancy may be an additional window of opportunity for interventions to protect the health and development of offspring (and improve the health of mothers).

Locally and globally, obesity is a significant issue in pregnancy. In Southampton, 50 per cent of mothers show excessive weight gain during pregnancy and 52 per cent of mothers are obese. Globally, gestational diabetes is now seen in up to 20 per cent of pregnancies.

These figures translate into worse outcomes for offspring. In the Southampton Women’s Survey, the infants of overweight mothers are themselves overweight at birth, and typically remain so at ages 4 and 6[[41]](#footnote-41). Gestational diabetes significantly increases the risk of offspring obesity. Perhaps most worrying, these effects can drive a ‘transgenerational escalation’ in excess weight.

The Southampton team is contributing to a range of complex interventions to address these issues. The UPBEAT study, for example, led by Lucilla Poston (KCL) is assessing a counselling-based approach aiming to improve the diet and exercise of overweight mothers[[42]](#footnote-42).

A second project draws on research showing that diet is very strongly influenced by mothers’ level of education and self-efficacy. Consumption of poor diets was seen in just 4 per cent of women with university degrees but 54 per cent of those with no qualifications[[43]](#footnote-43). A Southampton team is working with local Sure Start centres to delivery an intervention designed to boost the self-efficacy skills of mothers, with a view to improving the diet of themselves and their children[[44]](#footnote-44).

A third trial is examining the impact of vitamin D supplementation in mothers with vitamin D deficiency, seen in around 25 per cent of UK pregnancies[[45]](#footnote-45). As well as an increased risk of abnormal bone development, the offspring of vitamin-D-deficient mothers are more likely to be underweight at birth, but then show accelerated adiposity gain, becoming overweight in later childhood[[46]](#footnote-46).

Finally, a public engagement project, LifeLab[[47]](#footnote-47), aims to have an impact on ‘health literacy’ of young people, one consequence of which may ultimately be healthier pregnancies. In a cluster-randomised controlled trial being run in partnership with education researchers, some 4000 school students a year will have the opportunity to experience science directly at the university, with the aim of stimulating interest in science so students are more likely to view health messages as relevant to their own lives.

One important factor to consider in nutrition-oriented interventions is that nutrition cannot be considered in isolation. The prevalence of depression in overweight mothers, for example, is alarmingly high, highlighting the clear links between diet and mental health.

Furthermore, diet could be acting through multiple pathways. Obesity in mothers may be programming fetal physiology, but high glucose levels linked to gestational diabetes may act through alternative routes. In addition, although calories may be plentiful, certain micronutrients may be in short supply and affect fetal development. Overlaid on these biological factors are crucial psychological and social influences, ranging from the self-efficacy of mothers to the geography of food distribution and existence of ‘food deserts’, all of which affect mothers’ food intake.

### TUESDAY 15 OCTOBER

### EARLY MORNING SESSION: STRATEGIES FOR INTERVENTION (concluded)

### Telomeres and interventions: Is impaired telomere biology marker or mechanism for targeting interventions?

Telomeres, reviewed by Elissa Epel, act as protective caps for the ends of chromosomes. Telomeres shorten through cell division and in response to cellular stress, so telomere length provides a measure of cellular ageing. Although short telomeres are associated with a range of poor health outcomes, there is still some debate about whether shortening contributes directly to disease.

Telomeres are extended by telomerase. Human and animal models of telomerase deficiency develop age-related syndromes and earlier mortality[[48]](#footnote-48) (Armanios & Blackburn, Nature Review). Cellular senescence is a widely accepted mechanism of ageing, and telomere shortening may be one of the most common causes of senescence in humans. It is difficult to show a causal role in humans, but a growing number of studies are showing that telomere length is an important predictor of human disease, regardless of mechanism.

Many factors have been found to affect telomere length in adulthood, including chronic stress and psychiatric conditions. To date, nine studies have found an association between telomere length and childhood adversity (retrospectively reported). An overview of these studies suggested that telomere length might serve as a ‘deep biomarker’ of early-life stress[[49]](#footnote-49).

In children, telomere length has also been found to be sensitive to parental socioeconomic status[[50]](#footnote-50) and community-level stress[[51]](#footnote-51). As well as childhood adversity, maternal factors may also influence telomere length in offspring. After maternal stress, offspring telomere length was reduced in adulthood[[52]](#footnote-52), while prenatal exposure to smoking was also associated with telomere shortening in children[[53]](#footnote-53). Notably, studies in rats have shown that prenatal but not postnatal protein restriction is associated with telomere shortening and earlier mortality[[54]](#footnote-54).

Interestingly, one study has shown that the impact of adversity on telomere length could be mitigated by maternal responsiveness[[55]](#footnote-55). Maternal responsiveness had no impact on telomere length in children at low risk of adversity, but was able to block completely the decline in telomere length otherwise seen in high-risk children.

A key question is whether telomere shortening is contributing directly to ill-health. An intriguing study in mice points to a causal role, at least for depression[[56]](#footnote-56). Chronic stress leads to a drop in telomerase activity in the hippocampus, an effect that can be prevented by SSRIs. While inhibition of telomerase in the hippocampus led to depression-like behaviour, overexpression had an antidepressant effect and was able to block the negative impact of chronic stress. The protective effect of antidepressants was lost when telomerase (and subsequent neurogenesis) was blocked, suggesting the effect is dependent in part on telomerase.

While the direction of causality remains unclear, it may also change over the lifespan. Early in life, psychological stress may lead to telomere shortening, alongside other damaging changes. Later, shortened telomeres may themselves begin to further contribute to cellular ageing (cellular stress responses, senescence and inflammation). Hence, prenatal or early-life adversity may accelerate cellular ageing and telomere shortening, enhancing the risk of adult mental health and ageing-related conditions. These conditions may then create a positive feedback by loop by promoting further biological ageing (both telomere shortening and unhealthy behaviours)[[57]](#footnote-57).

A second key question is whether telomere shortening is reversible (and, if it is, whether this is beneficial to health and longevity)[[58]](#footnote-58). The short-term effects of various interventions have been assessed, including exercise, omega-3 supplementation, stress reduction and meditation, and the intense multicomponent Dean Ornish programme. The latter has shown both a significant short-term (three-month) increase in telomerase activity and lengthening of telomeres over five years[[59]](#footnote-59), though the numbers in the pilot study are small and the intervention might be difficult to apply on a large scale. However, this intervention is now reimbursed through insurance and will start to be disseminated, so could have a significant impact in the USA, at least among clinical samples already at high risk from a major condition such as cardiovascular disease.

A relaxation versus retreat study has examined the impact of a mindfulness-based stress reduction intervention at a health spa, finding some short-term increase in telomerase activity, particularly among experienced retreat participants. Hence at least in some cases, this cell ageing system may be affected even over short periods.

Epel also described other interventions that have examined the potential benefits of lowering stress, for example by mindfulness-based therapy. Some of the effects of early adversity may be mediated by maladaptive cognitive responses to stress. Interestingly, in Epel’s NIA pilot intervention on mindfulness for parental caregivers of children with autism spectrum disorder, preliminary analyses suggest that those who had early childhood adversity themselves (and often the most maladaptive ways of handling stress) benefited most from mindfulness training. The therapy may exert its strongest effects by promoting stress resilience, particularly in those with early adversity.

This idea has been tested in the ongoing NHLBI U01 MAMAS (Maternal Adiposity, Metabolism and Stress) intervention, in which obese pregnant women were given intensive mindfulness-based therapy to reduce stress and improve stress resilience and mindful eating. All the women experienced very adverse socioeconomic environments, including food insecurity and some experienced traumatic events during pregnancy. The intervention so far appears to have had significant success at preventing excess weight gain during pregnancy, though the numbers gaining excess weight remain high.

Overall, much remains to be learned about the role of telomere shortening, whether it mediates later-life ill-effects or is a biomarker of other more fundamental processes, whether it is reversible over the long term, and whether reversal has health benefits. Since telomere length is often measured in blood cells, it will also be important to differentiate effects due to telomerase-linked telomere lengthening versus replenishment of more naive cells into circulation. Additional longitudinal human studies and work on experimental animal models could begin to address these questions.

### Inflammation: A possible mediator and target for intervention?

Inflammation, reviewed by Andrea Danese, may be another factor mediating the long-term effects of early-life adversity. Inflammation is a component of innate immunity – the early, nonspecific immune response mobilised to prevent the spread of infection and promote tissue repair. While short-term activation is generally beneficial, long-term inflammatory responses are typically damaging and associated with multiple poor health outcomes.

Inflammatory responses can be enhanced by psychosocial stress, acting through the sympathetic nervous system. Again, in the short term this can be beneficial – stress is a kind of alarm system, so it may be helpful to enhance responses to threats such as pathogens. Chronic stress, however, may lead to persistent activation of inflammatory responses, with harmful consequences.

Homeostatic controls are in place to limit inflammatory activation, acting through mechanisms such as the parasympathetic nervous system and the HPA axis and glucocorticoid system.

Longitudinal studies, including the Dunedin Study, have identified an association between childhood maltreatment and adult levels of inflammation-associated markers such as C-reactive protein (CRP), which is associated with increased risk of cardiovascular disease[[60]](#footnote-60). A graded response was seen, with adult CRP levels correlating with the extent of maltreatment in childhood. A similar effect was seen for other inflammatory markers, including fibrinogen levels and white blood cell counts.

These physiological changes could provide a mechanistic link between early-life stress and later metabolic disease. Conditions such as atherosclerosis, for example, have a strong inflammatory component to them. But inflammation could also play a role in the neuropsychological consequences of adversity. Evidence is accumulating that inflammation can be an important contributory factor in depression[[61]](#footnote-61). Plausible biochemical mechanisms exist to explain this association, as inflammatory mediators can alter cell metabolism in ways that deplete serotonin, can trigger neurotoxicity through NMDA receptor stimulation, and can inhibit neurogenesis.

Many studies have shown that childhood maltreatment is an important risk factor for later-life depression. A meta-analysis suggests that maltreatment is particularly associated with recurrent and persistent depression, and with lack of response to treatment, particularly to pharmacological therapies and mixed psychological and pharmacotherapies[[62]](#footnote-62).

Controlling inflammation could thus be a way to interfere with the development of depression. Many studies have been carried out to examine the effects of SSRIs on inflammatory responses, mainly *in vitro*. A range of SSRIs, for example, were found to inhibit release of inflammatory mediators by glial cells after stimulation with bacterial lipopolysaccharide[[63]](#footnote-63). Some studies have shown that response to antidepressants is poorer in patients who have higher baseline levels of inflammatory mediators[[64]](#footnote-64).

Danese also described a small trial of cognitive-based compassion training, in which preliminary results suggest that CRP levels fall in line with the number of therapy sessions undertaken[[65]](#footnote-65).

One interesting question is the link between inflammation and telomere shortening. Does one cause the other, or might the relationship be bidirectional?

It is also difficult to disentangle the role of cortisol and glucocorticoids. Cortisol levels show considerable fluctuations, and the hormone acts within a complex system. Moreover, circulating levels may not be indicative of biological responses, as signalling will also depend on glucocorticoid receptor levels and function. There is growing interest in the use of cortisol measurements from hair samples, which might capture a better long-term picture of hormone levels.

### LATER MORNING SESSION: ‘LOW HANGING FRUIT’ AREAS OF PROJECTS THAT COULD BE CARRIED OUT NOW AND ARE LIKELY TO HAVE A RAPID YIELD

### Long-term follow up of already completed clinical trials

Gabriella Conti examined the question of whether it is possible to follow up existing adult interventions or experimental studies to address questions about reversibility.

Childhood interventions are, of course, very different from interventions in adulthood. In childhood the aim is generally not to address particular pathologies but to make up for adverse environmental inputs that children have received. In adults, interventions are often addressing a specific health problem, such as the risk of cardiovascular disease. In children, the aim is to protect pathways from damage or to reverse or compensate for early damage; in adults, pathways are likely to be damaged and it is not clear if this damage can be undone or alternative pathways can be enhanced to compensate.

Conti suggested that one way to address this issue is by examining different categories of intervention, those addressing deficiencies in attachment, stimulation and nutrition (while recognising that in practice these deficiencies can co-occur). Both human and animal studies have been carried out in each of these areas.

The long-term effects of insecure attachment have been demonstrated in rats[[66]](#footnote-66) and non-human primates[[67]](#footnote-67). Similarly, several human studies have identified long-term consequences of adverse childhood experiences on both mental[[68]](#footnote-68) and physical[[69]](#footnote-69) health.

Studies of adults that could be followed up include mentoring and surrogate parenting programmes, and initiatives such as the Nurse Family Partnership, a randomised trial showing improved social outcomes in teenagers whose mothers received home visits from nurses during pregnancy or after birth[[70]](#footnote-70). Beneficial changes were also seen in mothers, including fewer closely spaced pregnancies and less welfare dependency.

Various methods to boost attachment could be considered, potentially through drugs affecting epigenetic processes (so far explored only in animal models[[71]](#footnote-71)) or the oxytocin system, or through forms of psychosocial therapy. This category highlights the importance of pregnancy and tracking the impact of interventions on mothers and children.

Stimulation deficiencies are well known to have an impact on neural and cognitive development. Creating more stimulating environments can to some degree counteract these effects in childhood. Long-term studies examining the impact of interventions in childhood include the Perry Preschool Study[[72]](#footnote-72), a randomised controlled trial, begun in 1962, that tested the effects of a preschool programme on 123 African Americans from impoverished backgrounds. During the 1970s, the Abecedarian Project assessed an education initiative delivered to young children from poor backgrounds. Long-term follow up has revealed a lasting impact on both educational achievements[[73]](#footnote-73) and health[[74]](#footnote-74).

There is some evidence that cognitive stimulation can have an effect in adults, usually measured over the short term but sometimes over periods as long as five years[[75]](#footnote-75). It would be interesting to know more about the impact of SSRIs in this area, and the potential for targeting brain networks rather than neurotransmitters. It is also unclear whether early-life adversity has any impact on the effectiveness of adult interventions.

Nutrition has been very widely studied, and nutritional deficiencies have multiple effects through processes such as epigenetics and metabolic programming. More subtly, nutritional interventions may also have a behavioural impact, influencing healthy eating habits. There is some evidence, mainly from animal models, that the long-term metabolic consequences of early programming may be reversible[[76]](#footnote-76). Numerous randomised controlled trials of nutritional or multicomponent lifestyle interventions have been organised, including the PREMIER trial[[77]](#footnote-77), the British Family Heart Study[[78]](#footnote-78), and the Multiple Risk Factor Intervention Trial[[79]](#footnote-79), all of which provide opportunities for longer-term follow up and data collection on outcomes not previously assessed.

A key question for reversibility is whether the adult interventions provide any useful evidence on the potential to reverse the effects of early adversity. A key benefit of this approach is that it would take advantage of work that is already ongoing. There are some significant challenges, however. As well as the practical challenges of re-contacting participants, follow-up samples are likely to be biased and, as original studies were generally not looking at early-life adversity, some information would have to be collected retrospectively. Furthermore, adult interventions are typically addressing a limited range of health outcomes, yet early-life adversity has a wide range of potentially harmful downstream effects.

### Identifying adults with a history of adverse childhood exposures who would benefit from preventive intervention

Essi Viding addressed a range of general issues relating to intervention strategies. One key question is whether identifying everyone affected by an adverse childhood experience is too inclusive an approach – not everyone so affected will suffer long-term consequences.

However, starting with all individuals would ensure that none of the vulnerable slipped through the net, and would also help to identify resilience factors, intrinsic or extrinsic, and the circumstances under which they operate. These resilience factors might point to possible interventions, but this would have to be experimentally tested. A trait might be associated with resilience, but people may differ significantly in the extent to which that trait can be modified.

Furthermore, individuals who appear to be high functioning may have incurred a ‘tax’ from early-life adversity, and may not be achieving their full potential. Alternatively, effects of adversity may be apparent only when individuals encounter life crises. Some Holocaust survivors, for example, appear to have adjusted well but respond badly to serious illness in later life.

Cohort studies could shed light on this issue, by allowing comparisons to be made between matched individuals with and without childhood adversity, to see if the early experience has any impact on biological factors or psychosocial outcomes. Animal models could also be used to explore this question under controlled circumstances.

A further important question is whether interventions should be selective or universal. The use of selective interventions raises several questions, such as how individuals would be identified and what the optimal age of interventions would be.

Biomarkers are not yet understood well enough to have clinical utility. It is often not clear what they represent – such as early stages of disease or underlying vulnerabilities. Practical issues would have to be considered (techniques such as MRI, for example, are not always well suited to widespread use), as well as ethical concerns such as the risk of stigmatisation.

Catching detrimental effects at early ‘prodromal’ phases is an attractive idea, particularly as some outcomes, such as behavioural and mental health problems, are typically manifest in early adulthood. Later interventions might be more suitable for health outcomes characteristic of mid- to late life, such as metabolic disease. But even here, later-life outcomes may be significantly influenced by behavioural or other factors established in earlier life.

Cohorts have great potential to clarify the pathways between, say, depression or other mental health issues, health behaviours and physical health at later ages. It would be valuable to embed additional basic science research within cohorts to shed light on underlying mechanisms, and also to incorporate interventions to capture data on the impact of prior life events on the outcomes of health interventions.

However, complexity remains a considerable challenge. Many forms of adversity co-occur, developmental paths are affected by multiple interacting factors, and similar outcomes can have multiple causes. Animal studies may be better placed to dissect this complexity, with human studies being based on the best-understood areas of animal biology.

It is also important to consider the factors that might limit the uptake or success of interventions. Early-life adversity may affect motivation and the likelihood that an individual participates in an intervention known to be effective. Even if individuals who have experienced early-life adversity choose to take part in an intervention, they may have less capacity to engage with critical aspects of the intervention. Interventions may need to reflect participants’ underlying biology or personality type, as evidenced by Patricia Conrod’s work in prevention and treatment of drug and alcohol use. Her model is based on the idea that people arrive at addiction through different routes – some individuals self-medicate in response to anxiety while others show thrill-seeking tendencies. Interventions have been developed that reflect these differing personality traits[[80]](#footnote-80). Finally, it would also be important to consider the practitioner and programme factors that might limit uptake of an intervention, the theme of a large body of work on behaviour change.

### Identifying adults who are at risk by virtue of early exposure: Prospective versus retrospective reports

Data on early-life adversity can be collected either prospectively (e.g. in birth cohorts) or retrospectively (e.g. through surveys in adulthood). The relative value of these approaches has been discussed extensively. Andrea Danese described an analysis of data from the Dunedin Study that sheds light on the relationship between these measures.

The Dunedin Study includes prospectively collected as well as retrospectively reported data on maltreatment. Between ages 3 and 11, data were gathered on maternal rejection, harsh parental discipline, and disruptive changes in care-giving. At age 21, participants provided information on physical and sexual abuse between the ages of 3 and 11. A cumulative measure of maltreatment was obtained by summing participants’ experience of individual adversities, creating three categories of maltreatment: ‘no’, ‘probable’ (1–2 adversities) and ‘definite’ (more than two adversities).

At age 38, a standard survey tool, the Childhood Trauma Questionnaire, was used to gather retrospective data on maltreatment up to age 18. Individuals were again grouped into ‘no’, ‘probable’ and ‘definite’ categories.

The agreement between the two measures is relatively low, around 60 per cent, where 50 per cent would be expected entirely by chance. This is perhaps not entirely surprising, as different constructs are being measured. Subsets of the data (e.g. sexual abuse) might show closer agreement but would not allow full examination of maltreatment experiences.

Interestingly, though, both prospectively and retrospectively reported maltreatment were found to have similar-sized detrimental effects on IQ at age 38; the effect was still seen, though slightly diminished, when adjustments were made for IQ at age 11 and 13, suggesting that maltreatment (howsoever measured) is having an enduring impact, long after the reporting period for maltreatment has ended.

A similar effect was seen with a measure of long-term inflammation, CRP levels. In this case, prospectively reported maltreatment had a slightly larger effect on CRP levels in adulthood than retrospectively reported maltreatment.

Whatever the merits of retrospective and prospective data, this analysis suggests that, in practice, both measures are capturing important aspects of early-life experience. However, the two measures are not equivalent, and prospective measures seem to be more sensitive in detecting changes in stress-sensitive biological systems, such as inflammation.

The findings touch upon the question whether interventions should focus on those who have suffered maltreatment or those or perceive themselves to have been maltreated. There is also the intriguing question of why people report maltreatment at one point but not at another – what has led them to change their mind?

### Identifying adults who might have been especially vulnerable to early adversity but would benefit most from preventive interventions: Differential susceptibility

A striking feature of childhood adversity is that not all who are exposed to it suffer long-term ill-effects. In part this may be reflect genetic vulnerabilities, or ‘inherited susceptibility’. But, argued David Reiss, it may be more helpful to consider a concept of ‘differential susceptibility’[[81]](#footnote-81), which considers responses to favourable as well as adverse environments. Put simply, an inherited susceptibility is a genetic factor that predisposes to a worse outcome in an adverse environment; in differential susceptibility, a gene may have a negative impact in an adverse environmental context but also a beneficial impact in a positive environment.

In terms of reversibility, this distinction has profound consequences. It implies that the same factors that may increase an individual’s vulnerability to an adverse environment may also make them more responsive to treatments reversing that environmental challenge.

One way to examine this question is through adoption studies. Adopted children will maintain the genetic links with their biological parents but will be subject to the moderating environmental influence of their adoptive parents. A complementary approach is to genotype individuals and to assess whether possession of particular alleles influences responses to environmental factors. The most commonly studied genes are those implicated in neurotransmitter function, such as the serotonin transporter (5-HTT) and components of the dopamine system.

A complication in studies of gene–environment interactions is that the environment is rarely entirely independent of genetic influences. Mother and child share 50 per cent of their genes, for example, while genetic factors may themselves shape an environment (a child’s genetically influenced behaviour is likely to have an impact on parenting).

Reiss drew attention to three levels of stringency in assessing differential sensitivity. The first level is based on a single environmental factor, spanning positive and negative potential impacts, that is (as far as possible) independent of genetic make up. The second level expands the paradigm to two independent environmental variables. At this level, one of the environmental variables has a track record as favouring positive child development and the second has been shown to be noxious. The third, most rigorous level draws on randomised controlled trial methodology or random assignment of offspring to different environments in experimental settings.

An example of a ‘level 1’ demonstration was a study examining students’ alcohol consumption in relation to consumption across an entire school. Individual consumption increases slightly in line with figures for whole-school consumption, but this association is much more marked in students with two ‘short’ HTT alleles[[82]](#footnote-82). Such students show not only markedly elevated drinking in high-consumption schools, but also markedly lower drinking in low-consumption schools.

A similar pattern has been seen in adults. One study examined the impact of the DRD2 dopamine-related gene on harsh parenting practice during a period of economic instability, spanning deteriorating and improving economic conditions[[83]](#footnote-83). Parents with a ‘CC’ DRD2 genotype showed little variation in levels of harsh parenting during this period, but those with a ‘T’ genotype showed both elevated levels of harsh parenting practice during economic adversity and reduced levels as economic conditions improved.

An example of a ‘level 2’ demonstration has come from work examining the impact of marital hostility and warmth (which, perhaps surprisingly, appear to be independent of one another). In an adoption-based study, children of mothers with high frustration were more sensitive to marital hostility in their adoptive families (showing more anger at 18 months); conversely, they showed less anger when brought up in an environment marked by marital warmth.

Data from the Fragile Families Study show a similar effect. In this study, family relationships are highly dynamic, with fathers frequently moving in and out of households. Genes associated with the dopamine system have a marked impact on externalising behaviour at age 9, enhancing negative responses to the number of father exits and positive responses to the number of father entries into the household.

Gene–environment interactions can also be seen in treatment responses. 5-HTT genotype, for example, has been found to influence the responsiveness of stroke patients to psychotherapy[[84]](#footnote-84).

Experimental studies provide opportunities to carry out more controlled manipulation of the environment. In macaques, for example, the short allele of the 5-HTT gene has a significant bidirectional effect, increasing levels of aggression in peer-reared animals (an adverse environment) but reducing aggression levels in mother-reared animals (a positive environment)[[85]](#footnote-85). A similar effect is seen on alcohol consumption.

Such examples raise hopes that it may be possible to identify both those most at risk of being harmed by an adverse environment and, conversely, those most likely to respond to interventions. It is possible, however, that a ‘risk’ allele might be harmful in one context but beneficial in another, or may appear to convey inherited sensitivity in one context and differential susceptibility in another.

Genetic influences are traditionally seen as ‘fixed’, but it is becoming increasingly apparent that epigenetic modifications can change their impact over time. This could lead the effects of a genetic vulnerability to be more apparent at some life stages at others. Studies in monkeys are being used to assess gene–environment interactions at different developmental stages, and to try to link these difference to epigenetic changes.

The ENCODE programme is attempting to create a comprehensive map of the regulatory elements in the human genome[[86]](#footnote-86). Part of this work is to characterise epigenetic changes in reference tissues and how this relates to genetic variation. The work will provide a valuable reference framework for understanding how environmental factors may achieve long-term effects by altering gene activity in different tissues.

### AFTERNOON SESSION: SOME SUMMARISING POINTS

Final discussions drew out some of the important themes of the meeting, as well as a range of additional issues worthy of further consideration (with contributor’s initials in parentheses):

* The deep impact of early-life adversity presents a challenge to conventional adult studies and interventions, which rarely take account of past life history. Existing data from current studies could be re-analysed from this perspective. **(EE)**
* More sophisticated measures of stress responses are needed, to reflect different aspects of stress-response programming; a small battery of measures could be developed and used consistently across studies to aid cross-study comparisons. **(EE)**
* Early-life exposures take many forms, and it will be important to determine whether different types of adversity leave specific epigenetic ‘footprints’ in the genome; such markers could provide clues to biological mechanisms. Work on population cohorts, complemented by studies of ‘extreme’ exposures, could provide such information. **(CR)**
* Reversibility as a strategy may be possible, but given how many large population interventions in adults have had minimal impact, it will be important to apply very carefully. Periods of hormonal flux in particular may offer important windows for intervention. **(KG)**
* The role of telomeres could be examined in cohorts, potentially over multiple generations. **(KG)**
* More attention needs to be given to follow-up of mothers in inter-generational intervention studies, rather than just offspring. **(KG)**
* Cohorts are proving invaluable tools for establishing pathways between adversities and outcome. Although it is often challenging to combine data sets, more could be obtained from cross-cohort comparisons – both similarities and discordance could provide biologically interesting information. In terms of individuals, much could be gained from analysis of ‘off-diagonals’ – those who do much worse or better than their background would predict. **(JH)**
* Long-term follow-up of past interventions could reveal important outcomes outside those originally considered. Piggy-backing current lifestyle interventions, to integrate a life history perspective and focus on broader outcomes, could be a way to generate findings more rapidly and cost-effectively than launching new trials. **(JH)**
* Opportunities exist to enhance current cohorts to collect more biological information, for example through MRI/fMRI. **(JH)**
* More intensive phenotyping of children would be helpful, as long as it is done in a minimally invasive and ethical way. For example, routinely collected blood spots could provide useful biological information. **(AD)**
* As potential biological mediators are identified, markers of key biological processes could be integrated into clinical trials. **(AD)**
* No individual study is perfect; there is potentially much to be learned from comparing studies and understanding the causes of differences between them through meta-analyses. **(AD)**
* Timing is a critical issue, in terms of adversity and of optimal windows to intervene. Biomarkers providing insight into short-term effects of interventions, but of known relevance to later-life outcomes, would be highly valuable to assess the impact of interventions. **(RJ)**
* Policy initiatives are an additional route by which behaviour change could be achieved. A better understanding is needed of policy initiatives that have been effective in improving public health through behaviour change. **(RJ)**
* A key challenge is to break the ‘cycles of adversity’, whereby poor maternal practice in one generation becomes the norm for future generations. **(KG)**
* Although early interventions have many advantages, they will never achieve complete success, so adult interventions will still be required. **(DR)**
* Critical periods do seem to exist outside special situations such as cochlear implant use. They have the potential to facilitate significant neurobiological and behavioural changes. **(DR)**
* A realisation that health in later life is fundamentally dependent on childhood (and earlier) provides additional impetus to treatment of children; not only are immediate issues being tackled, but the impact of therapy on both physical and mental health will be felt decades into the future. **(DR)**
* Although there is enormous complexity, multiple adversities may be acting through common pathways, studied by different groups in different ways. Further research may provide clues to these pathways and how they lead to damaging outcomes, and also generate early markers of poor outcomes. **(EM)**
* Being able to accurately screen for and detect early markers of vulnerability could facilitate a ‘preventative intervention’ approach, with a resilience focus that targets help at the most vulnerable children before clinical disorders emerge. **(EM)**
* Neurocognitive research is using brain imaging to identify subtle predictive makers, but a broader approach – including measures of psychological processes and representations – may provide greater insight into a broader range of vulnerabilities and point to more targeted areas of need for prevention intervention strategies. **(EM)**
* Given pregnancy is such a critical point in the life course, it would be advantageous to establish it as a specific developmental outcome, to ensure mothers are well-prepared for the experience. **(DR)**
* Policy-makers need to be provided with evidence that this approach is desirable and that interventions are successful. **(KG)**
* As well as mothers, there is also an opportunity to target would-be fathers and to engage them in subjects such as planned parenthood. **(GC)**
* It would be helpful to know more about the links between ‘general’ biomarkers of adversity (shortened telomeres, inflammatory mediators) and specific neurocognitive and neurobiological markers linked to behaviour. **(EV)**
* It remains unclear which neurocognitive phenotypes are most significant for longer-term outcomes; these could differ at different ages. **(EV)**
* Methods such as fMRI might be able to identify such markers in a research setting, but simpler measures would be required for widespread use, for example in cohorts; a short neurocognitive battery would be useful, but difficult to develop across all domains. A broad but practical tool might be possible, to identify the most vulnerable. **(EV)**
* Interventions often target the extremes of adversity. However, since most adversities show a gradation across a population, greater impact can be achieved by targeting populations as a whole. **(CP)**
* In assessing the impact of early-life adversity, a focus on single outcomes may underestimate its full impact, as it has a detrimental effect on multiple adult outcomes. Similarly, the potential benefits of interventions will be underestimated unless impact on a range of adult outcomes is considered. **(CP)**
* Observational studies are proving extremely powerful; there is now great opportunity to integrate biological measures, such as telomere length and epigenetic modifications, to link social and biological outcomes. **(CP)**
* It may be possible to create ‘synthetic cohorts’ across the life course by linking together unrelated cohorts at different ages; there is also potential to increase collaboration between cohorts and cross-cohort comparisons. **(CP)**
* It is vital that cohort studies continue to use ‘old’ measures at future data collections, even if new/better measures become available, to ensure valid comparisons between ages can be made and allowing tracking over time. **(CP)**
* As biomarkers such as telomere length or levels of inflammatory mediators become better characterised, it would helpful to know how predictive they are, of poor adult outcomes generally or of specific outcomes. **(GC)**
* More could be learned from examining the impact of naturally occurring external events (such as economic changes or policy initiatives) on cohorts, including their effects on biomarkers; these could also be interpreted in the context of individuals’ genotypes. **(GC)**
* Quantification of the impact of biomarkers would also be helpful, to support cost–benefit analyses of interventions and generate evidence for policy-makers; the health-economic community could make a significant contribution in this area. **(GC)**
* Ongoing randomised controlled trials provide an opportunity to gather information at little additional cost; current trials may not be collecting sufficiently broad information on behavioural responses to interventions. **(GC)**
* Thought should be given to embedding randomised controlled trials within existing cohorts. Potentially these could be linked to the particular life stage cohort members are at (for example cognitive training in the 1958 cohort, to test its impact in later life). It might also be possible to test whether personality traits such as conscientiousness are malleable and can be modified to influence health or social outcomes. **(AG)**
* More may be gained by analysis of existing data. It would be interesting to know the extent to which data at one time are predictive of outcome at later stages, and to explore the reasons for any changes in trajectory. However, such analyses are statistically challenging. **(AG)**
* Most members of the 1958 cohort have been genotyped (and have contributed to multiple genome-wide association studies). Opportunities therefore exist to integrate genetic analyses into studies; pilot studies of epigenetic analysis are also being undertaken. **(AG)**
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