HHS Public Access

Author manuscript

Acta Physiol (Oxf). Author manuscript; available in PMC 2015 March 13.

Published in final edited form as:

Acta Physiol (Oxf). 2014 February ; 210(2): 277–287. doi:10.1111/apha.12189.

A mechanistic look at the effects of adversity early in life on cardiovascular disease risk during adulthood

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Abstract

Early origins of adult disease may be defined as adversity or challenges during early life that alter physiological responses and prime the organism to chronic disease in adult life. Adverse childhood experiences or early life stress (ELS) may be considered a silent independent risk factor capable of predicting future cardiovascular disease risk. Maternal separation (Mat-Sep) provides a suitable model to elucidate the underlying molecular mechanisms by which ELS increases the risk to develop cardiovascular disease in adulthood. The aim of this review is to describe the links between behavioural stress early in life and chronic cardiovascular disease risk in adulthood. We will discuss the following: (i) adult cardiovascular outcomes in humans subjected to ELS, (ii) Mat-Sep as an animal model of ELS as well as the limitations and advantages of this model in rodents and (iii) possible ELS-induced mechanisms that predispose individuals to greater cardiovascular risk. Overall, exposure to a behavioural stressor early in life sensitizes the response to a second stressor later in life, thus unmasking an exaggerated cardiovascular dysfunction that may influence quality of life and life expectancy in adulthood.

Keywords

adverse childhood experience; cardiovascular risk; early life stress; maternal separation

Developmental origins of adult disease may be defined as challenges during early life that alter physiological responses and potentially prime the organism to chronic disease in adult life. These atypical signalling pathways result from developmental plasticity, which is the ability of a single genotype to produce more than one alternative form of structure and/or function in response to environmental conditions (Barker *et al*. 2002, Gluckman & Hanson 2004, McMillen & Robinson 2005, Nuyt 2008, Nuyt & Alexander 2009).

In addition to the traditional adverse environmental factors, such as chemical compounds, toxins and diet, behavioural stress also has a significant impact in the developing organism (Forsdahl 1979, Felitti 1993, Dong *et al*. 2004). Specifically, early life stress (ELS), defined

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Conflict of interest

There is no conflict of interest to report.

as adverse childhood experience(s) capable of inducing behavioural and emotional stress, anxiety, fear and discomfort in the individual (Dong *et al*. 2004, Pace *et al*. 2006), changes the sensitivity of certain physiological responses that will precipitate an adaptive response to an environmental stressor later in life. Overall, compelling data suggest that repeated exposure to adversity in early life programmes a 'defensive' phenotype, which displays a functional resistance to stress-induced responses (Levine 2005, Lyons *et al*. 2010). However, in the context of late-life chronic disease, dysregulation of certain signalling pathways [i.e. inflammatory system and hypothalamic-pituitary-adrenal (HPA) axis] may favour exaggerated responses that contribute to the pathogenesis of cardiovascular disease, some types of cancer and respiratory disease (Miller *et al*. 2009).

The effects of ELS on the endocrine, inflammatory and neural system have been studied (Lindgarde *et al*. 1987). We propose the term cardiovascular priming to describe the relationship of early life behavioural stress and the subsequent sensitivity to cardiovascular outcomes. Adverse early life experiences would be considered a first 'hit' and may exert cardiovascular priming that may increase the susceptibility to over-or under-react in response to a secondary stressor, or second 'hit', in adulthood (Fig. 1). We identify ELS as a key component in the shaping of the adult capacity to maintain cardiovascular homeostasis.

The aim of this review is to describe the current possible mechanistic link(s) of behavioural stress early in life and chronic cardiovascular disease risk in adulthood. We will discuss the following: (i) adult cardiovascular outcomes in humans subjected to ELS, (ii) maternal separation (MatSep) as an animal model of ELS as well as the limitations and advantages of this model in rodents and, (iii) possible ELS-induced mechanisms that predispose individuals to greater cardiovascular risk as well as the role of the epigenome and the possible transgenerational effects of ELS and cardiovascular risk.

ELS and adult cardiovascular outcomes in humans

Early life stress, commonly occurring in the first decade of life, is induced by behavioural stressors or adverse childhood experiences and is highly correlative with ischaemic heart disease in adulthood, more so than the traditional risk factors (Taylor & Seeman 1999, Chida & Steptoe 2009, Alciati *et al*. 2011). Examples of behavioural stressors include natural disasters such as flooding, fires and earthquakes, physical and sexual abuse, witnessing violence, parents' divorce, parental loss or intrusive medical interventions. Importantly, low socio-economic status as well is a factor that strongly correlates with the presence of adversity and has been used to approximate ELS in many epidemiological studies (Taylor & Seeman 1999, Holness *et al*. 2000, Dong *et al*. 2004, Kelishadi *et al*. 2009, Chen *et al*. 2011, Alastalo *et al*. 2012).

Cohort retrospective studies that describe major associations between childhood adverse experiences and adult cardiovascular risk outcomes are summarized in Table 1A. ELS consistently demonstrated a cardiovascular risk phenotype, including exacerbation of inflammatory markers and lipid profiles that may enhance the underlying risk of cardiovascular disease (Danese *et al*. 2007, Kelishadi *et al*. 2009, Chen *et al*. 2011, Vig *et al*. 2010, Alastalo *et al*. 2013).

Currently, several cohort studies are designed to collect and analyse data provided by children associated with specific risk factors (Table 1B). There is a web site to find information regarding several cohort studies ongoing at http://www.birthcohorts.net. The main objectives of these prospective studies are to investigate children's health and ethnic disparities at birth as well as in later life, maternal lifestyle, medical, psycho-social and environmental post-natal conditions that may elucidate children's health in later life. These investigations are critical as prospective studies will allow a better understanding of the cause and effect in the adult cardiovascular outcomes of children exposed to ELS.

Maternal Separation as an animal model of ELS

The mitigating effect of ELS on both behavioural and neuroendocrine parameters in animal models representing extremes in trait anxiety might reflect an evolutionary advantage that is sustained as the genetic variability among individuals of different species. This adaptation would allow adequate responses to potentially dangerous stimuli in adulthood dependent on early life conditions. There are studies to show that ELS confers resiliency to later life stressors (Lyons *et al*. 2010). However, ELS may also exacerbate stress-induced responses, such as enhanced inflammatory or sympathetic responses, sensitizing the individual to future disease risk.

In humans, ELS has long been linked to anxiety disorders and depression in adulthood (Nugent *et al*. 2011, Shapero *et al*. 2013). Animal models of ELS have been extensively used to study the effects of ELS on the development of neurological disorders such as depression and anxiety disorders in adults. Adult and juvenile rats and mice exposed to ELS display heightened reactivity to stressors, increased anxiety as well as depression-like behaviours such as reduced anhedonia (George *et al*. 2010, Uchida *et al*. 2010, Schmidt *et al*. 2011). These ELS-induced pro-anxiety and prodepression traits have been suggested to correlate with the promotion of cardiovascular outcomes such as stroke, atherosclerosis and hypertension (Beutel *et al*. 2013, Rahman *et al*. 2013); however, these parameters have not been consistently measured and reported. Thus, validating the use of animal models of ELS to study parameters may contribute to the development of cardiovascular disease in adult life.

There have been many different types of alterations in maternal care with animal models used to approximate childhood adversity in humans. Two major approaches include (i) modifying the time spent with the dam by physically separating the dam and the pup, and (ii) modulating the quality of maternal care. The former approach, called MatSep, is a chronic behavioural stress model that involves temporarily separating or isolating offspring from the dam daily during the early post-natal life. MatSep has been performed in non-human primates, rabbits, pigs, guinea-pig, birds, and most extensively in rats and mice (Table 2). The variety of species, length of separation protocol as well as the time point during which experimental observations were made (i.e. neonatal, juvenile or adult) have resulted in a wide range of aberrant phenotypes described in the literature (Table 2). The most consistently used models are rodents due to their availability, cost-effectiveness and common use in physiological and molecular studies; thus, we will focus the remainder of our discussion on the rodent models.

Maternal separation in rats involves the removal of pups from the dam for 3–4 h a day starting at postnatal day 2 (P2) and ending at P14 (Lehmann *et al*. 2000, Lippmann *et al*. 2007, Loria *et al*. 2010a). Mat-Sep is overwhelmingly utilized as a model of ELS in behavioural studies. This protocol has yielded fairly consistent results in rats across many studies with regard to the behavioural outcomes in adults. MatSep in mice, however, have yielded highly variable behavioural outcomes in adults, and currently, there is an impetus to determine the optimal MatSep model in mice. It appears that mice are more resistant to Mat-Sep when compared with rats and must be separated for longer periods of time to induce behavioural outcomes as adults (George *et al*. 2010). Also, strain differences in MatSep mice have been extensively explored (Labarba *et al*. 1973, Savignac *et al*. 2011). For example, the innately anxious Balb-c mice appear to be more susceptible to the cognitive ill-effects of MatSep than C57BL6 mice, such as reduced recognition and spatial working memory (Mehta & Schmauss 2011).

Limitations and advantages of maternal separation as a model of ELS

As with many animal models of human disease, there are limitations; thus, we must be intimately aware of these to prevent overinterpretation of results gained from these valuable models. Although MatSep is often considered a model that induces a negative effect in stress-related emotional, metabolic and cardiovascular responses, numerous studies propose that chronic exposure to behavioural stress does not result in vulnerability but instead exaggerates arousal regulation and resilience (Levine 2005, Lyons *et al*. 2010), which will serve as a adaptive mechanism to fight stressors later in life. Nevertheless, we hypothesize that such exacerbated responses mediate the sensitization of the cardiovascular system.

In rodents, developmental stages during early postnatal life are equivalent to the third trimester in humans. A major criticism of MatSep is that it does not strictly represent childhood adversity in humans in terms of developmental stages. Yet the post-natal period in rodents involves sucking and the exposure to outputs from the external environment. In this regard, the developmental plasticity attained during the rodent's neonatal period heightens the impact of the ELS, exerting profound changes in the organ function. In essence, there is a mismatch of environment and developmental period. This mismatch may explain why there is a disparity in effects between rodent models and primate models (Lyons *et al*. 2010). In primates, some researchers have detected resilience rather than a behavioural instability in the face of MatSep (Lyons *et al*. 2010, Own & Patel 2012). However, this mismatch of development and environment between rodents and humans provides a useful experimental model to perform interventions avoiding *in utero* manipulations. Moreover, the renal development in rodents is completed in the early post-natal life during the hyporesponsive period. It is known that early development between mice and rats is slightly different. For instance, the stress hyporesponsive period is different between mice (PD1–PD12) and rats (PD4–PD14). These differences may be responsible for the disparity of outcomes, with mice being much more resistant to the effects of MatSep than rats (Savignac *et al*. 2011).

Concerning behavioural stress, animal models are simplified paradigms of integrated responses compared with humans. Stress in rodents displays a lack of length, memory and spatial perception that influences the short- and long-term adaptation to adversity. Emotional

stress in humans is often self-perpetuated from an initial stressor. In other animal species, stressors are often acute and non-self-perpetuated. MatSep certainly does not fully represent the spectrum of early life adversity in humans such as physical abuse, sexual abuse, mental abuse, natural disaster, war-time atrocities, etc.

Alterations in maternal warmth induce changes in molecular mediators regulating the HPA axis sensitivity in offspring (Caldji *et al*. 2000). The dam's separation from the pups may change or disturb their normal maternal care, enhancing the effects of the stressor in the pups once they are retuned with the litter (Meaney 2001, Champagne *et al*. 2004); however, a thorough in-depth study of this phenomenon is lacking. Some insight can be gained from rabbit models of MatSep where maternal lactation and circulating hormones have been shown to change during separation from pups (Cano *et al*. 2005b, Rebollar *et al*. 2006).

Although a number of concerns are pointed out, MatSep in rodents is currently one of the best approaches to model ELS in humans. Cardiovascular outcomes of the rodent model of MatSep closely mirrors epidemiological data regardless of the nature of the early life stress, lending support for the legitimacy of the model (Mascitelli *et al*. 2006). For example, in the human literature, ELS induces heightened inflammatory status that parallels what is observed in rodent models of ELS (Pace *et al*. 2006, Danese *et al*. 2007, O'Mahony *et al*. 2009, Herbert *et al*. 2012). Also, rodent models mimic the behavioural outcome of ELS in humans such as anxiety and depression (Uchida *et al*. 2010, Schmidt *et al*. 2011, Heim & Binder 2012). Our data now provide evidence that similar to humans, rodents exposed to MatSep have increased risk of developing hypertension and cardiovascular pathologies in adulthood. Given these similar outcomes, we conclude that MatSep is an appropriate model to study the molecular mechanisms by which ELS enhances adult cardiovascular disease risk.

Molecular alterations due to Maternal Separation in rodents

Early life stress can influence mechanism(s) of metabolic and mental disorders as well as cardiovascular disease in animal models (Tucker & Johnson 1984, Kaufman *et al*. 2007, Sanders & Anticevic 2007, Enthoven *et al*. 2008a, Samuelsson *et al*. 2008, Loria *et al*. 2010a). In rodents, MatSep has been shown to alter adult anxiety through changes in the HPA axis, sympathetic-adrenal-medullary (SAM) system, brain, SNS and general neuroendocrine function. These changes are likely to contribute to MatSep-induced cardiovascular outcomes (Loria *et al*. 2010b, 2011). Table 3 shows specific molecular alterations that Mat-Sep displays in adult rats related to the cardiovascular function and blood pressure control. Our group has reported consistently with others that MatSep rats display greater responsiveness to acute behavioural stress as well as to prohypertensive stimuli as adults. We showed that MatSep rats that lack functioning endothelin type B receptor display a blunted acute air-jet stress-induced rise in blood pressure when compared with MatSep wild-type control rats (Loria *et al*. 2010a). In addition, others have shown that heart rate is elevated in response to acute stress in MatSep borderline hypertensive rats (Sanders & Anticevic 2007).

Male MatSep WKY rats display an exaggerated response to angiotensin II (AngII)-induced responses *ex vivo* and *in vivo* (Loria *et al*. 2010b, 2011). Aortic vascular tissue from MatSep rats showed a greater vasoconstrictive response than tissue from control rats. In addition, the nitric oxide buffering capacity, necessary for a normal vascular function, is reduced in MatSep rats. In telemetry-instrumented rats, a chronic infusion of AngII induced an exacerbated hypertension, renal vascular damage and renal T cell infiltration. We reported that MatSep rats have reduced renal filtration capacity that is mediated by renal nerve activation (Loria *et al*. 2013). Thus, we proposed that MatSep in male rats induces a deranged renal response to prohypertensive secondary stressors. Interestingly, female MatSep rats also display enhanced AngII-induced hypertension; however, there is not a clear link suggesting a renal or sex hormone-dependent mechanism. Further investigations are required to elucidate the mechanism by which female MatSep rats are more susceptible to a prohypertensive stimuli.

Is the ELS-induced vascular dysfunction phenotype transmitted to the next generation?

Traditionally, definitions of inheritance have been limited to the passing of genetic information from one generation to the next. The long-term consequences of adverse social experiences during early life on maternal behaviour induce a mechanism by which traits can also be ‘inherited’ by the forthcoming generations. This epigenetic mechanism induces functionally relevant modifications of the genetic code. Examples of such modifications are DNA methylation and histone modification, both of which serve to regulate gene expression without altering the underlying DNA sequence. Thus, epigenetics is an emerging area of study that is relevant to many of the functional outcomes involved in the programming of the adult phenotype (Champagne & Meaney 2001, Cameron *et al*. 2008, Bogdarina *et al*. 2010).

A large body of literature shows that maternal behaviour mediates epigenetic changes in the offspring, especially with respect to the HPA axis and SAM system, specifically glucocorticoid receptor (GR) expression in the frontal cortex of the brain and the regulation of GR activity (Weaver *et al*. 2004, Meaney *et al*. 2007, Cameron *et al*. 2008, Szyf *et al*. 2005, Navailles *et al*. 2010, Klengel *et al*. 2013). Hippocampal samples were compared from deceased people who experienced childhood abuse and committed suicide, comparing these with non-abused controls (Suderman *et al*. 2012). DNA methylation profiles were studied for over 6.5 million base pairs around a locus that houses the GR gene. Childhood abuse alters HPA stress responses and increases the risk of suicide, both of which are associated with the epigenetic regulation of hippocampal GR expression (Fish *et al*. 2004, McGowan *et al*. 2009, Murgatroyd *et al*. 2009). More recently, Klengel *et al*. (2013) have shown that childhood trauma is linked to increased DNA demethylation of glucocorticoid response elements of the FK506 binding protein *5 (FKBP5)* gene, which is correlated with an increased risk of developing adult psychiatric disorders (Klengel *et al*. 2013). These data lend strong support for the hypothesis that ELS-induced adult cardiovascular disease risk has an epigenetic basis and thus may be transmitted transgenerationally.

Conclusions

Maternal separation in animals provides a model to elucidate the underlying molecular mechanisms by which ELS increases the susceptibility to develop cardiovascular disease. MatSep in rodents is a unique approach to model ELS, although there are limitations (Lippmann *et al*. 2007) that should be recognized. Some of the ELS-induced changes may not be functionally observed during 'normal' conditions of adult life, the exposure to a secondary challenge or stressor may induce an exaggerated physiological response and predispose the individual to greater cardiovascular risk. Therefore, exposure to a behavioural stressor early in life may not significantly influence the overall adult cardiovascular phenotype until a second stressor later in life reveals an exaggerated cardiovascular dysfunction that may influence the quality of life and life expectancy in later in adulthood. Animal studies will contribute to make a positive difference in health improvement by identifying potential mechanisms as targets and/or biomarkers for cardiovascular disease risk.

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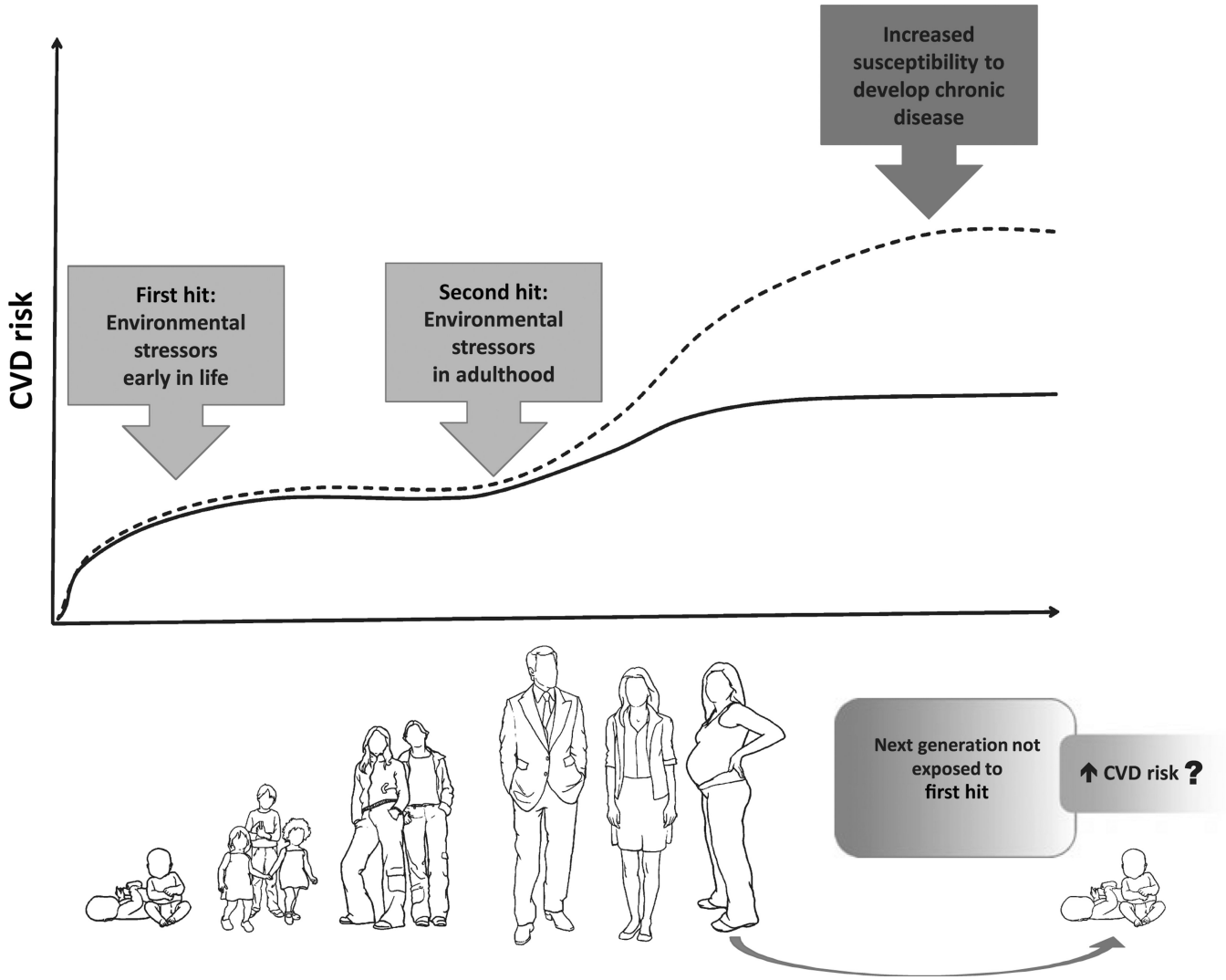

Figure 1.

Schematic of cardiovascular risk during the time course of life. Individuals exposed to a first stressor during early life are more susceptible to secondary stressors later in life. The impact in the phenotype may induce transgenerational effects.

Table 1

Clinical studies in cohorts exposed to ELS

(A) Retrospective studies

Cohort study	Stress period	Evaluation	Population	Outcomes
Wales and Sweden	1751–1930	1934	UK Sweden	Death rates fell as a result of better childhood living conditions (Kermack *et al*. 1934)
The Tromsø Study	1890	1964–1967 1994–2001	Norway	Positive correlation between childhood poverty/poor living conditions and adult coronary and atherosclerotic heart disease 3–6 decades later (Forsdahl 1978, Forsdahl *et al*. 2009)
British Birth	1946	1985	UK	Low socio-economic status correlated with higher blood pressure in 40-year-old patients (Wadsworth *et al*. 1985, Hardy *et al*. 2004, Kuh *et al*. 2008)
Helsinki Birth	1934–1944	2011	Finland	Participants separated during childhood for safety reasons used medications for coronary heart disease more frequently 60 year later (Alastalo *et al*. 2009, 2012, 2013)
Guangzhou Biobank	2003	2008	China	ELS was negatively associated with some cardiovascular risk factors, particularly among men (Schooling *et al*. 2011)

(B) Prospective studies

Study name	Start	End	Population	Outcomes
Dunedin health and development	1972	2006	New Zealand	Childhood maltreatment is an independent risk factor for inflammation, a mediator in the development of CVD (Danese *et al*. 2007)
1958 British Birth	1958	1991	UK	Study of combined social and biological risk factors revealed that increments across the distribution of childhood cognition are associated with the improvements in cardiovascular risk profile in midlife (Power *et al*. 1987, 2002, Power & Elliott 2006)
ABCD-Amsterdam	2003	2014	Holland	Explains socio-economic inequalities in childhood blood pressure and pre-hypertension (van Eijsden *et al*. 2011)
ELS clinic Stanford		Ongoing	USA	Early interventions for children and families who have experienced an acute or chronic stressor or traumatic event
Generation R	2002	Ongoing	Holland	Examines the growth, development and health of 10 000 children in a multi-ethnic population to identify early environmental and genetic causes of normal and abnormal growth and development
Adverse childhood experiences (ACE)	1995	Ongoing	USA	Over 17 000 members studied revealed a dose–response relationship between ACE and increased ischaemic heart disease risk (Felitti *et al*. 1998, Dong *et al*. 2004, Anda *et al*. 2009)

Table 2

Comparative models of maternal separation in different species

Species	Model	Affected parameters	References
Non-human primate	Maternal separation	Juvenile and adult social responses Serotonin transporter expression	Feng *et al*. (2011), Spencer-Booth & Hinde (1971), Bernstein & Dobrofsky (1981), Laudenslager *et al*. (1982), Lyons *et al*. (2001), Rilling *et al*. (2001) and Parker *et al*. (2005, 2007)
Pig	Early weaning	Stress-related gene expression in brain	Kanitz *et al*. (2004), Tuchscherer *et al*. (2004, 2006), Moeser *et al*. (2007), Kanitz *et al*. (2009) and McLamb *et al*. (2013)
	Maternal separation	Neuroendocrine responses Immunological responses	
Rabbit	Maternal separation	Neonatal metabolic parameters Circulating stress hormones	Cano *et al*. (2005a,b) and Rebollar *et al*. (2006)
Rat	Maternal separation	Neonatal metabolic parameters Adult anxiety HPA axis Renal hemodynamics Vascular inflammation Vascular reactivity	Tucker & Johnson (1984), Lehmann *et al*. (2000), Lippmann *et al*. (2007), Loria *et al*(2010a,b, 2011, 2013), Desbonnet *et al*. (2008) and O'Mahony *et al*. (2008)
Mouse	Maternal separation	Adult anxiety	Carlyle *et al*. (2013), George *et al*. (2010) and Savignac *et al*. (2011)
	Maternal separation with early weaning	Brain chromatin remodelling senzymes (HDACs) Gastrointestinal inflammatory profile Immunological response to infection	
Guinea-pig	Early weaning	Pup stress hormones	Hennessy (1988), Hennessy *et al*(2010, 1989, 2007), Hennessy & Sharp (1990) and Tamborski *et al*. (1990)
	Maternal separation	Circulating cortisol levels and vocalization in novel environment Core temperature and behaviour	
Bird	Maternal separation Corticosterone administration	Adult hypothalamic-pituitary-adrenal axis activation Mate choice	Banerjee *et al*. (2012) and Spencer *et al*. (2009)

Table 3

Molecular alterations due to MatSep reported in rodents

Molecular and/or structural alteration	Functional alteration
Central nervous system	
Hipoccampus: c-Fos, BDNF, serotonin, CREB.	Depression, anxiety, mood disorders
Prefrontal cortex: GR receptor, cytochrome oxidase.	Hypercapnic ventilatory response.
	Dysregulation of the HPA axis sensitivity (Lippmann *et al*. 2007, Meaney *et al*. 2007, Genest *et al*. 2004, O'Mahony *et al*. 2008).
HPA axis and SAM system	
Increased plasma corticosterone, CRH, ACTH.	Exaggerated behavioral and cardiovascular stress-related response (Enthoven *et al*. 2008b, Plotsky and Meaney, 1993, Renard *et al*. 2007).
Epigenetic regulation of FKBP5 gene.	
	Increased risk of adult psychiatric disorders, altered stress regulation, altered immune cell function (Klengel *et al*. 2013).
Renal and cardiovascular system	
Increased left ventricle weight and capillary density.	Mild effects on cardiomyocyte hypertrophy and myocardial
Lower AT2 receptor mRNA expression and function	fibrosis (Trombini *et al*. 2012).
in vasculature.	Reduced NO buffering capacity and increased AngII-induced
Greater renal NE-induced rise in blood pressure.	constriction (Loria *et al*. 2011, Loria *et al*. 2010a, Loria *et al*. 2010b).
	Lower renal filtration capacity. Impaired chronic blood pressure control (Loria *et al*. 2013).
Immune system	
Increased IL-1, IL-6, TNFa in response to immune challenge.	Exaggerated response to LPS and E coli infection (Meagher *et al*. 2010).
Metabolic regulation	
Reduced insulin and HOMA levels	Insulin resistance and metabolic syndrome
Higher adiponutrin, leptin and peroxisome proliferator-activated receptor gamma coactivator 1 alpha.	Increased body weight and metabolic syndrome (Spivey *et al*. 2011).

BDNF, brain derived neurotrophic factor; CREB, cyclic AMP response element binding protein; GR, glucocorticoid receptor; CRH, corticotropin releasing hormone; ACTH, Adrenocorticotropic hormone; FKBP5, FK506 binding protein; AT2: Angioten-sin II receptor type 2; NE, norepinephrine; IL-1, interleukin 1; IL-6, interleukin 6; TNFa, tumor necrosis factor alpha; HOMA, homeostatic model assessment; HPA, hypothalamic pituitary adrenal axis; NO, nitric oxide; LPS, lipopolysaccharide.