



Research paper

DNA methylation from birth to late adolescence and development of multiple-risk behaviours



F. de Vocht^{a,*}, M. Suderman^{a,b,1}, K. Tilling^{a,b}, J. Heron^a, L.D. Howe^{a,b}, R. Campbell^a, M. Hickman^a, C. Relton^{a,b}

^a School of Social and Community Medicine, University of Bristol, Bristol, UK

^b MRC Integrative Epidemiology Unit, UK

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ABSTRACT

Background: Risk behaviours in adolescence are linked to poor educational attainment and health and other outcomes in young adulthood. We explored whether there are molecular mechanisms associated with the development, or the result, of multiple risk behaviours (MRBs).

Methods: MRBs (antisocial behaviour and delinquency, traffic-related risk behaviour, risky sexual behaviour, lack of exercise) and their sumscore were characterized based on self-reported questions at age 7 and 17 within the ARIES subsample of the ALSPAC birth cohort, and were linked to DNA methylation at over 485,000 CpG sites at ages 0,7 and 17. Associations were determined for participants with complete data (n = 227–575).

Results: There was weak evidence of associations between cumulative MRBs and methylation at cg01783492 and cg16720578 at age 17. DNA methylation at age 17 was associated with risky sexual behaviour (cg22883332), lack of exercise (cg03152353, cg20056908, cg20571116) and substance use (cg02188400, cg13906377). No associations between DNA methylation and individual risk behaviours at age 7 were observed. DNA methylation at age 7 might predispose for traffic-related risk behaviour (cg24683561) and substance use (cg08761410) at age 17.

Limitations: Main limitations are absence of information on directly measured blood cell type proportions and tissue specificity, and a modest sample size.

Conclusions: Cumulative MRB in late adolescence was associated with effects on DNA methylation. More specifically, risky sexual behaviour and sedentary behaviour are associated with changes in DNA methylation, while DNA methylation in childhood may predict later traffic-related risky behaviour. For substance use effects in both temporal directions were observed.

1. Introduction

Risk behaviours in adolescence, such as substance use, alcohol consumption, poor diet, physical inactivity, unprotected sex and antisocial behaviour are common (Kipping et al., 2015), and associated with adverse health and other outcomes in later adolescence (Hale and Viner, 2016). Analysis of a UK birth cohort (the Avon Longitudinal Study of Parents and Children cohort study) showed that multiple risk behaviours (MRBs) in adolescence are common, with 74% of 15–16 year olds being physically inactive, 34% consuming alcohol at hazardous levels, and 42% being engaged in antisocial and criminal behaviour (MacArthur et al., 2012). Initiation of most risk behaviours generally occurs at ages 14–16 (Hale and Viner, 2016), while it has further been shown that those who initiate risk behaviours early were

more likely to be multiple risk-takers (DuRant et al., 1999).

These risky behaviours are linked to poor educational attainment and a range of morbidity and mortality outcomes in later life (Galambos and Tilton-Weaver, 1998; Rohde et al., 2001; Sandfort et al., 2008; Viner and Taylor, 2007), which has made the prevention of health risk behaviours by adolescents a focus for policy in the UK and internationally (Hale and Viner, 2012). It has been shown that risk behaviours, such as for example substance use, sexual risk and delinquency in adolescence (Hair et al., 2009; Hale and Viner, 2016; Jackson et al., 2012; Meader et al., 2016; Wiefferink et al., 2006) often cluster. Two broad theories have been proposed that may explain the correlations between adolescent risk behaviours: [1] ‘Gateway theory’ (Pudney, 2003), which suggests that engagement in one form of risk leads to others through a decrease in perceiving dangers and/or through

* Correspondence to: Population Health Sciences, University of Bristol, Canynge Hall, 39 Whatley Road, Bristol BS8 2PS, UK.

E-mail address: frank.devocht@bristol.ac.uk (F. de Vocht).

¹ Joint first authors.

Table 1
(Multiple) Risk Behaviour (MRB) categories at time point 2 (age ~ 17 years).

Sum scores	Description
MRB sum score (continuous)	A + B + C + D + E
MRB sum score (binary)	Low (\leq median) vs high ($>$ median) MRB risk score
MRB sum score (25th vs 75th)	Low (\leq 25th percentile) vs high (\geq 75th percentile) MRB risk score (25th–75th percentile removed from analysis)
Strata/individual risk behaviours	
A) Antisocial behaviour and delinquency	1) At least once in the past year: theft from vehicle, carrying a weapon, being rude/rowdy in public place, breaking into a vehicle, taking a car that is not their own, stealing from a shop, buying stolen goods, stealing money from someone else, burgling a house, kicked/hurt someone on purpose, used a cheque book/card not their own, damaged property not their own on purpose. 2) Has hurt themselves on purpose at least once in the last year 3) One or more forms of gambling over past 12 months
B) Traffic-related risk behaviour	1) Has been car passenger at least once in their lifetime where the driver (a) has had alcohol or (b) does not have valid licence or (c) chose not to wear a seat belt last time travelled in a car, van or taxi. 2) Has driven a scooter off road or w/o licence (or both) at least one time in lifetime 3) Has driven on / off road w/o licence at least once in lifetime 4) Did not use a helmet last time they rode a bike (within the recent four week period)
C) Risky sexual behaviour	1) Has had sexual intercourse and not used a condom on last occasion they had sex in the last 12 months 2) Multiple sexual partners (3+) in past year
D) Lack of physical exercise	1) Has typically over the past year exercised $<$ 5 times/wk
E) Substance use	1) Has used cannabis 2–4 times a month or more frequently in the last 12 months 2) Typically smokes at least one cigarette per week over the last 12 months 3) Alcohol Use Disorders Identification Test (AUDIT) score of 8 or more 4) Illicit drug and inhalant use (excluding cannabis) over past twelve months.

increased exposure to other risk behaviours, and ‘*Problem Behaviour theory*’ which purports that sets of behaviours that are defined as problematic and/or unconventional are enacted as a manifestation of disregard of social conventions or, depending on age, of maturity (Jessor et al., 1998). The implications of either theory throughout adolescence are that whereas Gateway theory predicts accumulating associations between risk behaviours with age, Problem Behaviour theory may result in a stable risk behaviour in late adolescence. This pattern has, for example, been observed for trajectories of substance abuse from early adolescence to adulthood which described how correlations between risk behaviours decrease with age, and similar patterns have been observed for drug use and sexual behaviour, but not for alcohol use (Hale and Viner, 2016). This decrease can be ascribed to a transition from general risk behaviour aetiology in adolescence to risk-specific influences in adulthood (Vrieze et al., 2012). Like most complex phenotypes, in addition to shared social/environmental factors, there may also be also be shared biological factors that influence the development of these multiple risk behaviours, and there is evidence that the generalized risk may be directly influenced by modifiable molecular factors in childhood or adolescence (Vrieze et al., 2012). In support of this, epigenetic processes have been shown to be associated with substance use in adolescents (Cecil et al., 2016).

Epigenetics, the study of heritable changes in gene expression not due to changes in DNA sequence, offers the potential to identify molecular mechanisms by which environmental and lifestyle exposures may affect health (Florath et al., 2014; Hannum et al., 2013). Epigenetic mechanisms include DNA methylation, histone modifications and microRNA, all of which act in concert to regulate gene expression (Groom et al., 2011). DNA methylation, the addition of methyl groups to nucleotide bases, is the most stable and most readily quantifiable epigenetic marker and has thus become the most widely studied. DNA methylation is affected by genetic variation (Gaunt et al., 2016), is sensitive to pre- and postnatal exogenous influences (de Vocht et al., 2015), and has also been linked to physical and psychiatric disorders, including addiction (Cecil et al., 2015). Recent technological advances have allowed the application of genomic technologies to epigenetics, facilitating the large scale generation of quantitative DNA methylation data across the genome (Mensaert et al., 2014).

In this study, we explored, for the first time, associations between multiple risk behaviours and DNA methylation measured at multiple time points across childhood, at birth, age 7 and age 17. Critically, two of the DNA methylation measurements were taken prior to the

behaviour which enables investigation of the temporal direction of the associations to address the question; are epigenetic changes observed at different time points risk factors for behaviour or are they consequences of the behaviour itself?

2. Methods

This study used DNA methylation data generated under the auspices of the Avon Longitudinal Study of Parents and Children (ALSPAC) (Boyd et al., 2013; Fraser et al., 2013). ALSPAC recruited 14,541 pregnant women with expected delivery dates between April 1991 and December 1992. Of these initial pregnancies, there were 14,062 live births and 13,988 children who were alive at 1 year of age. The study website contains details of all the data that are available through a fully searchable data dictionary (<http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary>). As part of the ARIES (Relton et al., 2015) project (<http://www.ariesepigenomics.org.uk>), a sub-sample of 1,018 ALSPAC mother–child pairs had DNA methylation measured using the Infinium HumanMethylation450 BeadChip (Illumina, Inc.) (Dedeurwaerder et al., 2011). Here, we use DNA methylation data generated from cord blood and venous blood samples at age 7 and again at age 15 or 17 years, leading to three measurements of DNA methylation per child. All DNA methylation wet-lab and preprocessing analyses were performed at the University of Bristol as part of the ARIES project and has been described in detail previously (Relton et al., 2015).

Informed consent was obtained from all ALSPAC participants and ethical approval was obtained from the ALSPAC Law and Ethics Committee as well as Local Research Committees.

2.1. Outcome

Multiple risk behaviour (MRB) was characterized based on self-reported questions broadly divided into five domains: antisocial behaviour and delinquency (2 questions), traffic-related risk behaviour (4 questions), risky sexual behaviour (2 questions), sedentary behaviour (1 question), and substance use (4 questions). Where questions were not binary already, behaviours were recoded to present (1) or absent (0) based on cut-off points informed by the literature (described in Kipping et al. (2015)). Dichotomised scores for each behaviour were summed per domain to obtain a summary domain score for ages ~ 7 and ~ 17, and for age 17 these in turn were added to obtain the MRB sum score; i.e. the primary outcome of this study (range 0–13 in theory, 0–9 in this

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