Balance ability in 7- and 10-year-old children: associations with prenatal lead and cadmium exposure and with blood lead levels in children in a prospective birth cohort study

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Balance ability in 7- and 10-year-old children: associations with prenatal lead and

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6	
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13	
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15	Word count: (excluding title page, abstract, references, figures and tables): 3429
16	

Abstract **Objectives** Most studies reporting evidence of adverse effects of lead and cadmium on balance have been conducted in high-exposure groups or have included adults. The effects of prenatal exposure have not been well studied, nor have the effects directly in children. The aim of the study was to identify the associations of lead (in utero and in childhood) and cadmium (in utero) exposure with balance ability in 7- and 10-year-old children. **Design** Prospective birth cohort study Participants Maternal lead and cadmium levels were measured in 4285 women enrolled in ALSPAC during pregnancy. Child lead levels were measured in a subsample of 582 children at age 30 months. **Main outcome measures** A total of 5042 children completed a heel-to-toe walking test at 7 years. At 10 years 6915 children underwent clinical tests of static and dynamic balance. Statistical analysis included logistic regression modelling comparing categories of ≥ 5 vs $< 5 \ \mu g/dl$ for lead and ≥ 1 vs < 1µg/l for cadmium with SPSS v19. **Results** Balance at age 7 years was not associated with elevated in utero lead or cadmium exposure (adjusted OR for balance dysfunction: Pb 1.02 (95% CI 0.96, 1.08); Cd 0.99 (0.80, 1.22)), or with elevated child blood lead level at age 30 months (adjusted OR 0.99 (0.93, 1.06)). Similarly, neither measures of static nor dynamic balance at age 10 years were associated with in utero lead or cadmium exposure, or child lead level. **Conclusions** These findings do not provide any evidence of an association of prenatal exposure to lead or cadmium, or lead levels in childhood, on balance ability in children. Confirmation in other cohorts is needed.

Word count: 264

4	41	Strengths and limitations of the study
5 6 7	42	• Data were collected prospectively in a population-based study
0	43	• The number of participants was large compared with several comparable studies
11	44	• Measures of Pb and Cd do not necessarily reflect lifetime exposure
	45	• Balance measures have a poor test-retest reliability
$\begin{array}{c} 14\\ 15\\ 16\\ 17\\ 18\\ 19\\ 20\\ 21\\ 22\\ 23\\ 24\\ 25\\ 26\\ 27\\ 28\\ 29\\ 30\\ 31\\ 32\\ 33\\ 34\\ 35\\ 36\\ 37\\ 38\\ 39\\ 40\\ 41\\ 42\\ 43\\ 44\\ 45\\ 46\\ 47\\ 48\\ 49\\ 50\\ 51\\ 52\\ 53\\ 54\\ 55\\ 56\\ 57\\ 58\\ 59\\ 60\\ \end{array}$	46	
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INTRODUCTION

Balance, or postural stability, is defined as the ability to keep the centre of gravity over the base of support.¹ The maintenance of balance underpins the ability to carry out nearly all daily activities. The control of balance is complex and is dependent on sensory inputs from the vestibular and visual systems, neural processing centres in the central nervous system, and motor inputs from the proprioceptive centre. Functional damage or deficits in any of these systems can lead to balance dysfunction, which can be associated with low self-esteem, anxiety and loss of confidence in children.²

Lead and cadmium are toxic metals and their effects on neurocognitive and behavioural functions are well documented.³⁻⁶ Lead passes freely through the placenta so that ratio of fetal to maternal blood lead is about 0.8, although the placenta can act as a partial barrier to cadmium.⁷ The fetus is particularly vulnerable to the effects of these metals because of high rates of cell division and development. The development of the inner ear and vestibular function spans the whole of the period of gestation (for example, the membranous labyrinth is complete by week 7 with development of the bony labyrinth from week 9 to 23; the vestibular apparatus is in an adult-like form by week 25, and is active by week 32; vestibular ganglions develop from week 12 and reach maturity at week 39, and so on⁸). Thus, prenatal exposure to lead and cadmium may have adverse effects on the development of the inner ear, and hence on vestibular function and balance ability in later childhood.

It was noted in the 1980s that children who survived acute lead encephalopathy had ataxia and experienced difficulties in maintaining postural balance.⁹ This led to a series of studies in children with more moderate levels of lead exposure showing that the child's lead level was associated with balance dysfunction and sway oscillation.¹⁰⁻¹⁴ To our knowledge, there are

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no reports of the effect of cadmium on balance ability in children. However, a recent study of lead and cadmium levels in adults in the US National Health and Nutrition Examination Survey (NHANES) found preliminary evidence of an association of lead and cadmium with balance and vestibular function.¹⁵ In addition, altered postural balance response has been reported in adult workers occupationally exposed to lead.¹⁶⁻¹⁸ and cadmium.¹⁹ These results require confirmation in other cohorts and particularly in children. The aims of our study were to investigate the associations of in utero exposure to lead and cadmium, and lead levels in children, on balance in childhood using data obtained from the Avon Longitudinal Study of Parents and Children (ALSPAC). **Methods** We first modelled associations of in utero exposure to lead and cadmium, using maternal blood levels during pregnancy, with clinical measures of balance (dynamic and static) at 7 and 10 years. We also investigated associations with questionnaire items related to balance repeated at 30 months, 42 and 81 months, and further items at 10 years. We also modelled the associations of child levels of lead with the balance variables. The ALSPAC study The study sample was derived from the ALSPAC study, a population-based study

90 investigating environmental and genetic influences on the health, behaviour and development

- of children. All pregnant women in the former Avon Health Authority with an expected
- 92 delivery date between 1 April 1991 and 31 December 1992 were eligible for the study;
- 93 14,541 pregnant women were initially enrolled, resulting in a cohort of 14,062 live births.²⁰

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94	The social and demographic characteristics of this cohort were similar to those found in UK
95	national census surveys ²¹ . Further details of ALSPAC are available at
96	www.bris.ac.uk/alspac.
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98	Collection, storage and analysis of blood samples
99	Maternal blood samples Whole blood samples were collected in acid-washed vacutainers
100	(Becton and Dickinson, Oxford, UK) by midwives as early as possible in pregnancy. The
101	median gestational age at the time of blood sampling was 11 weeks. The interquartile range
102	was 9–13 weeks, and 93% of the samples were collected at <18 weeks gestation. Whole
103	blood samples were stored in the original tube at 4°C at the collection site before being
104	transferred to the central Bristol laboratory within 1-4 days. Samples were at ambient
105	temperature during transfer (up to 3 h). They were then stored at 4°C until analysis. Samples
106	were analysed for lead using inductively-coupled plasma mass spectrometry in standard
107	mode (R. Jones; Centers for Disease Control (CDC), Bethesda, MD, USA; CDC Method
108	3009.1). The analyses were completed on 4284 women. One sample had a Pb level below the
109	limit of detection (0.29 μ g/dl); 1119 samples were below the lower limit of detection for Cd
110	(0.20 μ g/l). These samples were assigned a value of 0.7 times the lower limit of detection.
111	
112	Child blood samples Details of the selection of the subsample of children and analysis of
113	the blood samples have been reported previously in detail. ^{3 22} In brief, a 10% randomly
114	selected subsample of parents whose babies were born in the last 6 months of the ALSPAC
115	study were invited to attend a research clinic (Children in Focus, CIF). At age 30 months,
116	parental consent was sought for a venous blood sample, and was given by 81% of the 1135
117	children in the CIF group. The sample was drawn into lead-free tubes from 653 (71%) of

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children attending the clinic. However, 69 samples were insufficient, leaving 582 samples for
analysis. Analysis was by atomic absorption spectrometry (Southampton General Hospital,
UK) with appropriate quality controls.

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122 Balance variables

123 *Clinic measures* Full details of the balance outcomes including details of the measurements and validity have previously been published.²³ In brief, at age 7 years the heel-to-toe walking 124 test of the Movement Assessment Battery for Children²⁴ was conducted with the total number 125 of successful steps out of a maximum of 15 recorded (n=5402). At age 10 years a range of 126 127 tests were used to assess balance: (1) walking along a beam, heel-to-toe, eyes open; (2) heel-128 to-toe balance on a beam, eyes closed; (3) standing on one leg, eyes closed. Each child had 129 two attempts at beam-walking; for tests of static balance, children only had a second attempt if they failed to achieve the maximum score on the first attempt.²³ These tests were based on 130 131 standard clinical tests to assess balance in children and have significant commonality with the balance subtest of the both editions of the Bruininks-Oseretsky Test of Motor Proficiency.²⁵ 132 ²⁶ The measures are also in common use when testing balance informally in the paediatric 133 134 clinic.

135

Questionnaire items The primary caregiver (usually the mother) received a series of postal
self-completion questionnaires. The questionnaires are available from the study website
(http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/). When their child was
aged 18, 30, 42 and 81 months, the parent completing the questionnaire was asked to indicate
'Yes, can do well'/'Has only done once or twice'/'Has not yet started' in response to the
statement 'He/She can balance on one foot for at least 1 second'. When their child was aged

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10 years, the parent was asked to indicate 'Very well'/'Just OK'/'Can almost'/'Not at all' in 142 143 response to the following questions: How well can your child stand on one leg in a stable 144 position (e.g. when putting on trousers, skirt)?; How well can your child ride a bike (without

145 stabilisers)?; How well can your child walk in the dark?

146

147 Confounding variables

148 Information on passive smoking exposure during the week and at weekends was obtained

149 from questionnaires at 77 and 103 months. Information on traffic levels, type of

150 accommodation, lowest level of accommodation and maternal education were obtained at

151 from questionnaires completed by the mother during pregnancy. Dietary Ca and Fe intake at

152 7 years and 10 years were derived from food frequency questionnaires as previously

described in detail ²⁷. 153

154

155 Statistical analysis

156 Statistical analysis was carried out with IBM SPSS Statistics 21. Balance measures were derived as previously described.²³ In brief, for the heel-to-toe test at age 7 years, the number 157 158 of steps (maximum 15) was categorised into 0–5, 6–10 and 11–15 steps for categorical 159 associations, and 1–14 versus 15 steps for regression analyses. For the measure of dynamic 160 balance at 10 years (beam-walking test), the mean of two attempts was categorised into 161 quartiles. For measures of static balance at age 10 years (heel to toe balance on a beam with 162 eyes closed/standing on one leg eyes closed), the sum of the score (s) from both attempts was 163 calculated. Children who scored the maximum of 20 on the first attempt and so did not have a 164 second attempt were given a final score of 40. The final scores were put into four categories

165	(0-9, 10-19, 20-39 and 40). All of the four static balance tests with eyes closed were
166	summed to create a static balance eyes closed variable (SBEC).
167	Blood lead and cadmium levels were put into two categories (<5, \geq 5 µg/dl for lead and <1,
168	$\geq 1 \ \mu g/l$ for Cd). These categories were chosen in accordance with the levels of concern of the
169	US Centers for Disease Control, the US Association of Occupation and Environmental
170	Clinics and the American College of Obstetricians and Gynaecologists for Pb, ²⁸⁻³¹ and the
171	German Federal Environmental Agency for Cd. ³² Blood levels were also categorised into
172	quartiles.
173	Chi square tests were used to compare categorical variables. Unadjusted and adjusted logistic
174	regression analyses were used to investigate the association of blood levels with balance
175	variables.
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177	RESULTS
177 178	RESULTS As previously reported, the mean child blood lead level was $4.22\pm3.12 \mu g/dl (n=582)^{3/22}$; the
178	As previously reported, the mean child blood lead level was $4.22\pm3.12 \ \mu g/dl \ (n=582)^{3} \ ^{22}$; the
178 179	As previously reported, the mean child blood lead level was $4.22\pm3.12 \ \mu g/dl \ (n=582)^{3} \ ^{22}$; the mean prenatal blood lead level was $3.67\pm1.47 \ \mu g/dl \ (n=4285)$ and the mean prenatal
178 179 180	As previously reported, the mean child blood lead level was $4.22\pm3.12 \ \mu g/dl \ (n=582)^{3} \ ^{22}$; the mean prenatal blood lead level was $3.67\pm1.47 \ \mu g/dl \ (n=4285)$ and the mean prenatal
178 179 180 181	As previously reported, the mean child blood lead level was $4.22\pm3.12 \ \mu g/dl \ (n=582)^{3} \ ^{22}$; the mean prenatal blood lead level was $3.67\pm1.47 \ \mu g/dl \ (n=4285)$ and the mean prenatal cadmium level was $0.58\pm0.63 \ \mu g/l \ (n=4286)$. ^{33 34}
178 179 180 181 182	As previously reported, the mean child blood lead level was $4.22\pm3.12 \ \mu g/dl \ (n=582)^{3} \ ^{22}$; the mean prenatal blood lead level was $3.67\pm1.47 \ \mu g/dl \ (n=4285)$ and the mean prenatal cadmium level was $0.58\pm0.63 \ \mu g/l \ (n=4286)$. ^{33 34}
178 179 180 181 182 183	As previously reported, the mean child blood lead level was $4.22\pm3.12 \ \mu g/dl \ (n=582)^{3} \ ^{22}$; the mean prenatal blood lead level was $3.67\pm1.47 \ \mu g/dl \ (n=4285)$ and the mean prenatal cadmium level was $0.58\pm0.63 \ \mu g/l \ (n=4286)$. ^{33 34} Associations of measures of balance with prenatal lead and cadmium levels and with child lead levels
178 179 180 181 182 183 184	As previously reported, the mean child blood lead level was $4.22\pm3.12 \ \mu g/dl \ (n=582)^{3} \ ^{22}$; the mean prenatal blood lead level was $3.67\pm1.47 \ \mu g/dl \ (n=4285)$ and the mean prenatal cadmium level was $0.58\pm0.63 \ \mu g/l \ (n=4286)$. ^{33 34} Associations of measures of balance with prenatal lead and cadmium levels and with child lead levels Associations with in utero exposure to lead and cadmium

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> dynamic balance (beam walking) or static balance (SBEC) and maternal blood lead or cadmium levels in pregnancy (all p>0.4) (Table 1). In logistic regression models adjusted for sex, passive smoking, and calcium and iron intake, there was no evidence of any association between maternal blood lead or cadmium levels and measure of balance in the child at 7 and 10 years (all p>0.1) (Table 2). When the models were repeated with quintiles of maternal blood lead or cadmium level rather than a dichotomous variable, there was also no evidence of any associations (all p>0.01 with the exception of maternal blood lead for the odds of static balance dysfunction at 10 years where there was a protective effect (p for trend 0.038) (Supplementary Table 1). Associations with child lead level There was no evidence of any association between the results of the heel-to-toe test at age 7 years and child lead level (p for trend=0.146) (Table 3). Similarly, at age 10 years there were no associations between dynamic balance (beam walking) or static balance (SBEC) and child

blood lead levels (p for trend=0.798 and p=0.918, respectively) (Table 3). In logistic

203 regression models adjusted for sex, passive smoking, and calcium and iron intake, there was

- 204 no evidence of any association between child blood levels at 30 months and measure of
- balance at 7 and 10 years (Table 4; all p for trend >0.3). When the models were repeated with
- 206 quintiles of child blood lead rather than a dichotomous variable, there was also no evidence
- of any associations (all p for trend >0.1) with the exception of static balance where there was
- a weakly protective effect (p for trend=0.038 (Supplementary Table 1).

		Age (years)	Category	Maternal Pb (µg/dl)			Maternal Cd (µg/l)		
		(years)		<5	≥5	P value for trend	<1	≥1	P value for trend
	Heel to toe test	7	0–5 steps 6–10 steps 11–15 steps	520 (27.1) 273 (14.2) 1128 (58.7)	82 (26.5) 45 (14.5) 183 (59.0)	0.861	520 (26.6) 270 (13.8) 1164 (59.6)	81 (29.1) 49 (17.6) 148 (53.2)	0.112
	Beam walking (dynamic balance)	10	Q1 Q2 Q3 Q4	431 (23.4) 461 (25.0) 456 (24.8) 494 (26.8)	70 (24.1) 80 (27.6) 66 (22.8) 74 (25.5)	0.450	439 (23.3) 484 (25.6) 463 (24.5) 502 (26.6)	62 (25.3) 57 (23.3) 59 (24.1) 67 (27.3)	0.897
	Static balance eyes closed score (SBEC) (static balance)	10	Q1 Q2 Q3 Q4	460 (24.4) 459 (25.4) 430 (23.8) 459 (25.4)	74 (25.8) 58 (20.2) 83 (28.9) 72 (25.1)	0.558	471 (25.4) 455 (24.6) 457 (24.7) 469 (25.3)	63 (25.8) 62 (25.4) 57 (23.4) 62 (25.4)	0.842
211	Values are n (%).		יע	4 <i>JJ</i> (2 <i>J</i> . 4)				02 (23.4)	
212	Q, quartile.								
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 Table 2
 Associations of in utero lead and cadmium exposure with balance measures in the child at 7 and 10 years old in ALSPAC

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	Age (years)	Pre	enatal lead exposure	e	Prenatal cadmium exposure			
	0,	OR of balan (95% CI)	ce dysfunction	P value	OR of balan (95% CI)	ce dysfunction	P value	
Heel to toe test	7	Unadjusted	1.02 (0.97, 1.08)	0.503	Unadjusted	0.82 (0.70, 0.95)	0.010	
		Adjusted ^a	1.02 (0.96, 1.08)	0.555	Adjusted ^a	0.99 (0.80, 1.22)	0.904	
Dynamic balance	10	Unadjusted	1.01 (0.95, 1.08)	0.790	Unadjusted	1.00 (0.84, 1.21)	0.946	
		Adjusted ^b	1.02 (0.95, 1.09)	0.692	Adjusted ^b	1.20 (0.95, 1.52)	0.135	
Static balance	10	Unadjusted	0.98 (0.92, 1.05)	0.569	Unadjusted	1.06 (0.88, 1.28)	0.523	
		Adjusted ^b	0.98 (0.92, 1.06)	0.661	Adjusted ^b	1.00 (0.79, 1.26)	0.995	

Logistic regression showing odds ratio of balance dysfunction (95% CI).

^aAdjusted for: sex, passive smoking at 77 months old (weekdays and weekends), and Ca and Fe intake at 7 years. 220

^bAdjusted for: sex, passive smoking at 103 months old (weekdays and weekends), and Ca and Fe intake at 10 years.

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	Test	Age (years)	Category	Child P	'b (µg/dl)	P value for trend
				<5	≥5	_
	Heel to toe test	7	0–5 steps 6–10 steps	82 (25.8) 52 (16.4)	34 (30.9) 22 (20.0)	0.146
			11–15 steps	185 (57.9)	54 (49.1)	
	Beam walking (dynamic balance)	10	Q1	74 (24.0)	24 (23.5)	0.798
			Q2	82 (26.6)	30 (29.4)	
			Q3	72 (23.4)	23 (22.5)	
			Q4	80 (26.0)	25 (24.5)	
	Static balance eyes closed score (SBEC) (static balance)	10	Q1	80 (26.5)	22 (22.0)	0.918
			Q2	70 (23.2)	30 (30.0)	
			Q3	77 (25.5)	24 (24.0)	
			Q4	75 (24.8)	24 (24.0)	
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26	Values are n (%).					
27	Q, quartile.					
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Table 3 Associations of child lead level at 30 months with measures of balance at 7 and 10 years in AI SPAC

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Table 4 Child blood lead level at 30 months and balance measures at 7 and 10 years old in ALSPAC

		Age (years)	OR of balance d	ysfunction (95% CI)	P value
	Heel to toe test	7	Unadjusted	0.99 (0.93, 1.05)	0.618
			Adjusted ^a	0.99 (0.93, 1.06)	0.778
	Dynamic balance	10	Unadjusted	1.03 (0.96, 1.11)	0.422
			Adjusted ^b	1.01 (0.93, 1.09)	0.814
	Static balance	10	Unadjusted	1.04 (0.96, 1.12)	0.345
			Adjusted ^b	1.03 (0.94, 1.12)	0.540
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238	Associations with questionnaire items at 18-81 months and at 10 years
239	There was no evidence of any associations between child blood lead level at 30 months and
240	the ability to stand on one foot for at least 1 second at 30, 42 or 81 months (all p>0.6;
241	Supplementary Table 2). There was no evidence of any associations between maternal blood
242	lead level during pregnancy and the ability of the child to stand on one foot for at least 1
243	second at 18, 30, 42 or 81 months (all p>0.3) (Supplementary Table 2). There was no
244	evidence of any associations between maternal blood cadmium level during pregnancy and
245	the ability of the child to stand on one foot for at least 1 second at 42, or 81 months (all
246	p>0.4), but there were associations at 18 and 30 months (p<0.001 and p=0.003, respectively;
247	maternal cadmium $\geq 1 \ \mu g/l$ was associated with being more likely to be able to stand on one
248	foot well) (Supplementary Table 2).
249	There was no evidence of any association of elevated child lead level, or in utero lead or
250	cadmium exposure, with ability to stand on one leg or to walk in the dark at 10 years (all
251	p>0.09, chi-square test) (Supplementary Table 3). However, prenatal lead level ≥5 µg/dl was
252	associated with not being able to ride a bike without stabilisers (p=0.007), whereas child lead
253	level $\geq 5 \ \mu g/dl$ and prenatal cadmium $\geq 1 \ \mu g/l$ were weakly associated with being able to ride a
254	bike without stabilisers very well (p=0.050 and p=0.075 respectively). When these
255	associations were modelled in a logistic regression analysis adjusted for variables that could
256	affect availability of a bicycle and being able to ride a bicycle locally (traffic level on the
257	home street, type of accommodation, lowest level of accommodation), and maternal
258	education, there was very weak evidence for an association of child lead level being
259	associated with being able to ride a bike well without stabilisers (OR in unadjusted model
260	2.79 (95% CI 0.096, 8.10), p=0.059; OR in adjusted model OR 2.57 (95% CI 0.87, 7.62),
261	p=0.089). The association was stronger for prenatal lead level in the unadjusted model, but
262	the effect was attenuated with adjustment (OR in unadjusted model 0.59 (95% CI 0.40, 0.87),

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p=0.007; OR in adjusted model 0.73 (95% CI 0.47, 1.14), p=0.167); for prenatal cadmium level again the weak effect was attenuated by adjustment (unadjusted OR 1.69 (95% CI 0.94, 3.01, p=0.078); adjusted OR 1.44 (95% CI 0.75, 2.75, p=0.274). DISCUSSION We did not find any evidence of an association of prenatal exposure to lead or cadmium, or lead levels in childhood, on balance ability (static and dynamic) in children. Counterintuitively, there was a suggestion that higher child lead levels and in utero lead exposure were associated with the ability to ride a bike without stabilisers at age 10 years, but these effects were negated when the associations were adjusted for variables that included the lowest level of accommodation and traffic levels outside the home. This is the first study, to our knowledge, reporting on the associations between in utero exposure to lead and cadmium and balance ability of the child, and adds to the few studies on child lead levels and balance ability. Postural balance is controlled by a complex interaction of sensorimotor processes, including visual, proprioception and the vestibular system. In our study the measure of static balance with eyes closed eliminated vision and minimised proprioceptive inputs, thereby enabling the

assessment of vestibular information as the primary input. Use of clinical measures similar to

these is commonplace in epidemiological studies (e.g. ³⁵⁻³⁸), as the tests are in common

clinical usage and require little or no specialist equipment. However, although the vestibular

dominant condition of tests of standing balance (reduced base of support with eyes closed) has been shown to correlate well with more expensive systems such as computerised dynamic posturography (considered to be the 'gold standard' method for assessing balance function) in

adults,³⁹ there are questions about whether such a correlation exists in children.⁴⁰ It has even

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been suggested that computerised measures using a force-platform and clinical tests such as those used by ALSPAC give complementary rather than concurrent information.⁴¹ A cautious approach should therefore be taken if seeking to compare studies using these two different types of outcome measure. Most studies on lead levels and balance in children have included children with relatively high lead levels (means in each study of 11.6 to 20.7 μ g/dl) and measured balance with a force platform system,¹⁰⁻¹³ and have found negative associations. There are several reason for our results being in contrast to these studies. First, the mean child blood lead level in our study $(4.22 \mu g/dl)$ was lower than reported in these earlier studies, and may have been too low either to have been sufficient to cause balance dysfunction. Alternatively, the effect on balance might have been too small to be detectable with our tests, although a study in Inuit children had levels that were more comparable to the present study (mean $5.4 \,\mu g/dl$) showed a significant association with sway oscillations.¹⁴ Second, we used a series of assessments based on clinical tests to measure balance rather than a force platform or measurement of sway oscillations and this may account for differences in the findings. As discussed earlier, clinical and force platform measures may be giving complementary rather than concurrent

information: whereas posturography is a measure of the motor and sensory strategies used to control balance, clinical tests evaluate the results of that balance control.⁴¹ Measuring sway oscillations using a force platform will also be more sensitive than the ALSPAC measures, which measured time before a procedural fault such as touching the floor with either foot or lifting a foot off the beam. Third, early exposure to lead and/or cadmium could damage the vestibular system, but the plasticity of the balance system might compensate for this so that there is no functionally measurable effect. This is in accordance with measures of balance in the present study indirectly assessing the vestibular system. This could also account for effects being reported in adults, in whom plasticity is less effective for overall balance

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312	compensation, but not in children. It is also possible that vestibular system (to include
313	peripheral (ear) and central (brain) components of the vestibular pathway) dysfunction caused
314	by in utero exposure to lead or cadmium may not be apparent in childhood but may manifest
315	in later life. Finally, it is also possible that studies showing non-significant results have
316	tended not to have been published.
317	To our knowledge, there are no studies that have examined the effect of in utero exposure to
318	lead or cadmium on balance ability in the child. Our results provide preliminary evidence for
319	lack of effect, but this requires confirmation on other cohorts.
320	The strengths of the study are that: (1) it is a population-based study; (2) the data were
321	collection prospectively; and (3) the numbers included in the study were large compared with
322	several other studies. There are several limitations to the study. First, measures of blood lead
323	and cadmium do not necessarily reflect lifetime exposure. Bone lead, which makes up more
324	than 95% of the body lead, can be measured by K x-ray fluorescence, ⁴² but this is expensive,
325	technically demanding and may not always be ethically permissible in children. This
326	limitation is of less consequence for in utero exposure as the maternal blood level largely
327	determines the fetal blood level. Second, there may be confounders we were unable to
328	account for. Third, we were unable to control for lead and cadmium separately in the models
329	because of multicollinearity. Finally, the balance measures used by ALSPAC had low test-
330	retest reliability, ²³ which is a common problem with measures of childhood balance. ⁴³⁻⁴⁵ The
331	measure of ability to balance on one foot for 1 s, a test which was originally developed by
332	Chamberlain and Davey ⁴⁶ in 1976, has been particularly criticised for having poor test
333	validity as it is difficult to discriminate a failed attempt from a successful attempt. ⁸ It should
334	ideally form part of a battery of clinical measures, perhaps with a longer duration of standing.

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335	These combined effects may have led to random misclassification in our balance assessments
336	and dilution of the estimates of the effects of lead and cadmium exposure.
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338	CONCLUSIONS
339	We did not find any evidence of an association of prenatal exposure to lead or cadmium with
340	balance ability in children. In contrast to previous studies, we did not find any association of
341	child blood lead with balance ability in children. This may reflect variation in the methods
342	used to assess balance in different studies, or may be related to the lower mean lead level in
343	the children in the present study than in previous studies. Further work in other cohorts is
344	needed to confirm the results.
345	Contributions: CMT and RH conceived the study; CMT carried out the data analysis; CMT
346	and RH drafted the paper; JG, AE and AH participated in the design of the study; all authors
347	helped to draft the manuscript, and read and approved the final manuscript.
348	Data Sharing: Further details of ALSPAC are available at www.bris.ac.uk/alspac. This
349	website includes details of how to access data.
350	Ethics approval: Ethics approval for the study was obtained from the ALSPAC Ethics and
351	Law Committee and the Local Research Ethics Committees.
352	Competing interests: The authors declare that there are no competing interests
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355	includes interviewers, computer and laboratory technicians, clerical workers, research
356	scientists, volunteers, managers, receptionists and nurses.

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Quartile		Prenatal exposure					
	Maternal Pb	Maternal Cd	b	-			
	OR of balance	P value	OR of balance	P value	OR of balance	P value	
	dysfunction (95% CI)	for trend	dysfunction (95% CI)	for trend	dysfunction (95% CI)	for trend	
Heel to toe test at	7 years ^d						
1	1.00 (Ref)	0.441	(Ref)	0.189	(Ref)	0.203	
2	0.94 (0.72, 1.22)		1.17 (0.91, 1.52)		1.44 (0.83, 2.52)		
3	1.16 (0.90, 1.51)		0.90 (0.69, 1.18)		0.88 (0.49, 1.57)		
4	1.11 (0.85, 1.44)		0.94 (0.66, 1.33)		0.85 (0.47, 1.53)		
Dynamic balance	at 10 years ^e						
1	(Ref)	0.148	(Ref)	0.332	(Ref)	0.629	
2	1.34 (0.99, 1.81)		0.85 (0.65, 1.12)		0.80 (0.41, 1.56)		
3	1.09 (0.81, 1.46)		0.95 (0.71, 1.26)		1.08 (0.54, 2.14)		
4	1.09 (0.81, 1.46)		1.10 (0.76, 1.59)		0.86 (0.43, 1.72)		
Static balance at			1.10 (0.70, 1.57)		0.00 (0.13, 1.72)		
1	(Ref)	0.038	(Ref)	0.605	(Ref)	0.297	
2	0.68 (0.50, 0.92)		1.11 (0.84, 1.48)		0.71 (0.36, 1.39)		
3	0.85 (0.62, 1.16)		1.11 (0.83, 1.49)		1.20 (0.59, 2.47)		
4	0.89 (0.65, 1.23)		0.97 (0.67, 1.41)		0.87 (0.427, 1.78)		
² Maternal Cd quar Child Pb quartiles ¹ Adjusted for: sex,	iles: Q1 0.20–2.66, Q2 2.67–3.4 tiles: Q1 0.14–0.14, Q2 0.20–0. : Q1 0.83–2.18, Q2 2.28–3.32, passive smoking at 77 months passive smoking at 103 months	29, Q3 0.30– Q3 3.42–5.18 old (weekday	0.72, Q4 0.73–6.30 μg/l. , Q4 5.28–27.56 μg/dl. s and weekends), and Ca a	und Fe intake			

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Prenatal exposure Child Pb (µg/dl) Age Category (months) Maternal Pb (µg/dl) Maternal Cd (µg/l) ≥5 <1 ≥1 P value <5 >5 P value <5 P value (chi (chi (chi 12 square) square) square) 1Stand on 1 18 Yes, can do well 1397 (50.8%) 237 (51.9%) 0.680 1350 (49.5%) 280 (58.6%) < 0.001 -1£pot for 1 s 15 Only done 1-2 1352 (49.2%) 220 (48.4%) 1376 (50.5%) 198 (41.4%) times/Not yet 16 started 17 1Stand on 1 Yes, can do well 1853 (70.6%) 313 (71.5%) 1811 (69.7%) 270 (69.6%) 95 (70.4%) 30 0.711 352 (76.5%) 0.003 0.865 1900t for 1 s Only done 1-2 772 (29.4%) 125 (28.5%) 789 (30.3%) 108 (23.5%) 118 (30.4%) 40 (29.6%) times/Not yet started 22 Stand on 1 23 foot for 4 s 24 42 Yes, does well 1862 (72.4%) 290 (70.2%) 0.366 1836 (71.9%) 316 (73.7%) 0.442 288 (73.8%) 104 (73.8%) 0.934 Yes, not very 711 (27.6%) 123 (29.8%) 719 (28.1%) 113 (26.3%) 102 (26.2%) 37 (26.2%) well/Not yet done 26 Stand on 1 27 foot for 8 s 28 Yes, can do well 81 2052 (95.0%) 339 (95.8%) 0.537 2077 (95.1%) 314 (94.9%) 0.826 329 (94.5%) 106 (93.0%) 0.538 Yes, but not 108 (5.0%) 15 (4.2%) 106 (4.9%) 17 (5.1%) 19 (5.5%) 8 (7.0%) well/Has not yet done/ Unable to try/Not had a chance 32 33 Values are n (%). 26

Supplementary Table 2 Associations of responses to questionnaire items related to balance at 18–81 months old in ALSPAC

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Supplementary Table 3 Associations of responses to questionnaire items related to balance at 10 years old in ALSPAC

Test	Category	Prenatal exposure					Child Pb (µg/dl)			
	Maternal Pb (μg/dl) Maternal Cd (μg/l)									
		<5	≥5	P value	<1	≥1	P value	<5	≥5	P value
Stand on one leg	Very well	1411 (76.1%)	219 (74.7%)	0.623	1455 (76.5%)	177 (71.7%)	0.094	236 (76.1%)	79 (76.0%)	0.972
	Just OK/ Can	444 (23.9%)	74 (25.3%)		447 (23.5%)	70 (28.3%)		75 (23.9%)	25 (24.0%)	
	almost/ Not at all									
Ride a bike	Very well	1715 (92.5%)	259 (87.8%)	0.007	1741 (91.4%)	234 (94.7%)	0.075	278 (90.0%)	100 (96.2%)	0.050
without stabilisers										
	Just OK/ Can	140 (7.5%)	36 (12.2%)		163 (8.6%)	13 (5.3%)		31 (10.0%)	4 (3.8%)	
	almost/ Not at all	10(7 (75.0%)		0.600	1.110 (75.6%)	100 (74.1%)	0.602			0.000
Walk in dark	Very well	1367 (75.2%)	222 (76.6%)	0.628	1410 (75.6%)	180 (74.1%)	0.603	225 (75.3%)	78 (75.7%)	0.923
	Just OK/ Can	450 (24.8%)	68 (23.4%)		455 (24.4%)	63 (25.9%)		74 (24.7%)	25 (24.6%)	
	almost/ Not at all									
Chi squar	re test.									
					455 (24.4%)					
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Balance ability in 7- and 10-year-old children: associations with prenatal lead and cadmium

exposure and with blood lead levels in children in a prospective birth cohort study

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Balance ability in 7	- and 1	0-year-old children: associations with prenatal lead and cadmium	
exposure and with	blood le	ead levels in children in a prospective birth cohort study	
Caroline M Taylor, I	Rachel I	Humphriss, Amanda Hall, Jean Golding, Alan M Emond	
STROBE Statement	-check	tlist of items that should be included in reports of observational studies	
	Item No	Recommendation	Line no.
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the	2 and
		abstract (<i>b</i>) Provide in the abstract an informative and balanced summary of what was done and what was found	23 18-38
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	49-76
Objectives	3	State specific objectives, including any prespecified hypotheses	77-79
Methods			
Study design	4	Present key elements of study design early in the paper	82-86
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	89-153
Participants	6	(<i>a</i>) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of	82-96
i ul dolpullos	Ū	selection of participants. Describe methods of follow-up	02 90
		<i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of	
		case ascertainment and control selection. Give the rationale for the choice of	
		cases and controls	
		Cross-sectional study—Give the eligibility criteria, and the sources and methods	
		of selection of participants	
		(b) Cohort study—For matched studies, give matching criteria and number of	
		exposed and unexposed	
		Case-control study—For matched studies, give matching criteria and the number	
		of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and	99-153
		effect modifiers. Give diagnostic criteria, if applicable	
Data sources/	8*	For each variable of interest, give sources of data and details of methods of	99-153
measurement		assessment (measurement). Describe comparability of assessment methods if	
		there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	94-95
Study size	10	Explain how the study size was arrived at	89-96
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable,	156-
	12	describe which groupings were chosen and why	172
	1.7	(a) Describe all statistical methods, including those used to control for	156-
Statistical methods	12	confounding	175

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2		(c) Explain how missing data were addressed
3		(d) Cohort study—If applicable, explain how loss to follow-up was addressed
4		<i>Case-control study</i> —If applicable, explain how matching of cases and controls
5		was addressed
6		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account
7 8		of someling strategy
9		
10		(\underline{e}) Describe any sensitivity analyses
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		BMJ Open	Page 3	30
Results				
Participants	13*	 (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage 	Table 1- 4	_
		(c) Consider use of a flow diagram		_
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	89-96	Protec
		(b) Indicate number of participants with missing data for each variable of interest		
		(c) Cohort study—Summarise follow-up time (eg, average and total amount)		_ 0
Outcome data	15*	Cohort study—Report numbers of outcome events or summary measures over time	Tables 1-4	opyrig
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure		Int, Inci
		Cross-sectional study—Report numbers of outcome events or summary measures		
Main results	16	(<i>a</i>) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	185-208	Protected by copyright, including for uses related to text and data
		(b) Report category boundaries when continuous variables were categorized		es r
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		elateo
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses		to text
Discussion				ahu
Key results	18	Summarise key results with reference to study objectives	268-276	Qa
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	322-336	Э
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	339-344	ining, Ai t
Generalisability	21	Discuss the generalisability (external validity) of the study results	343	rain
Other information	on			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	355-360	Al training, and similar technologies.
	-	rately for cases and controls in case-control studies and, if applicable, for exposed and hort and cross-sectional studies.		ar tecrir
published exampl available on the V	es of t Veb si s.org/,	and Elaboration article discusses each checklist item and gives methodological background and transparent reporting. The STROBE checklist is best used in conjunction with this article (freely tes of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is e-statement.org.		hologies.
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Balance ability in 7- and 10-year-old children: associations with prenatal lead and cadmium exposure and with blood lead levels in children in a prospective birth cohort study

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Balance ability in 7- and 10-year-old children: associations with prenatal lead	l and
cadmium exposure and with blood lead levels in children in a prospective bir	th cohort
study	
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13	
14	Keywords: Lead, Cadmium, Vestibular function, Balance, Children, Pregnancy, ALSP
15	Word count: (excluding title page, abstract, references, figures and tables): 3560
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17 Abstract

Objectives Most studies reporting evidence of adverse effects of lead and cadmium on balance have been conducted in high-exposure groups or have included adults. The effects of prenatal exposure have not been well studied, nor have the effects directly in children. The aim of the study was to identify the associations of lead (in utero and in childhood) and cadmium (in utero) exposure with balance ability in 7- and 10-year-old children.

23 Design Prospective birth cohort study

Participants Maternal blood lead (n=4284) and cadmium (n=4286) levels were measured by
inductively coupled plasma mass spectrometry in women enrolled in the Avon Longitudinal
Study of Parents and Children (ALSPAC) during pregnancy. Child lead levels were measured in a
subsample of 582 of ALSPAC children at age 30 months.

Main outcome measures Children completed a heel-to-toe walking test at 7 years. At 10 years the children underwent clinical tests of static and dynamic balance. Statistical analysis included logistic regression modelling comparing categories of ≥ 5 vs $< 5 \mu g/dl$ for lead and ≥ 1 vs $< 1 \mu g/l$ for cadmium with SPSS v19.

Results Balance at age 7 years was not associated with elevated in utero lead or cadmium exposure

33 (adjusted OR for balance dysfunction: Pb 1.01 (95% CI 0.95, 1.01), n=1732; Cd 0.95 (0.77, 1.20),

n=1734), or with elevated child blood lead level at age 30 months (adjusted OR 0.98 (0.92, 1.05),

n=354). Similarly, neither measures of static nor dynamic balance at age 10 years were associated

36 with in utero lead or cadmium exposure, or child lead level.

37 Conclusions These findings do not provide any evidence of an association of prenatal exposure to
38 lead or cadmium, or lead levels in childhood, on balance ability in children. Confirmation in other
39 cohorts is needed.

40 Word count: 281

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Strengths and limitations of the study
• Data were collected prospectively in a population-based study
• The number of participants was large compared with several comparable studies
• Measures of Pb and Cd do not necessarily reflect lifetime exposure
 Measures of FD and Cd up not necessarily refect meanine exposure Balance measures have a poor test-refest reliability
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INTRODUCTION

Balance, or postural stability, is defined as the ability to keep the centre of gravity over the base of support.¹ The maintenance of balance underpins the ability to carry out nearly all daily activities. Balance impairment in adults is also a major cause of falls and of fall-related injuries, such as hip fracture, which can cause isolation and make it difficult to live independently. The control of balance is complex and is dependent on sensory inputs from the vestibular and visual systems, neural processing centres in the central nervous system, and motor inputs from the proprioceptive centre. Functional damage or deficits in any of these systems can lead to balance dysfunction, which can be associated with low self-esteem, anxiety and loss of confidence in children.²

Lead and cadmium are toxic metals: the effects of lead on neurocognitive and behavioural functions in children are well documented,³⁻⁵ but those of cadmium are clear.⁶⁻⁸ Lead passes freely through the placenta so that ratio of fetal to maternal blood lead is about 0.8, although the placenta can act as a partial barrier to cadmium.⁹ The fetus is particularly vulnerable to the effects of these metals because of high rates of cell division and development. The development of the inner ear and vestibular function spans the whole of the period of gestation (for example, the membranous labyrinth is complete by week 7 with development of the bony labyrinth from week 9 to 23; the vestibular apparatus is in an adult-like form by week 25, and is active by week 32; vestibular ganglions develop from week 12 and reach maturity at week 39, and so on^{10}). Thus, prenatal exposure to lead and cadmium may have adverse effects on the development of the inner ear, and hence on vestibular function and balance ability in later childhood.

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It was noted in the 1980s that children who survived acute lead encephalopathy had ataxia and experienced difficulties in maintaining postural balance.¹¹ This led to a series of studies in children with somewhat more moderate levels of lead exposure (5.0 to 20.7 μ g/dl) showing that the child's lead level was associated with balance dysfunction and sway oscillation.¹²⁻¹⁶ To our knowledge, there are no reports of the effect of cadmium on balance ability in children. However, a recent study of lead and cadmium levels in adults in the US National Health and Nutrition Examination Survey (NHANES) found preliminary evidence of an association of lead and cadmium with balance and vestibular function.¹⁷ In addition, altered postural balance response has been reported in adult workers occupationally exposed to lead.¹⁸⁻²⁰ and cadmium.²¹ These results require confirmation in other cohorts and particularly in children.

The aims of our study were to investigate the associations of in utero exposure to lead and cadmium, and lead levels in children, on balance in childhood using data obtained from the Avon Longitudinal Study of Parents and Children (ALSPAC).

85 Methods

We first modelled associations of in utero exposure to lead and cadmium, using maternal blood levels during pregnancy, with clinical measures of balance (dynamic and static) at 7 and 10 years. We also investigated associations with questionnaire items related to balance repeated at 30 months, 42 and 81 months, and further items at 10 years. We also modelled the associations of child levels of lead with the balance variables.

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92	The ALSPAC study
93	The study sample was derived from the ALSPAC study, a population-based study
94	investigating environmental and genetic influences on the health, behaviour and development
95	of children. All pregnant women in the former Avon Health Authority with an expected
96	delivery date between 1 April 1991 and 31 December 1992 were eligible for the study;
97	14,541 pregnant women were initially enrolled, resulting in a cohort of 14,062 live births. ²²
98	The social and demographic characteristics of this cohort were similar to those found in UK
99	national census surveys. ²³ Further details of ALSPAC are available at
100	www.bris.ac.uk/alspac.
101	
102	Collection, storage and analysis of blood samples
103	Maternal blood samples Whole blood samples were collected in acid-washed vacutainers
104	(Becton and Dickinson, Oxford, UK) by midwives as early as possible in pregnancy. The
105	median gestational age at the time of blood sampling was 11 weeks. The interquartile range
106	was 9–13 weeks, and 93% of the samples were collected at <18 weeks gestation. Whole
107	blood samples were stored in the original tube at 4°C at the collection site before being
108	transferred to the central Bristol laboratory within 1-4 days. Samples were at ambient
109	temperature during transfer (up to 3 h). They were then stored at 4°C until analysis. Samples
110	were analysed for lead using inductively coupled plasma mass spectrometry in standard mode
111	by R. Jones at the Centers for Disease Control (CDC), Bethesda, MD, USA (CDC Method
112	3009.1). Quality control was monitored as outlined in Golding, et al. ²⁴ The analyses were
113	completed on 4284 samples for Pb and 4286 for Cd. One sample had a Pb level below the
114	limit of detection (0.29 μ g/dl); 1119 samples were below the lower limit of detection for Cd

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115	(0.20 μ g/l). These samples were assigned a value of 0.7 times the lower limit of detection
116	$(LOD/\sqrt{2}).^{2526}$

118	<i>Child blood samples</i> Details of the selection of the subsample of children and analysis of
119	the blood samples have been reported previously in detail. ^{3 27} In brief, a 10% randomly
120	selected subsample of parents whose babies were born in the last 6 months of the ALSPAC
121	study were invited to attend a research clinic (Children in Focus, CIF). At age 30 months,
122	parental consent was sought for a venous blood sample, and was given by 81% of the 1135
123	children in the CIF group. The sample was drawn into lead-free tubes from 653 (71%) of
124	children attending the clinic. However, 69 samples were insufficient, leaving 582 samples for
125	analysis. Analysis was by atomic absorption spectrometry (Southampton General Hospital,
126	UK) with appropriate quality controls.

Balance variables

Clinic measures Full details of the balance outcomes including details of the measurements and validity have previously been published.²⁸ In brief, at age 7 years the heel-to-toe walking test of the Movement Assessment Battery for Children²⁹ was conducted with the total number of successful steps out of a maximum of 15 recorded. At age 10 years a range of tests were used to assess balance: (1) walking along a beam, heel-to-toe, eyes open; (2) heel-to-toe balance on a beam, eyes closed; (3) standing on one leg, eyes closed. Each child had two attempts at beam-walking; for tests of static balance, children only had a second attempt if they failed to achieve the maximum score on the first attempt.²⁸ These tests were based on standard clinical tests to assess balance in children and have significant commonality with the balance subtest of the both editions of the Bruininks–Oseretsky Test of Motor Proficiency.³⁰

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139	³¹ The measures are also in common use when testing balance informally in the paediatric
140	clinic.
141	
140	Question size items. The primery equation (usually the methor) received a series of post

142	Questionnaire items The primary caregiver (usually the mother) received a series of postal
143	self-completion questionnaires. The questionnaires are available from the study website
144	(http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/). When their child was
145	aged 18, 30, 42 and 81 months, the parent completing the questionnaire was asked to indicate
146	'Yes, can do well'/'Has only done once or twice'/'Has not yet started' in response to the
147	statement 'He/She can balance on one foot for at least 1 second'. When their child was aged
148	10 years, the parent was asked to indicate 'Very well'/'Just OK'/'Can almost'/'Not at all' in
149	response to the following questions: How well can your child stand on one leg in a stable
150	position (e.g. when putting on trousers, skirt)?; How well can your child ride a bike (without
151	stabilisers)?; How well can your child walk in the dark?
152	

Confounding variables

Information on passive smoking exposure during the week and at weekends was obtained

- from questionnaires at 77 and 103 months. Information on traffic levels, type of
- accommodation, lowest level of accommodation and maternal education were obtained at
- from questionnaires completed by the mother during pregnancy. Dietary Ca and Fe intake at
- 7 years and 10 years were derived from food frequency questionnaires as previously
- described in detail. ³²

Statistical analysis

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162	Statistical analysis was carried out with IBM SPSS Statistics 21. Balance measures were
163	derived as previously described. ²⁸ In brief, for the heel-to-toe test at age 7 years, the number
164	of steps (maximum 15) was categorised into 0-5, 6-10 and 11-15 steps for categorical
165	associations, and 1-14 (failed to complete in 20 s) versus 15 steps (successfully completed in
166	20 s) for regression analyses. For the measure of dynamic balance at 10 years (beam-walking
167	test), the mean of two attempts was categorised into quartiles. For measures of static balance
168	at age 10 years (heel to toe balance on a beam with eyes closed/standing on one leg eyes
169	closed), the sum of the score (s) from both attempts was calculated. Children who scored the
170	maximum of 20 on the first attempt and so did not have a second attempt were given a final
171	score of 40. The final scores were put into four categories (0–9, 10–19, 20–39 and 40). All of
172	the four static balance tests with eyes closed were summed to create a static balance eyes
173	closed variable (SBEC).
174	Blood lead and cadmium levels were put into two categories (<5 , $\ge 5 \mu g/dl$ for lead and <1 ,
175	$\geq 1 \ \mu g/l$ for Cd). These categories were chosen in accordance with the levels of concern of the
176	US Centers for Disease Control, the US Association of Occupational and Environmental
177	Clinics and the American College of Obstetricians and Gynecologists for Pb, ³³⁻³⁶ and the
178	German Federal Environmental Agency for Cd. ³⁷ Blood levels were also categorised into
179	quartiles.
180	Chi square tests were used to compare categorical variables. Unadjusted and adjusted logistic
181	regression analyses were used to investigate the association of blood levels with balance
182	variables.
183	

As previously reported, the mean child blood lead level was $4.22\pm3.12 \,\mu\text{g/dl} (n=582)^{3.27}$; the mean prenatal blood lead level was $3.67 \pm 1.47 \,\mu g/dl$ (n=4284) and the mean prenatal cadmium level was $0.58\pm0.63 \,\mu$ g/l (n=4286).^{38 39} Mothers who consented to provide a blood sample were better educated and older than mothers who did not.³⁸ Children who had lead levels measured were from families where the mother was better educated and more likely to be a homeowner, and was there was a better home environment with fewer adversities.³ Associations of measures of balance with prenatal lead and cadmium levels and with child lead levels Associations with in utero exposure to lead and cadmium There was no evidence of any association between the results of the heel-to-toe test at age 7 years and maternal lead or cadmium level during pregnancy (p=0.441 and p=0.189, respectively) (Table 1). Similarly, at age 10 years there were no associations between dynamic balance (beam walking) or static balance (SBEC) and maternal blood lead or cadmium levels in pregnancy (all p>0.1) (Table 1). In logistic regression models adjusted for sex, passive smoking, and calcium and iron intake, there was no evidence of any association between maternal blood lead or cadmium levels and measure of balance in the child at 7 and 10 years (all p>0.1) (Table 2). When the models were repeated with guintiles of maternal blood lead or cadmium level rather than a dichotomous variable, there was also no evidence of any associations (all p>0.1 with the exception of maternal blood lead for the odds of static balance dysfunction at 10 years where there was a protective effect (p for trend 0.038) (Supplementary Table 1).

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209	There was no evidence of any association between the results of the heel-to-toe test at age 7
210	years and child lead level (p for trend=0.146) (Table 3). Similarly, at age 10 years there were
211	no associations between dynamic balance (beam walking) or static balance (SBEC) and child
212	blood lead levels (p for trend=0.798 and p=0.918, respectively) (Table 3). In logistic
213	regression models adjusted for sex, passive smoking, and calcium and iron intake, there was
214	no evidence of any association between child blood levels at 30 months and measure of
215	balance at 7 and 10 years (Table 4; all p for trend >0.3). When the models were repeated with
216	quintiles of child blood lead rather than a dichotomous variable, there was also no evidence
217	of any associations (all p for trend >0.1) with the exception of static balance where there was
218	a weakly protective effect (p for trend=0.038 (Supplementary Table 1).

219 220 Maternal Pb (µg/dl) Maternal Cd (µg/l) Age Category (years) <5 ≥5 P value <1 ≥1 P value (chi (chi square) square) Heel to toe test 7 0–5 steps 520 (27.1) 81 (29.1) 82 (26.5) 521 (26.6) 0.861 0.112 273 (14.2) 270 (13.8) 6-10 steps 45 (14.5) 49 (17.6) 11-15 steps 1128 (58.7) 183 (59.0) 1164 (59.6) 148 (53.2) Beam walking (dynamic balance) Q1 62 (25.3) 10 431 (23.4) 70 (24.1) 0.450 439 (23.3) 0.897 461 (25.0) 57 (23.3) Q2 80 (27.6) 484 (25.6) Q3 456 (24.8) 66 (22.8) 59 (24.1) 463 (24.5) Q4 494 (26.8) 74 (25.5) 503 (26.6) 67 (27.3) Static balance eyes closed score Q1 460 (24.4) 74 (25.8) 472 (25.5) 63 (25.8) 10 0.558 0.842 (SBEC) (static balance) Q2 459 (25.4) 58 (20.2) 62 (25.4) 455 (24.6) 83 (28.9) Q3 430 (23.8) 457 (24.7) 57 (23.4) 04 459 (25.4) 72 (25.1) 469 (25.3) 62 (25.4) Values are n (%). 221 Q, quartile. 222 223 12 Enseignement Superieur (ABES) . Protected by copyrightsing the herestiel and the text and the think of the initial of the initial technologies. 47 48 I ab aupidgrapoildig apresent at 202, 21 and no moo.imd.naqoimd//.qff from http://dff.from http://dff.from

Table 1 Associations of in utero lead and cadmium exposure with measures of balance in the child at 7 and 10 years in ALSPAC

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224	Table 2	Associations of in utero lead and cadmium exposure with balance measures in the child at 7 and 10 years old in ALSPAC
225		

	Age	Prenatal lead exposure				Prenatal cadmium exposure			
	(years)	ars) OR of balance dysfunction P n OR of balance dysfunction		Р	n				
			95% CI)	value		()	95% CI)	value	
Heel to toe test	7	Unadjusted	1.01 (0.96, 1.07)	0.503	2231	Unadjusted	0.81 (0.70, 0.94)	0.010	2233
		Adjusted ^a	1.01 (0.95, 1.01)	0.555	1732	Adjusted ^a	0.95 (0.77, 1.20)	0.904	1734
Dynamic balance	10	Unadjusted	1.01 (0.95, 1.08)	0.790	2132	Unadjusted	1.00 (0.84, 1.21)	0.946	2134
		Adjusted ^b	1.02 (0.95, 1.09)	0.692	1761	Adjusted ^b	1.20 (0.95, 1.52)	0.135	1763
Static balance	10	Unadjusted	0.98 (0.92, 1.05)	0.569	2095	Unadjusted	1.06 (0.88, 1.28)	0.523	2097
		Adjusted ^b	0.98 (0.92, 1.06)	0.661	1734	Adjusted ^b	1.00 (0.79, 1.26)	0.995	1736

Logistic regression showing odds ratio of balance dysfunction (95% CI).

^aAdjusted for: sex, passive smoking at 77 months old (weekdays and weekends), and Ca and Fe intake at 7 years.

^bAdjusted for: sex, passive smoking at 103 months old (weekdays and weekends), and Ca and Fe intake at 10 years.

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	Test	Age (years) Category Child Pb (µg/dl)		b (µg/dl)	P value (chi _ square)		
				<5	≥5	_ (14,11,0)	
	Heel to toe test	7	0–5 steps	82 (25.8)	34 (30.9)	0.146	
			6–10 steps	52 (16.4)	22 (20.0)		
			11–15 steps	184 (57.9)	54 (49.1)		
	Beam walking (dynamic balance)	10	Q1	74 (24.0)	24 (23.5)	0.798	
			Q2	68 (22.1)	19 (18.6)		
			$\overline{Q3}$	86 (27.9)	34 (33.3)		
			Q4	80 (26.0)	25 (24.5)		
	Static balance eyes closed score	10	Q1	80 (26.5)	22 (22.0)	0.918	
	(SBEC) (static balance)				20 (20 0)		
			Q2	70 (23.2)	30 (30.0)		
			Q3	77 (25.5)	24 (24.0)		
_			Q4	75 (24.8)	24 (24.0)		
5							
6	Values are n (%).						
7	Q, quartile.						
8							
0							
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Table 4 Child blood lead level at 30 months and balance measures at 7 and 10 years old in ALSPAC

	Age (years)	OR of balance d	ysfunction (95% CI)	P value	n
Heel to toe test	7	Unadjusted 0.98 (0.92, 1.0		0.618	428
		Adjusted ^a	0.98 (0.92, 1.05)	0.778	354
Dynamic balance	10	Unadjusted	1.03 (0.96, 1.11)	0.422	410
		Adjusted ^b	1.01 (0.93, 1.09)	0.814	363
Static balance	10	Unadjusted	1.04 (0.96, 1.12)	0.345	402
		Adjusted ^b	1.03 (0.94, 1.12)	0.540	357
usted for: sex, passive smok usted for: sex, passive smok		weekdays and weekend	ds), and Ca and Fe intake at	10 years.	
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248	Associations with questionnaire items at 18-81 months and at 10 years
249	There was no evidence of any associations between child blood lead level at 30 months and
250	the ability to stand on one foot for at least 1 second at 30, 42 or 81 months (all p>0.6;
251	Supplementary Table 2). There was no evidence of any associations between maternal blood
252	lead level during pregnancy and the ability of the child to stand on one foot for at least 1
253	second at 18, 30, 42 or 81 months (all p>0.3) (Supplementary Table 2). There was no
254	evidence of any associations between maternal blood cadmium level during pregnancy and
255	the ability of the child to stand on one foot for at least 1 second at 42, or 81 months (all
256	p>0.4), but there were associations at 18 and 30 months (p<0.001 and p=0.003, respectively;
257	maternal cadmium $\geq 1 \ \mu g/l$ was associated with being more likely to be able to stand on one
258	foot well) (Supplementary Table 2).
259	There was no evidence of any association of elevated child lead level, or in utero lead or
260	cadmium exposure, with ability to stand on one leg or to walk in the dark at 10 years (all
261	p>0.09, chi-square test) (Supplementary Table 3). However, prenatal lead level ≥5 µg/dl was
262	associated with not being able to ride a bike without stabilisers (p=0.007), whereas child lead
263	level $\geq 5 \ \mu g/dl$ and prenatal cadmium $\geq 1 \ \mu g/l$ were weakly associated with being able to ride a
264	bike without stabilisers very well (p=0.050 and p=0.075 respectively). When these
265	associations were modelled in a logistic regression analysis adjusted for variables that could
266	affect availability of a bicycle and being able to ride a bicycle locally (traffic level on the
267	home street, type of accommodation, lowest level of accommodation), and maternal
268	education, there was very weak evidence for an association of child lead level being
269	associated with being able to ride a bike well without stabilisers (OR in unadjusted model
270	2.79 (95% CI 0.096, 8.10), p=0.059, n=413; OR in adjusted model OR 2.57 (95% CI 0.87,
271	7.62), p=0.089, n=387). The association was stronger for prenatal lead level in the unadjusted
272	model, but the effect was attenuated with adjustment (OR in unadjusted model 0.59 (95% CI

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273	0.40, 0.87), p=0.007, n=2150; OR in adjusted model 0.73 (95% CI 0.47, 1.14), p=0.167,
274	n=1904); for prenatal cadmium level again the weak effect was attenuated by adjustment
275	(unadjusted OR 1.69 (95% CI 0.94, 3.01, p=0.078, n=2151; adjusted OR 1.44 (95% CI 0.75,
276	2.75, p=0.274, n=1905).
277	
278	DISCUSSION
279	We did not find any evidence of an association of prenatal exposure to lead or cadmium, or
280	lead levels in childhood, on balance ability (static and dynamic) in children.
281	Counterintuitively, there was a suggestion that higher child lead levels and in utero lead
282	exposure were associated with the ability to ride a bike without stabilisers at age 10 years, but
283	these effects were negated when the associations were adjusted for variables that included the
284	lowest level of accommodation and traffic levels outside the home. This is the first study, to
285	our knowledge, reporting on the associations between in utero exposure to lead and cadmium
286	and balance ability of the child, and adds to the few studies on child lead levels and balance
287	ability.
288	Postural balance is controlled by a complex interaction of sensorimotor processes, including
289	visual, proprioception and the vestibular system. In our study the measure of static balance
290	with eyes closed eliminated vision and minimised proprioceptive inputs, thereby enabling the
291	assessment of vestibular information as the primary input. Use of clinical measures similar to
292	these is commonplace in epidemiological studies (e.g. ⁴⁰⁻⁴³), as the tests are in common
293	clinical usage and require little or no specialist equipment. However, although the vestibular
294	dominant condition of tests of standing balance (reduced base of support with eyes closed)
295	has been shown to correlate well with more expensive systems such as computerised dynamic
296	posturography (considered to be the 'gold standard' method for assessing balance function) in

adults,⁴⁴ there are questions about whether such a correlation exists in children.⁴⁵ It has even
been suggested that computerised measures using a force-platform and clinical tests such as
those used by ALSPAC give complementary rather than concurrent information.⁴⁶ A cautious
approach should therefore be taken if seeking to compare studies using these two different
types of outcome measure.

Most studies on lead levels and balance in children have included children with relatively high lead levels (means in each study of 11.6 to 20.7 μ g/dl) and measured balance with a force platform system.¹²⁻¹⁵ and have found negative associations. There are several reasons for our results being in contrast to these studies. First, the mean child blood lead level in our study (4.22 μ g/dl) was lower than reported in these earlier studies, and may have been too low either to have been sufficient to cause balance dysfunction. Alternatively, the effect on balance might have been too small to be detectable with our tests, although a study in Inuit children had levels that were more comparable to the present study (mean 5.4 μ g/dl) showed a significant association with sway oscillations.¹⁶ Second, we used a series of assessments based on clinical tests to measure balance rather than a force platform or measurement of sway oscillations and this may account for differences in the findings. As discussed earlier, clinical and force platform measures may be giving complementary rather than concurrent information: whereas posturography is a measure of the motor and sensory strategies used to control balance, clinical tests evaluate the results of that balance control.⁴⁶ Measuring sway oscillations using a force platform will also be more sensitive than the ALSPAC measures, which measured time before a procedural fault such as touching the floor with either foot or lifting a foot off the beam. Third, early exposure to lead and/or cadmium could damage the vestibular system, but the plasticity of the balance system might compensate for this so that there is no functionally measurable effect. This is in accordance with measures of balance in the present study indirectly assessing the vestibular system. This could also account for

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322 effects being reported in adults, in whom plasticity is less effective for overall balance 323 compensation, but not in children. It is also possible that vestibular system (to include peripheral (ear) and central (brain) components of the vestibular pathway) dysfunction caused 324 by in utero exposure to lead or cadmium may not be apparent in childhood but may manifest 325 in later life. Finally, it is also possible that studies showing non-significant results have 326 327 tended not to have been published. 328 To our knowledge, there are no studies that have examined the effect of in utero exposure to 329 lead or cadmium on balance ability in the child. Our results provide preliminary evidence for 330 lack of effect, but this requires confirmation on other cohorts. 331 The strengths of the study are that: (1) it is a population-based study; (2) the data were

332 collection prospectively; and (3) the numbers included in the study were large compared with 333 several other studies. There are several limitations to the study. First, measures of blood lead 334 and cadmium do not necessarily reflect lifetime exposure. Bone lead, which makes up more than 95% of the body lead, can be measured by K x-ray fluorescence,⁴⁷ but this is expensive, 335 technically demanding and may not always be ethically permissible in children. This 336 limitation is of less consequence for in utero exposure as the maternal blood level largely 337 338 determines the fetal blood level. Second, there was a high proportion of blood cadmium 339 levels below the limit of detection, which may make the results less reliable than for lead. 340 Third, there may be confounders we were unable to account for. Fourth, we were unable to control for lead and cadmium separately in the models because of multicollinearity. Fifth, the 341 342 apparently protective effect of Finally, the balance measures used by ALSPAC had low testretest reliability,²⁸ which is a common problem with measures of childhood balance.⁴⁸⁻⁵⁰ The 343 344 measure of ability to balance on one foot for 1 s, a test which was originally developed by Chamberlain and Davey ⁵¹ in 1976, has been particularly criticised for having poor test 345

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351 CONCLUSIONS

We did not find any evidence of an association of prenatal exposure to lead or cadmium with balance ability in children. In contrast to previous studies, we did not find any association of child blood lead with balance ability in children. This may reflect variation in the methods used to assess balance in different studies, or may be related to the lower mean lead level in the children in the present study than in previous studies. Further work in other cohorts is needed to confirm the results.

358 Data sharing statement: No additional data available.

Contributors statement: CMT conceived the study and undertook data analysis in

360 conjunction with RH, AH and JG. CMT took the lead in writing the manuscript with critical

- 361 revisions and additions from RH, AH, JG and AME. All authors contributed to and approved
 - the final version of the manuscript.
 - Ethics approval: Ethics approval for the study was obtained from the ALSPAC Ethics and
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Balance ability i	n 7- and 10-year-old children: a	associations with pre	natal lead and cadmium			dood lead levels in child	lren in a
prospective birth	n cohort study				inclu	о б б л	
Caroline M Taylo	or, Rachel Humphriss, Amanda H	Iall, Jean Golding, Ala	an M Emond		including for uses		
upplementary	Table 1 Associations of qu	intiles of in utero lea	d and cadmium exposure		eignemet	<u> </u>	e in the child
t 7 and 10 years	s in ALSPAC	6			Superi		1
Quartile		Prenatal e			d dy	Child	l Pb ^c
	Materna OR of balance dysfunction (95% CI)	P value for trend	Maternal OR of balance dysfunction (95% CI)	P value for trend	=. m -	R of balance ysfunction (95% CI)	P value for trend
Heel to toe test a							
1	1.00 (Ref)	0.349 (n=1732)	(Ref)	0.133 (n=1457		Ref)	0.234 (n=354)
2	0.94 (0.72, 1.22)	× ,	1.17 (0.91, 1.53)		3 3	.47 (0.82, 2.63)	× ,
3	1.17 (0.90, 1.53)		0.91 (0.69, 1.20)		\	.96 (0.52, 1.78)	
4	1.18 (0.82, 1.41)		0.90 (0.62, 1.27)	<u>u</u>		.78 (0.52, 1.42)	
Dynamic balanc				0.433 (n=1763	an 🚦		
1	(Ref)	0.981 (n=1761)	(Ref)	0.433 (n=1763		Ref)	0.290 (n=363)
	1.34 (0.99, 1.81)	· · · ·	0.85 (0.65, 1.12)		3. (.80 (0.41, 1.56)	× ,
2	1.34 (0.22, 1.01)						
2 3			0.95 (0.71, 1.26)		ar	P.08 (0.54, 2.14)	
2 3 4	1.34 (0.99, 1.81) 1.09 (0.81, 1.46) 1.09 (0.81, 1.46)		0.95 (0.71, 1.26) 1.10 (0.76, 1.59)		ar tec	1 .08 (0.54, 2.14) 3 .86 (0.43, 1.72)	
3 4	1.09 (0.81, 1.46) 1.09 (0.81, 1.46)		0.95 (0.71, 1.26) 1.10 (0.76, 1.59)	5	ar techno	1.08 (0.54, 2.14) .86 (0.43, 1.72)	
3 4	1.09 (0.81, 1.46) 1.09 (0.81, 1.46)	0.811 (n=1734)		0.851 (n=1736	ar technolog		0.891 (n=357)
3 4	1.09 (0.81, 1.46) 1.09 (0.81, 1.46) 10 years ^e	0.811 (n=1734)	1.10 (0.76, 1.59)	0.851 (n=1736	ar technologies	1 .86 (0.43, 1.72) (Ref)	0.891 (n=357)
3 4 Static balance at 1	1.09 (0.81, 1.46) 1.09 (0.81, 1.46) 10 years ^e (Ref)	0.811 (n=1734)	1.10 (0.76, 1.59) (Ref)	0.851 (n=1736	ar technologies	.86 (0.43, 1.72)	0.891 (n=357)

103 months old (weekdays and weekends), and Ca and Fe intake at 7 years. For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtmb ^eAdjusted for: sex, passive smoking at 103 months old (weekdays and weekends), and Ca and Fe intake at 10 years.

BMJ Open

Page 27 of 3	:1				BM	J Open iire items relate		ijopen-20 1 by cop			
1 <u>2</u>		pplementary Table	2 Associations	s of responses to			d to balance at				
3 4	Age (months)	Category			Prenatal	exposure		09635 or t, includ		Child Pb (µg/dl)	
5	(Mat	ternal Pb (µg/dl)		Ma	aternal Cd (µg/l)		-		
7 8 9			<5	≥5	P value (chi square)	<1	≥1	P Salar Balar Balar Salar Salar	<5	>5	P value (chi square)
10 Stand on 1 11 12 12 12	18	Yes, can do well	1397 (50.8%)	237 (51.9%)	0.680	1353 (49.5%)	280 (58.6%)		-	-	-
13 14		Only done 1–2 times/Not yet started	1352 (49.2%)	220 (48.4%)		1376 (50.5%)	198 (41.4%)	5. Downlo ent Supe I to text a	-	-	
15 Stand on 1 16 16 foot for 1 s 17	30	Yes, can do well	1853 (70.6%)	313 (71.5%)	0.711	1815 (69.7%)	352 (76.5%)		270 (69.6%)	95 (70.4%)	0.865
18 19		Only done 1–2 times/Not yet started	772 (29.4%)	125 (28.5%)		789 (30.3%)	108 (23.5%)	5. Downloaded from http://bmjopen.b nent Superieur (ABES) . 1 to text and data mining_Al training 0.44Al training	118 (30.4%)	40 (29.6%)	
20 21 21 22 22 22	42	Yes, does well	1862 (72.4%)	290 (70.2%)	0.366	1838 (71.9%)	316 (73.7%)	0.440	288 (73.8%)	204 (73.8%)	0.984
22 23 24		Yes, not very well/Not yet done	711 (27.6%)	123 (29.8%)		720 (28.1%)	113 (26.3%)	0.44Al training	102 (26.2%)	37 (26.2%)	
2§tand on 1 2§pot for 8 s 27 28 29	81	Yes, can do well Yes, but not well/Has not yet done/ Unable to try/Not had a chance	2052 (95.0%) 108 (5.0%)	339 (95.8%) 15 (4.2%)	0.537	2079 (95.1%) 106 (4.9%)	314 (94.9%) 17 (5.1%)	and similar	329 (94.5%) 19 (5.5%)	106 (93.0%) 8 (7.0%)	0.538
<u>30</u> 31	Values are							une :			
32 33 34 35 36 37 38 39								June 13, 2025 at Agence Bi technologies.			
39 40 41 42 43 44 45 46 47			For peer	review only - h	ttp://bmjope	en.bmj.com/site	/about/guideliı	Bibliographique de l			

		ons of responses t		BMJ	Open		ijopen-201 1 by copyr			Page 28 of 3
1 2 3 Supplementary 7 4	Table 3 Association	ons of responses t	o questionnaire i	tems related	to balance at 10) years old in A	5-009635 on ight, in A C LSPAudi			
⁵ Test	Category			Prenatal ex	xposure		30 ng		Child Pb (µg/dl)	
6 7			ternal Pb (µg/dl)			ternal Cd (µg/l				
8 9		<5	≥5	P value (chi square)	<1	≥1	Pavalue ex(mp sguare)	<5	≥5	P value (chi square)
10- 11 Stand on one leg 12 13	Very well Just OK/ Can almost/ Not at all	1411 (76.1%) 444 (23.9%)	219 (74.7%) 74 (25.3%)	0.623	1455 (76.5%) 448 (23.5%)	177 (71.7%) 70 (28.3%)	2015. Downloaded fro greenent Superieur (AB greenent Superieur (AB) greenent Superieur (AB)	236 (76.1%) 74 (23.9%)	79 (76.0%) 25 (24.0%)	0.972
14 Ride a bike 15 without stabilisers	Very well	1715 (92.5%)	259 (87.8%)	0.007	1742 (91.4%)	234 (94.7%)	0.0770 0.0770 and	278 (90.0%)	100 (96.2%)	0.050
16 17	Just OK/ Can almost/ Not at all	140 (7.5%)	36 (12.2%)		163 (8.6%)	13 (5.3%)	yed fro 9ur (Att 1 data i	31 (10.0%)	4 (3.8%)	
¹⁸ Walk in dark 19 20 21	Very well Just OK/ Can almost/ Not at all	1367 (75.2%) 450 (24.8%)	222 (76.6%) 68 (23.4%)	0.628	1411 (75.6%) 455 (24.4%)	180 (74.1%) 63 (25.9%)	ABES) . ABES) . A Mining, A	225 (75.3%) 74 (24.7%)	78 (75.7%) 25 (24.6%)	0.923
22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47		For pee	er review only - h		n.bmj.com/site/		omjopen.bmj.com/ on June 13, 2025 at Agence Bibliographique de l I training, and similar technologies.			

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Balance ability in 7- and 10-year-old children: associations with prenatal lead and cadmium

exposure and with blood lead levels in children in a prospective birth cohort study

Caroline M Taylor, Rachel Humphriss, Amanda Hall, Jean Golding, Alan M Emond

STROBE Statement-checklist of items that should be included in reports of observational studies

Line no.
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23
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(c) Explain how missing data were addressed (d) Cohort study—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls

Continued on next page

		BMJ Open	
Results Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible,	Table 1-
1		examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and	89-96
data		information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
	1.5 %	(c) Cohort study—Summarise follow-up time (eg, average and total amount)	m 11
Outcome data	15*	Cohort study—Report numbers of outcome events or summary measures over time	Tables 1-4
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study-Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their	185-208
		precision (eg, 95% confidence interval). Make clear which confounders were adjusted for	
		and why they were included	
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a	
0.1 1	1.5	meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	268-276
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or	322-336
		imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	339-344
Generalisability	21	Discuss the generalisability (external validity) of the study results	343
· · · · ·		Discuss the generalisation (external variancy) of the study results	343
Other information	on		
Enndina	22	Cive the servers of funding and the role of the fundant for the present study and if	255 260
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Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	355-360
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Balance ability in 7- and 10-year-old children: associations with prenatal lead and cadmium exposure and with blood lead levels in children in a prospective birth cohort study

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Secondary Subject Heading:	Epidemiology, Paediatrics
Keywords:	Lead, Cadmium, Vestibular function, Balance, Pregnancy, ALSPAC



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Balance ability in 7- and 10-year-old children: associations with prenatal lead	l and
cadmium exposure and with blood lead levels in children in a prospective bir	th cohort
study	
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³ Children's Hearing Centre, University Bristol NHS Foundation Trust, Bristol, UK	X
*Corresponding author: <u>caroline.m.taylor@bristol.ac.uk</u>	
Keywords: Lead, Cadmium, Vestibular function, Balance, Children, Pregnancy, A	ALSPAC
Word count: (excluding title page, abstract, references, figures and tables): 3560	
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12	*Corresponding author: caroline.m.taylor@bristol.ac.uk
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14	Keywords: Lead, Cadmium, Vestibular function, Balance, Children, Pregnancy, ALSP
15	Word count: (excluding title page, abstract, references, figures and tables): 3560
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17 Abstract

Objectives Most studies reporting evidence of adverse effects of lead and cadmium on balance have been conducted in high-exposure groups or have included adults. The effects of prenatal exposure have not been well studied, nor have the effects directly in children. The aim of the study was to identify the associations of lead (in utero and in childhood) and cadmium (in utero) exposure with balance ability in 7- and 10-year-old children.

23 Design Prospective birth cohort study

Participants Maternal blood lead (n=4284) and cadmium (n=4286) levels were measured by
inductively coupled plasma mass spectrometry in women enrolled in the Avon Longitudinal
Study of Parents and Children (ALSPAC) during pregnancy. Child lead levels were measured in a
subsample of 582 of ALSPAC children at age 30 months.

Main outcome measures Children completed a heel-to-toe walking test at 7 years. At 10 years the children underwent clinical tests of static and dynamic balance. Statistical analysis included logistic regression modelling comparing categories of ≥ 5 vs $< 5 \mu g/dl$ for lead and ≥ 1 vs $< 1 \mu g/l$ for cadmium with SPSS v19.

Results Balance at age 7 years was not associated with elevated in utero lead or cadmium exposure

33 (adjusted OR for balance dysfunction: Pb 1.01 (95% CI 0.95, 1.01), n=1732; Cd 0.95 (0.77, 1.20),

n=1734), or with elevated child blood lead level at age 30 months (adjusted OR 0.98 (0.92, 1.05),

n=354). Similarly, neither measures of static nor dynamic balance at age 10 years were associated

36 with in utero lead or cadmium exposure, or child lead level.

37 Conclusions These findings do not provide any evidence of an association of prenatal exposure to
38 lead or cadmium, or lead levels in childhood, on balance ability in children. Confirmation in other
39 cohorts is needed.

40 Word count: 281

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Strengths and limitations of the study
• Data were collected prospectively in a population-based study
• The number of participants was large compared with several comparable studies
• Measures of Pb and Cd do not necessarily reflect lifetime exposure
 Measures of Pb and Cd do not necessarily reflect filterine exposure Balance measures have a poor test–retest reliability
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INTRODUCTION

Balance, or postural stability, is defined as the ability to keep the centre of gravity over the base of support.¹ The maintenance of balance underpins the ability to carry out nearly all daily activities. Balance impairment in adults is also a major cause of falls and of fall-related injuries, such as hip fracture, which can cause isolation and make it difficult to live independently. The control of balance is complex and is dependent on sensory inputs from the vestibular and visual systems, neural processing centres in the central nervous system, and motor inputs from the proprioceptive centre. Functional damage or deficits in any of these systems can lead to balance dysfunction, which can be associated with low self-esteem, anxiety and loss of confidence in children.²

Lead and cadmium are toxic metals: the effects of lead on neurocognitive and behavioural functions in children are well documented.³⁻⁵ but those of cadmium are less clear.⁶⁻⁸ Lead passes freely through the placenta so that ratio of fetal to maternal blood lead is about 0.8, although the placenta can act as a partial barrier to cadmium.⁹ The fetus is particularly vulnerable to the effects of these metals because of high rates of cell division and development. The development of the inner ear and vestibular function spans the whole of the period of gestation (for example, the membranous labyrinth is complete by week 7 with development of the bony labyrinth from week 9 to 23; the vestibular apparatus is in an adult-like form by week 25, and is active by week 32; vestibular ganglions develop from week 12 and reach maturity at week 39, and so on^{10}). Thus, prenatal exposure to lead and cadmium may have adverse effects on the development of the inner ear, and hence on vestibular function and balance ability in later childhood.

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It was noted in the 1980s that children who survived acute lead encephalopathy had ataxia and experienced difficulties in maintaining postural balance.¹¹ This led to a series of studies in children with somewhat more moderate levels of lead exposure (5.0 to 20.7 μ g/dl) showing that the child's lead level was associated with balance dysfunction and sway oscillation.¹²⁻¹⁶ To our knowledge, there are no reports of the effect of cadmium on balance ability in children. However, a recent study of lead and cadmium levels in adults in the US National Health and Nutrition Examination Survey (NHANES) found preliminary evidence of an association of lead and cadmium with balance and vestibular function.¹⁷ In addition, altered postural balance response has been reported in adult workers occupationally exposed to lead.¹⁸⁻²⁰ and cadmium.²¹ These results require confirmation in other cohorts and particularly in children.

The aims of our study were to investigate the associations of in utero exposure to lead and cadmium, and lead levels in children, on balance in childhood using data obtained from the Avon Longitudinal Study of Parents and Children (ALSPAC).

85 Methods

We first modelled associations of in utero exposure to lead and cadmium, using maternal blood levels during pregnancy, with clinical measures of balance (dynamic and static) at 7 and 10 years. We also investigated associations with questionnaire items related to balance repeated at 30 months, 42 and 81 months, and further items at 10 years. We also modelled the associations of child levels of lead with the balance variables.

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91	
92	The ALSPAC study
93	The study sample was derived from the ALSPAC study, a population-based study
94	investigating environmental and genetic influences on the health, behaviour and development
95	of children. All pregnant women in the former Avon Health Authority with an expected
96	delivery date between 1 April 1991 and 31 December 1992 were eligible for the study;
97	14,541 pregnant women were initially enrolled, resulting in a cohort of 14,062 live births. ²²
98	The social and demographic characteristics of this cohort were similar to those found in UK
99	national census surveys. ²³ Further details of ALSPAC are available at
100	www.bris.ac.uk/alspac.
101	
102	Collection, storage and analysis of blood samples
103	Maternal blood samples Whole blood samples were collected in trace-element free
104	vacutainers (Becton and Dickinson, Oxford, UK) by midwives as early as possible in
105	pregnancy. The median gestational age at the time of blood sampling was 11 weeks. The
106	interquartile range was 9–13 weeks, and 93% of the samples were collected at <18 weeks
107	gestation. Whole blood samples were stored in the original tube at 4°C at the collection site
108	before being transferred to the central Bristol laboratory within 1-4 days. Samples were at
109	ambient temperature during transfer (up to 3 h). They were then stored at 4°C until analysis.
110	Samples were analysed for lead and cadmiumusing inductively coupled plasma mass
111	spectrometry in standard mode by R. Jones at the Centers for Disease Control (CDC),
112	Bethesda, MD, USA (CDC Method 3009.1). Quality control was monitored as outlined in
113	Golding, et al. ²⁴ The analyses were completed on 4284 samples for lead and 4286 for
114	cadmium. One sample had a lead level below the limit of detection (0.29 μ g/dl); 1119

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samples were below the lower limit of detection for cadmium (0.20 μ g/l). These samples were assigned a value of 0.7 times the lower limit of detection (LOD/ $\sqrt{2}$).^{25 26}

117

Child blood samples Details of the selection of the subsample of children and analysis of 118 the blood samples have been reported previously in detail.^{3 27} In brief, a 10% randomly 119 selected subsample of parents whose babies were born in the last 6 months of the ALSPAC 120 121 study were invited to attend a research clinic (Children in Focus, CIF). At age 30 months, parental consent was sought for a venous blood sample, and was given by 81% of the 1135 122 123 children in the CIF group. The sample was drawn into lead-free tubes from 653 (71%) of 124 children attending the clinic. However, 69 samples were insufficient, leaving 582 samples for 125 analysis. Analysis was by atomic absorption spectrometry (Southampton General Hospital, UK) with appropriate quality controls. 126

127

128 Balance variables

Clinic measures Full details of the balance outcomes including details of the measurements 129 and validity have previously been published.²⁸ In brief, at age 7 years the heel-to-toe walking 130 test of the Movement Assessment Battery for Children²⁹ was conducted with the total number 131 132 of successful steps out of a maximum of 15 recorded. At age 10 years a range of tests were used to assess balance: (1) walking along a beam, heel-to-toe, eyes open; (2) heel-to-toe 133 134 balance on a beam, eyes closed; (3) standing on one leg, eyes closed. Each child had two 135 attempts at beam-walking; for tests of static balance, children only had a second attempt if they failed to achieve the maximum score on the first attempt.²⁸ These tests were based on 136 standard clinical tests to assess balance in children and have significant commonality with the 137 balance subtest of the both editions of the Bruininks–Oseretsky Test of Motor Proficiency.³⁰ 138

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139	³¹ The measures are also in common use when testing balance informally in the paediatric
140	clinic.
141	
142	Questionnaire items The primary caregiver (usually the mother) received a series of postal
143	self-completion questionnaires. The questionnaires are available from the study website
144	(http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/). When their child was
145	aged 18, 30, 42 and 81 months, the parent completing the questionnaire was asked to indicate
146	'Yes, can do well'/'Has only done once or twice'/'Has not yet started' in response to the
147	statement 'He/She can balance on one foot for at least 1 second'. When their child was aged
148	10 years, the parent was asked to indicate 'Very well'/'Just OK'/'Can almost'/'Not at all' in
149	response to the following questions: How well can your child stand on one leg in a stable
150	position (e.g. when putting on trousers, skirt)?; How well can your child ride a bike (without
151	stabilisers)?; How well can your child walk in the dark?
152	

Confounding variables

Information on passive smoking exposure during the week and at weekends was obtained

from questionnaires at 77 and 103 months. Information on traffic levels, type of

accommodation, lowest level of accommodation and maternal education were obtained at

from questionnaires completed by the mother during pregnancy. Dietary Ca and Fe intake at

7 years and 10 years were derived from food frequency questionnaires as previously

described in detail. ³²

Statistical analysis

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162	Statistical analysis was carried out with IBM SPSS Statistics 21. Balance measures were
163	derived as previously described. ²⁸ In brief, for the heel-to-toe test at age 7 years, the number
164	of steps (maximum 15) was categorised into 0-5, 6-10 and 11-15 steps for categorical
165	associations, and 1-14 (failed to complete in 20 s) versus 15 steps (successfully completed in
166	20 s) for regression analyses. For the measure of dynamic balance at 10 years (beam-walking
167	test), the mean of two attempts was categorised into quartiles. For measures of static balance
168	at age 10 years (heel to toe balance on a beam with eyes closed/standing on one leg eyes
169	closed), the sum of the score (s) from both attempts was calculated. Children who scored the
170	maximum of 20 on the first attempt and so did not have a second attempt were given a final
171	score of 40. The final scores were put into four categories (0–9, 10–19, 20–39 and 40). All of
172	the four static balance tests with eyes closed were summed to create a static balance eyes
173	closed variable (SBEC).
174	Blood lead and cadmium levels were put into two categories (<5 , $\ge 5 \mu g/dl$ for lead and <1 ,
175	$\geq 1 \ \mu g/l$ for Cd). These categories were chosen in accordance with the levels of concern of the
176	US Centers for Disease Control, the US Association of Occupational and Environmental
177	Clinics and the American College of Obstetricians and Gynecologists for Pb, ³³⁻³⁶ and the
178	German Federal Environmental Agency for Cd. ³⁷ Blood levels were also categorised into
179	quartiles.
180	Chi square tests were used to compare categorical variables. Unadjusted and adjusted logistic
181	regression analyses were used to investigate the association of blood levels with balance
182	variables.
183	
184	RESULTS

As previously reported, the mean child blood lead level was $4.22\pm3.12 \,\mu\text{g/dl} (n=582)^{3.27}$; the mean prenatal blood lead level was $3.67 \pm 1.47 \,\mu g/dl$ (n=4284) and the mean prenatal cadmium level was $0.58\pm0.63 \,\mu$ g/l (n=4286).^{38 39} Mothers who consented to provide a blood sample were better educated and older than mothers who did not.³⁸ Children who had lead levels measured were from families where the mother was better educated and more likely to be a homeowner, and was there was a better home environment with fewer adversities.³ Associations of measures of balance with prenatal lead and cadmium levels and with child lead levels Associations with in utero exposure to lead and cadmium There was no evidence of any association between the results of the heel-to-toe test at age 7 years and maternal lead or cadmium level during pregnancy (p=0.441 and p=0.189, respectively) (Table 1). Similarly, at age 10 years there were no associations between dynamic balance (beam walking) or static balance (SBEC) and maternal blood lead or cadmium levels in pregnancy (all p>0.1) (Table 1). In logistic regression models adjusted for sex, passive smoking, and calcium and iron intake, there was no evidence of any association between maternal blood lead or cadmium levels and measure of balance in the child at 7 and 10 years (all p>0.1) (Table 2). When the models were repeated with guintiles of maternal blood lead or cadmium level rather than a dichotomous variable, there was also no evidence of any associations (all p>0.1 with the exception of maternal blood lead for the odds of static balance dysfunction at 10 years where there was a protective effect (p for trend 0.038) (Supplementary Table 1).

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209	There was no evidence of any association between the results of the heel-to-toe test at age 7
210	years and child lead level (p for trend=0.146) (Table 3). Similarly, at age 10 years there were
211	no associations between dynamic balance (beam walking) or static balance (SBEC) and child
212	blood lead levels (p for trend=0.798 and p=0.918, respectively) (Table 3). In logistic
213	regression models adjusted for sex, passive smoking, and calcium and iron intake, there was
214	no evidence of any association between child blood levels at 30 months and measure of
215	balance at 7 and 10 years (Table 4; all p for trend >0.3). When the models were repeated with
216	quintiles of child blood lead rather than a dichotomous variable, there was also no evidence
217	of any associations (all p for trend >0.1) with the exception of static balance where there was
218	a weakly protective effect (p for trend=0.038 (Supplementary Table 1).
	a weakiy protective effect (p for field=0.058 (Supprementary Table 1).

219 220 Maternal Pb (µg/dl) Maternal Cd (µg/l) Age Category (years) <5 ≥5 P value <1 ≥1 P value (chi (chi square) square) Heel to toe test 7 0–5 steps 520 (27.1) 81 (29.1) 82 (26.5) 521 (26.6) 0.861 0.112 273 (14.2) 270 (13.8) 6-10 steps 45 (14.5) 49 (17.6) 11-15 steps 1128 (58.7) 183 (59.0) 1164 (59.6) 148 (53.2) Beam walking (dynamic balance) Q1 62 (25.3) 10 431 (23.4) 70 (24.1) 0.450 439 (23.3) 0.897 461 (25.0) 57 (23.3) Q2 80 (27.6) 484 (25.6) Q3 456 (24.8) 66 (22.8) 59 (24.1) 463 (24.5) Q4 494 (26.8) 74 (25.5) 503 (26.6) 67 (27.3) Static balance eyes closed score Q1 460 (24.4) 74 (25.8) 472 (25.5) 63 (25.8) 10 0.558 0.842 (SBEC) (static balance) Q2 459 (25.4) 58 (20.2) 62 (25.4) 455 (24.6) 83 (28.9) Q3 430 (23.8) 457 (24.7) 57 (23.4) 04 459 (25.4) 72 (25.1) 469 (25.3) 62 (25.4) Values are n (%). 221 Q, quartile. 222 223 12 Enseignement Superieur (ABES) . Protected by copyrightsing the herestiel and the text and the think of the initial of the initial technologies. 47 48 I ab aupidgrapoildig apresent at 202, 21 and no moo.imd.naqoimd//.qff from http://dff.from http://dff.from

Table 1 Associations of in utero lead and cadmium exposure with measures of balance in the child at 7 and 10 years in ALSPAC

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224	Table 2	Associations of in utero lead and cadmium exposure with balance measures in the child at 7 and 10 years old in ALSPAC
225		

	Age	Prenatal lead exposure			Prenatal cadmium exposure				
	(years)	OR of ba	lance dysfunction	Р	n	OR of bal	ance dysfunction	Р	n
			95% CI)	value		()	95% CI)	value	
Heel to toe test	7	Unadjusted	1.01 (0.96, 1.07)	0.503	2231	Unadjusted	0.81 (0.70, 0.94)	0.010	2233
		Adjusted ^a	1.01 (0.95, 1.01)	0.555	1732	Adjusted ^a	0.95 (0.77, 1.20)	0.904	1734
Dynamic balance	10	Unadjusted	1.01 (0.95, 1.08)	0.790	2132	Unadjusted	1.00 (0.84, 1.21)	0.946	2134
		Adjusted ^b	1.02 (0.95, 1.09)	0.692	1761	Adjusted ^b	1.20 (0.95, 1.52)	0.135	1763
Static balance	10	Unadjusted	0.98 (0.92, 1.05)	0.569	2095	Unadjusted	1.06 (0.88, 1.28)	0.523	2097
		Adjusted ^b	0.98 (0.92, 1.06)	0.661	1734	Adjusted ^b	1.00 (0.79, 1.26)	0.995	1736

Logistic regression showing odds ratio of balance dysfunction (95% CI).

^aAdjusted for: sex, passive smoking at 77 months old (weekdays and weekends), and Ca and Fe intake at 7 years.

^bAdjusted for: sex, passive smoking at 103 months old (weekdays and weekends), and Ca and Fe intake at 10 years.

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	Test	Age (years) Category		Child Pb (µg/dl)		P value (chi _ square)	
				<5	≥5		
	Heel to toe test	7	0–5 steps	82 (25.8)	34 (30.9)	0.146	
			6–10 steps 11–15 steps	52 (16.4) 184 (57.9)	22 (20.0) 54 (49.1)		
	Beam walking (dynamic balance)	10	Q1 Q2 Q3 Q4	74 (24.0)	24 (23.5)	0.798	
			Q_2	68 (22.1) 86 (27.0)	19 (18.6)		
			Q3	86 (27.9)	34 (33.3)		
			Q4	80 (26.0)	25 (24.5)		
	Static balance eyes closed score (SBEC) (static balance)	10	Q1	80 (26.5)	22 (22.0)	0.918	
			Q2	70 (23.2)	30 (30.0)		
			Q3	77 (25.5)	24 (24.0)		
			Q4	75 (24.8)	24 (24.0)		
35							
36	Values are n (%).						
37	Q, quartile.						
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Table 4 Child blood lead level at 30 months and balance measures at 7 and 10 years old in ALSPAC

	Age (years)	OR of balance d	ysfunction (95% CI)	P value	n
Heel to toe test	7	Unadjusted	0.98 (0.92, 1.04)	0.618	428
		Adjusted ^a	0.98 (0.92, 1.05)	0.778	354
Dynamic balance	10	Unadjusted	1.03 (0.96, 1.11)	0.422	410
		Adjusted ^b	1.01 (0.93, 1.09)	0.814	363
Static balance	10	Unadjusted	1.04 (0.96, 1.12)	0.345	402
		Adjusted ^b	1.03 (0.94, 1.12)	0.540	357
usted for: sex, passive smok usted for: sex, passive smok		weekdays and weekend	ds), and Ca and Fe intake at	10 years.	
			məngiəsn∃ ກາງດີປະຊາຊາດຢາດແຫຼງໄດ້ແຫຼງ ກາງເປັນເອີ້າເຊື່ອງຄາດ ກາງເປັນເອີ້າເຊື່ອງຄາດ ກາງເປັນເອີ້າເຊື່ອງຄາດ ກາງເປັນເອີ້າເຊື່ອງຄາດ ກາງເປັນເອີ້າເຊື່ອງກາງເອີ້າເຊື່ອງ ກາງເອີ້າເຊື່ອງກາງເອີ້າເຊື່ອງ ກາງເອີ້າເຊື່ອງກາງເອີ້າເຊື່ອງກາງເອີ້າເຊື່ອງ ກາງເອີ້າເຊື່ອງກາງເອີ້າເຊື່ອງກາງເອີ້າເຊື່ອງ ກາງເອີ້າເຊື່ອງກາງເອີ້າເຊື່ອງກາງເອີ້າເຊື່ອງກາງເອີ້າເອີ້າເຊື່ອງ ກາງເອີ້າເຊື່ອງກາງເອີ້າເຊື່ອງກາງເອີ້າເອີ້າເອີ້າເອີ້າເອີ້າເອີ້າເອີ້າເອີ້າ		

248	Associations with questionnaire items at 18-81 months and at 10 years
249	There was no evidence of any associations between child blood lead level at 30 months and
250	the ability to stand on one foot for at least 1 second at 30, 42 or 81 months (all p>0.6;
251	Supplementary Table 2). There was no evidence of any associations between maternal blood
252	lead level during pregnancy and the ability of the child to stand on one foot for at least 1
253	second at 18, 30, 42 or 81 months (all p>0.3) (Supplementary Table 2). There was no
254	evidence of any associations between maternal blood cadmium level during pregnancy and
255	the ability of the child to stand on one foot for at least 1 second at 42, or 81 months (all
256	p>0.4), but there were associations at 18 and 30 months (p<0.001 and p=0.003, respectively;
257	maternal cadmium $\geq 1 \ \mu g/l$ was associated with being more likely to be able to stand on one
258	foot well) (Supplementary Table 2).
259	There was no evidence of any association of elevated child lead level, or in utero lead or
260	cadmium exposure, with ability to stand on one leg or to walk in the dark at 10 years (all
261	p>0.09, chi-square test) (Supplementary Table 3). However, prenatal lead level ≥5 µg/dl was
262	associated with not being able to ride a bike without stabilisers (p=0.007), whereas child lead
263	level $\geq 5 \ \mu g/dl$ and prenatal cadmium $\geq 1 \ \mu g/l$ were weakly associated with being able to ride a
264	bike without stabilisers very well (p=0.050 and p=0.075 respectively). When these
265	associations were modelled in a logistic regression analysis adjusted for variables that could
266	affect availability of a bicycle and being able to ride a bicycle locally (traffic level on the
267	home street, type of accommodation, lowest level of accommodation), and maternal
268	education, there was very weak evidence for an association of child lead level being
269	associated with being able to ride a bike well without stabilisers (OR in unadjusted model
270	2.79 (95% CI 0.096, 8.10), p=0.059, n=413; OR in adjusted model OR 2.57 (95% CI 0.87,
271	7.62), p=0.089, n=387). The association was stronger for prenatal lead level in the unadjusted
272	model, but the effect was attenuated with adjustment (OR in unadjusted model 0.59 (95% CI

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273	0.40, 0.87), p=0.007, n=2150; OR in adjusted model 0.73 (95% CI 0.47, 1.14), p=0.167,
274	n=1904); for prenatal cadmium level again the weak effect was attenuated by adjustment
275	(unadjusted OR 1.69 (95% CI 0.94, 3.01, p=0.078, n=2151; adjusted OR 1.44 (95% CI 0.75,
276	2.75, p=0.274, n=1905).
277	
278	DISCUSSION
279	We did not find any evidence of an association of prenatal exposure to lead or cadmium, or
280	lead levels in childhood, on balance ability (static and dynamic) in children.
281	Counterintuitively, there was a suggestion that higher child lead levels and in utero lead
282	exposure were associated with the ability to ride a bike without stabilisers at age 10 years, but
283	these effects were negated when the associations were adjusted for variables that included the
284	lowest level of accommodation and traffic levels outside the home. This is the first study, to
285	our knowledge, reporting on the associations between in utero exposure to lead and cadmium
286	and balance ability of the child, and adds to the few studies on child lead levels and balance
287	ability.
288	Postural balance is controlled by a complex interaction of sensorimotor processes, including
289	visual, proprioception and the vestibular system. In our study the measure of static balance
290	with eyes closed eliminated vision and minimised proprioceptive inputs, thereby enabling the
291	assessment of vestibular information as the primary input. Use of clinical measures similar to
292	these is commonplace in epidemiological studies (e.g. ⁴⁰⁻⁴³), as the tests are in common
293	clinical usage and require little or no specialist equipment. However, although the vestibular
294	dominant condition of tests of standing balance (reduced base of support with eyes closed)
295	has been shown to correlate well with more expensive systems such as computerised dynamic
296	posturography (considered to be the 'gold standard' method for assessing balance function) in

adults,⁴⁴ there are questions about whether such a correlation exists in children.⁴⁵ It has even
been suggested that computerised measures using a force-platform and clinical tests such as
those used by ALSPAC give complementary rather than concurrent information.⁴⁶ A cautious
approach should therefore be taken if seeking to compare studies using these two different
types of outcome measure.

Most studies on lead levels and balance in children have included children with relatively high lead levels (means in each study of 11.6 to 20.7 μ g/dl) and measured balance with a force platform system.¹²⁻¹⁵ and have found negative associations. There are several reasons for our results being in contrast to these studies. First, the mean child blood lead level in our study (4.22 μ g/dl) was lower than reported in these earlier studies, and may have been too low to have been sufficient to cause balance dysfunction. Alternatively, the effect on balance might have been too small to be detectable with our tests, although a study in Inuit children had levels that were more comparable to the present study (mean 5.4 μ g/dl) showed a significant association with sway oscillations.¹⁶ Second, we used a series of assessments based on clinical tests to measure balance rather than a force platform or measurement of sway oscillations and this may account for differences in the findings. As discussed earlier, clinical and force platform measures may be giving complementary rather than concurrent information: whereas posturography is a measure of the motor and sensory strategies used to control balance, clinical tests evaluate the results of that balance control.⁴⁶ Measuring sway oscillations using a force platform will also be more sensitive than the ALSPAC measures, which measured time before a procedural fault such as touching the floor with either foot or lifting a foot off the beam. Third, early exposure to lead and/or cadmium could damage the vestibular system, but the plasticity of the balance system might compensate for this so that there is no functionally measurable effect. This is in accordance with measures of balance in the present study indirectly assessing the vestibular system. This could also account for

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effects being reported in adults, in whom plasticity is less effective for overall balance
compensation, but not in children. It is also possible that vestibular system (to include
peripheral (ear) and central (brain) components of the vestibular pathway) dysfunction caused
by in utero exposure to lead or cadmium may not be apparent in childhood but may manifest
in later life. Finally, it is also possible that studies showing non-significant results have

To our knowledge, there are no studies that have examined the effect of in utero exposure to lead or cadmium on balance ability in the child. Our results provide preliminary evidence for lack of effect, but this requires confirmation on other cohorts.

331 The strengths of the study are that: (1) it is a population-based study; (2) the data were 332 collection prospectively; and (3) the numbers included in the study were large compared with 333 several other studies. There are several limitations to the study. First, measures of blood lead 334 and cadmium do not necessarily reflect lifetime exposure. Bone lead, which makes up more than 95% of the body lead, can be measured by K x-ray fluorescence,⁴⁷ but this is expensive, 335 technically demanding and may not always be ethically permissible in children. This 336 limitation is of less consequence for in utero exposure as the maternal blood level largely 337 338 determines the fetal blood level. Second, there was a high proportion of blood cadmium 339 levels below the limit of detection, which may make the results less reliable than for lead. 340 Third, there may be confounders we were unable to account for. Fourth, we were unable to control for lead and cadmium separately in the models because of multicollinearity. Finally, 341 the balance measures used by ALSPAC had low test-retest reliability,²⁸ which is a common 342 problem with measures of childhood balance.⁴⁸⁻⁵⁰ The measure of ability to balance on one 343 foot for 1 s, a test which was originally developed by Chamberlain and Davey⁵¹ in 1976, has 344 been particularly criticised for having poor test validity as it is difficult to discriminate a 345

failed attempt from a successful attempt.¹⁰ It should ideally form part of a battery of clinical
measures, perhaps with a longer duration of standing. These combined effects may have led
to random misclassification in our balance assessments and dilution of the estimates of the
effects of lead and cadmium exposure.

351 CONCLUSIONS

We did not find any evidence of an association of prenatal exposure to lead or cadmium with balance ability in children. In contrast to previous studies, we did not find any association of child blood lead with balance ability in children. This may reflect variation in the methods used to assess balance in different studies, or may be related to the lower mean lead level in the children in the present study than in previous studies. Further work in other cohorts is needed to confirm the results.

Data sharing statement: No additional data available.

Contributors statement: CMT conceived the study and undertook data analysis in

360 conjunction with RH, AH and JG. CMT took the lead in writing the manuscript with critical

- 361 revisions and additions from RH, AH, JG and AME. All authors contributed to and approved
 - the final version of the manuscript.
 - 363 Ethics approval: Ethics approval for the study was obtained from the ALSPAC Ethics and
 364 Law Committee and the Local Research Ethics Committees.

Competing interests: The authors declare that there are no competing interests

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	OR of balance dysfunction (95% CI)	P value for trend	OR of balance dysfunction (95% CI)	P value for trend	=. m ·	eysfunction (95% CI)	P value for trend	
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1	1.00 (Ref)	0.349 (n=1732)	(Ref)	0.133 (n-1.457)		Ref)	0.234 (n=354)	
2	0.94 (0.72, 1.22)	× /	1.17 (0.91, 1.53)	× ×	tra	.47 (0.82, 2.63)	· · · · ·	
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103 months old (weekdays and weekends), and Ca and Fe intake at 7 years. For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtmb ^eAdjusted for: sex, passive smoking at 103 months old (weekdays and weekends), and Ca and Fe intake at 10 years.

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Page 27 of 3	1				BM	J Open iire items relate		ijopen-20 d by cop			
1 <u>2</u>		pplementary Table	2 Associations	s of responses to			d to balance at	. <u> </u>			
3 4	Age (months)	Category			Prenatal	exposure		09635 or t, includ		Child Pb (µg/dl)	
5	(Mat	ternal Pb (µg/dl)		Ma	aternal Cd (µg/l)		-		
7 8 9			<5	≥5	P value (chi square)	<1	≥1	P Salar Balar Balar Salar Salar	<5	>5	P value (chi square)
10 Stand on 1 11 12 12 12	18	Yes, can do well	1397 (50.8%)	237 (51.9%)	0.680	1353 (49.5%)	280 (58.6%)		-	-	-
13 14		Only done 1–2 times/Not yet started	1352 (49.2%)	220 (48.4%)		1376 (50.5%)	198 (41.4%)	5. Downlo ent Supe I to text a	-	-	
15 16 16 foot for 1 s 17	30	Yes, can do well	1853 (70.6%)	313 (71.5%)	0.711	1815 (69.7%)	352 (76.5%)		270 (69.6%)	95 (70.4%)	0.865
18 19		Only done 1–2 times/Not yet started	772 (29.4%)	125 (28.5%)		789 (30.3%)	108 (23.5%)	5. Downloaded from http://bmjopen.b nent Superieur (ABES) . 1 to text and data mining_Al training 0.44Al training	118 (30.4%)	40 (29.6%)	
20 21 21 22 22 22	42	Yes, does well	1862 (72.4%)	290 (70.2%)	0.366	1838 (71.9%)	316 (73.7%)	0.440	288 (73.8%)	204 (73.8%)	0.984
22 23 24		Yes, not very well/Not yet done	711 (27.6%)	123 (29.8%)		720 (28.1%)	113 (26.3%)	0.44Al training	102 (26.2%)	37 (26.2%)	
2§tand on 1 2§pot for 8 s 27 28 29	81	Yes, can do well Yes, but not well/Has not yet done/ Unable to try/Not had a chance	2052 (95.0%) 108 (5.0%)	339 (95.8%) 15 (4.2%)	0.537	2079 (95.1%) 106 (4.9%)	314 (94.9%) 17 (5.1%)	and similar	329 (94.5%) 19 (5.5%)	106 (93.0%) 8 (7.0%)	0.538
<u>30</u> 31	Values are							une :			
32 33 34 35 36 37 38								June 13, 2025 at Agence technologies.			
38 39 40 41 42 43 44 45			For peer	review only - h	ttp://bmjop	en.bmj.com/site	/about/guidelin	Bibliographique			
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1 2 3 Supplementary 7 4	2 3 Supplementary Table 3 Associations of responses to questionnaire items related to balance at 10 years old in ALSPACS 4 4 5 6 9 6 9										
⁵ Test	Category			Prenatal ex	A		30 ng	(Child Pb (µg/dl)		
6 7			ternal Pb (µg/dl)			ternal Cd (µg/l					
8 9		<5	≥5	P value (chi square)	<1	≥1	Pavalue ex(mp sguaire)	<5	≥5	P value (chi square)	
10- 11 Stand on one leg 12 13	Very well Just OK/ Can almost/ Not at all	1411 (76.1%) 444 (23.9%)	219 (74.7%) 74 (25.3%)	0.623	1455 (76.5%) 448 (23.5%)	177 (71.7%) 70 (28.3%)	2015. Downloaded fro greenent Superieur (AB greenent Superieur (AB) greenent Superieur (AB) greenent Superieur (AB) greenent Superieur (AB) greenent (AB) greenent Superieur (AB) greenent (AB	236 (76.1%) 74 (23.9%)	79 (76.0%) 25 (24.0%)	0.972	
14 Ride a bike 15 without stabilisers	Very well	1715 (92.5%)	259 (87.8%)	0.007	1742 (91.4%)	234 (94.7%)	0.0770 0.0770 and	278 (90.0%)	100 (96.2%)	0.050	
16 17	Just OK/ Can almost/ Not at all	140 (7.5%)	36 (12.2%)		163 (8.6%)	13 (5.3%)	ded fro eur (At I data I	31 (10.0%)	4 (3.8%)		
¹⁸ Walk in dark 19 20 21	Very well Just OK/ Can almost/ Not at all	1367 (75.2%) 450 (24.8%)	222 (76.6%) 68 (23.4%)	0.628	1411 (75.6%) 455 (24.4%)	180 (74.1%) 63 (25.9%)	ABES) . ABES) . A Mining, A	225 (75.3%) 74 (24.7%)	78 (75.7%) 25 (24.6%)	0.923	
22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47		For pee	er review only - h		n.bmj.com/site/		omjopen.bmj.com/ on June 13, 2025 at Agence Bibliographique de l I training, and similar technologies.				

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Balance ability in 7- and 10-year-old children: associations with prenatal lead and cadmium

exposure and with blood lead levels in children in a prospective birth cohort study

Caroline M Taylor, Rachel Humphriss, Amanda Hall, Jean Golding, Alan M Emond

STROBE Statement-checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Line no.
Title and abstract		(<i>a</i>) Indicate the study's design with a commonly used term in the title or the abstract	2 and 23
		(b) Provide in the abstract an informative and balanced summary of what was	18-38
		done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being	49-76
C		reported	
Objectives	3	State specific objectives, including any prespecified hypotheses	77-79
Methods			
Study design	4	Present key elements of study design early in the paper	82-86
Setting	5	Describe the setting, locations, and relevant dates, including periods of	89-153
		recruitment, exposure, follow-up, and data collection	
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of	82-96
		selection of participants. Describe methods of follow-up	
		Case-control study—Give the eligibility criteria, and the sources and methods of	
		case ascertainment and control selection. Give the rationale for the choice of	
		cases and controls	
		Cross-sectional study—Give the eligibility criteria, and the sources and methods	
		of selection of participants	
		(b) Cohort study—For matched studies, give matching criteria and number of	
		exposed and unexposed	
		Case-control study—For matched studies, give matching criteria and the number	
		of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and	99-153
		effect modifiers. Give diagnostic criteria, if applicable	
Data sources/	8*	For each variable of interest, give sources of data and details of methods of	99-153
measurement		assessment (measurement). Describe comparability of assessment methods if	
		there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	94-95
Study size	10	Explain how the study size was arrived at	89-96
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable,	156-
		describe which groupings were chosen and why	172
Statistical methods	12	(a) Describe all statistical methods, including those used to control for	156-
		confounding	175

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(c) Explain how missing data were addressed (d) Cohort study—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls

Continued on next page

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Results Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible,	Table 1-	Protected by copyright, including for uses related to text and data min
Ĩ		examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4	
		(b) Give reasons for non-participation at each stage		_
		(c) Consider use of a flow diagram		
Descriptive	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and	89-96	Prote
data		information on exposures and potential confounders		- čte
		(b) Indicate number of participants with missing data for each variable of interest		- ä
Outcome data	15*	 (c) Cohort study—Summarise follow-up time (eg, average and total amount) Cohort study—Report numbers of outcome events or summary measures over time 	Tables	- v
Outcome data	15.	Conor study—Report numbers of outcome events of summary measures over time	1-4	opyri
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure		ght, inc
		Cross-sectional study-Report numbers of outcome events or summary measures		bul
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their	185-208	ing
		precision (eg, 95% confidence interval). Make clear which confounders were adjusted for		for
		and why they were included		_ us
		(b) Report category boundaries when continuous variables were categorized		ן הייני
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a		elat
		meaningful time period		_ed t
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses		o text
Discussion				and
Key results	18	Summarise key results with reference to study objectives	268-276	dat
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or	322-336	a m
		imprecision. Discuss both direction and magnitude of any potential bias		_ ⊒.(
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	339-344	ig, Al
Generalisability	21	Discuss the generalisability (external validity) of the study results	343	-tra
•		Discuss the generalisating (external value) of the study results	545	- inin
Other informatio)n			_ <u>ʻ</u> Q
Funding	22	Give the source of funding and the role of the funders for the present study and if	355-360	മ
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable for the original study on which the present article is based	355-360	and :
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	355-360	and sim
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*Give informatior unexposed groups	n sepa s in co	applicable, for the original study on which the present article is based rately for cases and controls in case-control studies and, if applicable, for exposed and hort and cross-sectional studies.	355-360	and similar technolog
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