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# BMJ Open

## Can we moderate our own exposure to bisphenol A (BPA) through dietary intervention?

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Manuscripts

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3 1 Can we moderate our own exposure to bisphenol A (BPA) through dietary  
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6 intervention?  
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43 24 **Declaration of competing issues**  
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46 25 The authors have no competing interests to declare.  
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## 27 **ABSTRACT**

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### 29 **Objective**

30 Bisphenol A has been associated adverse human health outcomes and exposure to this  
31 compound is near-ubiquitous in the Western world. We aimed to examine whether self-  
32 moderation of BPA exposure is possible by altering diet in a real-world setting.

### 33 **Design**

34 An Engaged Research dietary intervention study designed, implemented and analysed by  
35 healthy teenagers from 6 schools and undertaken in their own homes.

### 36 **Participants**

37 104 students aged between 18 and 19 years from schools in the South West of the UK  
38 provided diet diaries and urine samples for analysis. Questionnaires and freeform comments  
39 on the ease of use were collected for qualitative analyses.

### 40 **Intervention**

41 Researcher participants designed a set of literature-informed guidelines for reduction of  
42 dietary BPA to be followed for 7 days.

### 43 **Main outcome measure**

44 Creatinine-adjusted urinary BPA levels were taken before and after the intervention.  
45 Information on packaging and food/drink ingested was used to calculate a BPA risk score for  
46 anticipated exposure. A qualitative analysis was carried out to identify themes addressing  
47 long term sustainability of the diet.

### 48 **Results**



1  
2  
3 49 BPA was detected in urine of 86% of participants at baseline at a median value of 1.34 ng/ml  
4  
5 50 (IQR 1.82). No effect of the intervention diet on BPA levels was identified overall ( $p = 0.25$ ),  
6  
7 51 but there was a positive association in those participants who showed a drop in urinary BPA  
8  
9 52 concentration post intervention and their initial BPA level ( $p = 0.003$ ). Qualitative analysis  
10  
11 53 identified themes around feelings of lifestyle restriction and the inadequacy of current  
12  
13 54 labelling practices.

## 15 16 17 55 **Conclusions**

18  
19 56 We found no evidence in this self-administered intervention study that it was possible to  
20  
21 57 moderate BPA exposure by diet in a real world setting. Furthermore, our study participants  
22  
23 58 indicated that they would be unlikely to sustain such a diet long term, due to the difficulty in  
24  
25 59 identifying BPA-free foods.

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3 61 **Article Summary**  
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7 63 *Strengths of the study*  
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11 65 • This study represents the largest assessment to date of the potential for moderating  
12 one's own BPA exposure through diet  
13  
14  
15 67 • The study was carried out in a real-world setting rather than a regulated, controlled  
16 environment.  
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18  
19 69 • The study was carried out in teenagers, the demographic with amongst the highest  
20 exposure.  
21  
22  
23  
24 71 • Qualitative analysis reveals challenges with sustaining such a diet.  
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27 72 *Limitations of the study*  
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- 29  
30 73 • Calculation of a risk score is challenging due to the pervasive nature of BPA  
31 contamination  
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**What is already known on this topic**

- Bisphenol A (BPA) is an endocrine disrupting chemical ubiquitously present in our diet and environment. It has been associated with a variety of adverse human health outcomes in animal models, in human populations and in human in-vitro work.
- Previous studies have shown that it may be possible to reduce BPA exposure by following a researcher-supplied very controlled diet for a period of 3 days.

**What this study adds**

- Our study suggests that although it may be possible to reduce dietary BPA in a controlled setting, it is not possible to do so in a community-based 'real world' setting.
- Qualitative research suggests that even if it were possible to reduce BPA exposure by dietary means, the restrictions placed on lifestyle and the current inadequacies in labelling of BPA containing foods means that such a diet would be impossible to follow long-term, in the real world.
- Improved labelling of foods and packaging of foodstuffs suspected to contain BPA may allow consumers an informed choice on their own exposure.

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## 79 INTRODUCTION

80

81 Bisphenol A is one of the world's highest production volume chemicals. It is used in the  
82 manufacture of polycarbonate and other plastic consumer products, in heat resistant papers,  
83 dental sealants and in the epoxy resin-based lining of food and drink containers [1]. BPA can  
84 be found above the detection limit in the urine of the majority of people worldwide [2].  
85 Concern has been raised for public health, since BPA is classified as an endocrine disrupting  
86 chemical (EDC) which has been linked with several disorders in cell and animal models [3-  
87 5]. Epidemiological data in humans is more contentious, due to relatively small sample sizes  
88 and issues around causality [6]. The Endocrine Society concluded in 2015 that current  
89 evidence suggests that BPA and other endocrine disrupting chemicals may have effects on  
90 several reproductive, cardiovascular and metabolic traits in humans [7]. The current opinion  
91 of food regulatory bodies such as the European Food Standards Agency (EFSA) is that  
92 sufficient uncertainty remains to be able to exclude effects on the reproductive, immune,  
93 nervous, metabolic and cardiovascular systems and on cancer development [3] whilst the  
94 European Chemicals Agency (ECHA) has recently reclassified BPA as a chemical of very  
95 high concern due to its endocrine disrupting properties [8].

96

97 There has been wide interest in the sources of BPA and the potential for individuals to reduce  
98 their own exposure. Human exposure has been reported from inhalation of dust, uptake  
99 across the skin from thermal papers and till receipts and release from dental sealants. The  
100 main source is the ingestion of food and drink contaminated with BPA leached from  
101 packaging materials [1, 9]. BPA is rapidly metabolised in the gut wall and liver and removed  
102 from the blood by the kidneys, with a terminal half-life of 6 hours after oral ingestion [10].  
103 BPA has been detected in food samples packaged in glass, plastic, paper and paperboard

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3 104 cartons, with an average concentration of 0.46 ng/g, rising to over 700 ng/g for certain canned  
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5 105 foods. Conversely, in a dietary intervention study in which 22 volunteers consumed a 3 day  
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7 106 fresh food diet which excluded canned or packaged foods, there was a 66% reduction in  
8  
9 107 urinary BPA excretion compared to concentrations before the intervention [11]. This latter  
10  
11 108 study involved full dietary replacement of foodstuffs, an approach which is impractical for  
12  
13 109 the population at large. A follow up study found that households who followed written  
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15 110 recommendations produced by health care professionals showed no significant change in  
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17 111 their BPA exposure [12].  
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24 113 We present an alternative, citizen-science based approach, where student volunteers designed  
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26 114 and undertook their own intervention diet, following provision of educational materials. We  
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28 115 questioned whether adherence to a self-designed and self-administered 'real world' diet over  
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30 116 7 days would lead to significant reductions in excreted urinary BPA, and if so, whether such a  
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32 117 diet was likely to be sustainable in the long term.  
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## 119 **METHODS**

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### 121 **Participant group**

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123 We chose adolescents because they represent a demographic with high BPA exposure  
124 (aggregated exposure of 1.449 µg/kg body weight per day) [3, 13]. 104 students aged 17-19  
125 from 6 local schools signed up to participate in this engaged research project, representing the  
126 largest intervention study in the population demographic with the highest BPA exposure to  
127 date [13]. Study size was arrived upon based on anticipated effect sizes from previous work  
128 of this nature [11], and we allowed for a 10% dropout rate. Students designed all of the

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3 129 materials required for completion of the study (study protocols, food diaries, lifestyle  
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5 130 questionnaires, patient information sheets and consent forms (see Supplementary Information  
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7 131 files 2 to 5).  
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### 13 133 **Ethical Permission**

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19 135 Ethical permission was granted by the University of Exeter Medical School Ethics  
20  
21 136 Committee (reference number 15/07/074) and the study was carried out in accordance with  
22  
23 137 the Declaration of Helsinki.  
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26 138

### 29 139 **The intervention diet**

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33 141 Students designed a “real world” diet designed to reduce consumption of BPA by avoidance  
34  
35 142 of processed foods and foods packaged in known sources of BPA [1, 9]; supplementary  
36  
37 143 information file 2). We requested that calorific intake was maintained as near to their usual  
38  
39 144 diet as possible and recorded details of their daily diet including all food and drink, and its  
40  
41 145 associated packaging, in a self-reported food diary (Supplementary information file 3). A  
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43 146 ‘BPA risk score’ based on instances of known or suspected exposure for each participant was  
44  
45 147 then calculated. Risk scores from the final day of the intervention only were also taken, since  
46  
47 148 this is most relevant to the sample collected at visit 2. Information on lifestyle factors  
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49 149 including sex, BMI and time of urine collection was also collected (Supplementary  
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51 150 information file 4).  
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## 152 **Sample collection and measurement of urinary BPA**

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154 Urine samples were collected into BPA-free bottles (Vacutest Kima, Italy) immediately  
155 before and after the intervention, and were frozen at -20°C within 4 hours. Each participant  
156 was sampled in the same time-slot at both visits to account for circadian variation in BPA  
157 metabolism. Samples were transported on dry ice to a commercial laboratory (Rovaltain  
158 Research Company, Aixain, France) where analysis of total BPA was assessed by gas  
159 chromatography-tandem mass spectrometry. Experimental methods were validated for  
160 linearity, detection limit and accuracy and specificity of quantification based on the Standard  
161 NF T 90-201 for determination of xenobiotics. A quality control check of known standards  
162 injected every 6 samples at two levels of concentration (0.5 ng/ml and 5 ng/ml) was  
163 quantified with each batch of unknown samples. Water-only samples were included as  
164 negative controls. Urinary creatinine was measured at the Royal Devon and Exeter Hospital  
165 using the Jaffe method on the Roche P800 platform (Roche, Mannheim, Germany), to allow  
166 correction for urine dilution. Results were expressed as a BPA:creatinine ratio. Samples  
167 where BPA was detected but quantifying at or around the limits of quantification (LoQ) were  
168 scored as  $LoQ/\sqrt{2}$  according to the method of Hornung and Reed [14].

169

## 170 **Statistical Analysis**

171

172 Study population demographics for urinary BPA adjusted for creatinine at visits 1 and 2 were  
173 assessed to generate a  $\Delta$ BPA continuous variable. BPA risk scores were calculated as a  
174 continuous variable. The relationship between urinary BPA levels before and after the 7 day  
175 intervention was assessed using a repeated-measure ANOVA, adjusted for sex, time of  
176 sampling and BMI, with and without correction for creatinine. The relationship between  
177 urinary BPA at visit 1 and whether or not the participants had lower BPA at visit 2 was also

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3 178 examined by binary logistic regression, adjusted for sex, time of sampling and BMI. Here,  
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5 179 samples showing small changes < 0.5ng/ml in either direction were omitted to avoid natural  
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7 180 stoichiometric variation around zero. The relationship between change in BPA ( $\Delta$ BPA) and  
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9 181 BPA risk score was assessed by linear regression, adjusted for sex, time of sampling and BMI  
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11 182 both with and without adjustment for creatinine. Statistical analysis was carried out using  
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13 183 SPSS, v.22 (IBM, USA).  
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### 18 185 **Impact of following reduced BPA diet on lifestyle**

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21 187 We carried out quantitative and qualitative analysis to address long-term sustainability of the  
22  
23 188 diet. Data on the impact of following the diet on feelings of dietary restriction, time spent  
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25 189 sourcing or preparing meals, calorific intake and long term sustainability were collected via a  
26  
27 190 questionnaire (See Supplementary information file 4). The questionnaire also included a  
28  
29 191 freeform section where participants could write about their experiences following the diet in a  
30  
31 192 non-prescribed fashion for qualitative analysis. Qualitative data was assessed for thematic  
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33 193 content by two experienced qualitative researchers. Key themes were independently  
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35 194 identified and coded until agreement was reached.  
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## 42 196 **RESULTS**

### 43 197 **Participant Characteristics**

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49 200 There were 104 volunteer participants in this engaged research study. Information on the  
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51 201 characteristics of the study cohort are given in table 1.  
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**Table 1: Characteristics of the study population.** Data were available on 99 out of 104 participants. IQR = interquartile range, SD = Standard deviation. The units of BPA are ng/ml and BMI is defined as Kg/m<sup>2</sup>. LoQ = limit of quantification. Urinary BPA levels are given both as unadjusted data and as a BPA (ng/ml) to creatinine (mg/ml) ratio.

<b>Unadjusted urinary BPA at visit 1 (n = 98)</b>	
median (IQR)	1.37 (2.52)
95% confidence intervals	1.58 to 2.57
mean (SD)	2.07 (2.51)
Number of samples below LoQ (0.1ng/ml)	16
Minimum value (ng/ml)	0.07
Maximum value (ng/ml)	13.55
<b>Creatinine-adjusted urinary BPA at visit 1 (n = 98)</b>	
median (IQR)	1.34 (1.82)
95% confidence intervals	1.38 to 2.13
mean (SD)	1.75 (1.82)
Number of samples below LoQ (0.1ng/ml)	16
Minimum value (ng/ml)	0.05
Maximum value (ng/ml)	9.52
<b>Unadjusted urinary BPA at visit 2 (n = 99)</b>	
median (IQR)	1.91 (2.68)
95% confidence intervals	2.15 to 4.56
mean (SD)	3.35 (6.18)
Number of samples below LoQ (0.1ng/ml)	12
Minimum value (ng/ml)	0.07
Maximum value (ng/ml)	49.6
<b>Creatinine-adjusted urinary BPA at visit 2 (n = 99)</b>	
median (IQR)	1.31 (2.24)
95% confidence intervals	1.46 to 8.34
mean (SD)	4.90 (16.8)
Number of samples below LoQ (0.1ng/ml)	12
Minimum value (ng/ml)	0.04
Maximum value (ng/ml)	139.33
<b>Unadjusted ΔBPA (n = 94)</b>	
median (IQR)	0.14
95% confidence intervals	0.15 to 2.41
mean (SD)	1.28 (5.79)
Minimum value	-8.02
Maximum value	49.5
<b>Adjusted ΔBPA (n = 94)</b>	
median (IQR)	0.02 (2.61)
95% confidence intervals	-0.23 to 6.53
mean (SD)	3.15 (16.5)
Minimum value	-8.6

Maximum value	133.45
<b>BPA risk score (n = 99)</b>	
median (IQR)	15.0 (10.3)
95% confidence intervals	15.5 to 18.4
mean (SD)	17.0 (7.12)
<b>Demographics (n= 99)</b>	
Sex - % male	44
Exposure to estrogens - % of cohort	14
BMI- median (IQR)	20.7 (3.45)
BMI- mean (SD)	21.2 (3.07)

207

208 BPA was detected in the urine of 86% of subjects at visit 1 prior to the intervention. Missing  
 209 samples were due to non-attendance of participants or non-provision of a suitable sample.  
 210 Samples below the limit of quantification of 0.1ng/ml were scored as 0.07 ng/ml (LoQ/ $\sqrt{2}$ ).

211

**212 Creatinine-adjusted urinary BPA concentrations do not change significantly after**  
**213 following an intervention diet designed to reduce BPA exposure for 7 days.**

214

215 The median change in creatinine-adjusted urinary BPA between visits ( $\Delta$ BPA) was 0.02  
 216 ng/ml with an interquartile range of 2.61 ng/ml. We identified no changes in urinary BPA  
 217 between visits ( $p = 0.25$ ; figure 1a). 3 outliers with very high urinary BPA readings at visit 2  
 218 were excluded from the analysis, since these samples lay outside the linear range of analysis,  
 219 so confidence in quantification was poor. No confounding factors included in the analysis  
 220 were associated with change in BPA ( $p = 0.78, 0.43$  and  $0.36$  for sex, time of sample  
 221 collection and BMI respectively). We also identified no change in BPA levels between visits  
 222 using data uncorrected for creatinine ( $p = 0.20$ ).

223

224 Similarly, no relationship between change in urinary BPA ( $\Delta$ BPA) and BPA risk score was  
 225 identified (beta coefficient 0.08, standard error 0.07,  $p = 0.55$ ; figure 1b). No associations  
 226 were noted between change in urinary BPA and BPA risk score in data not adjusted for

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3 227 creatinine ( $p = 0.27$ ). We found no association between  $\Delta$ BPA and BPA risk score when  
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5 228 considering only the exposure on the day prior to testing, taking into account the short half-  
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7 229 life of BPA ( $p = 0.16$  and  $p = 0.33$  for adjusted and unadjusted data respectively). We  
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9 230 conclude that the 'real world' diet designed to reduce BPA exposure had no effect on  
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11 231 creatinine-adjusted urinary BPA concentrations in our cohort over a period of 7 days in our  
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13 232 dataset.  
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18 234 **Participants with highest starting urinary BPA levels were more likely to demonstrate**  
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20 235 **lower BPA levels at visit 2.**  
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25 237 We found an inverse relationship between initial BPA levels and whether a participant had  
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27 238 reduced BPA levels at visit 2 ( $p = 0.003$ ). These data indicate that the participants in the  
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29 239 cohort with the highest creatinine-adjusted urinary BPA levels at visit 1 were more likely to  
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31 240 demonstrate a drop in their urinary BPA at visit 2 (figure 2).  
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37 242 **Following the intervention diet has significant effects on participant lifestyle**  
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43 244 Participants indicated that following the diet had no significant cost implications on family  
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45 245 finances, with 50% of participants reporting that it had cost more, and 50% reporting that  
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47 246 costs had decreased or remained the same. Although participants did not spend longer  
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49 247 preparing their food, 78% of participants reported that their shopping took longer. 58% of  
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51 248 participants reported that the diet did not affect their calorific intake. 91% of participants  
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53 249 reported that they felt at least slightly restricted in their food choices. 27% of participants  
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3 250 reported that they felt very restricted. Finally, 66% of participants stated that they would find  
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5 251 it hard or very hard to follow the diet long term.  
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### 10 253 **Qualitative analysis of the effect of following the diet on lifestyle**

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14 255 We identified 5 overriding themes in our qualitative analysis of the effect of following the  
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16 256 diet on lifestyle. These were 1) the widespread use of plastics possibly containing BPA in  
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18 257 food packaging (“almost everything is packaged in plastic” – participant 70, “Literally  
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20 258 everything involved plastic” – participant 28). 2) Lack of clarity in labelling of products and  
21  
22 259 packaging potentially containing BPA (“I found it really hard to know what foods I could eat  
23  
24 260 ... there is never a guarantee it is BPA free” – participant 43, “The biggest problem was that  
25  
26 261 a lot of packaging doesn’t state what type of plastic it is or whether it contains BPA” –  
27  
28 262 participant 74). 3) The perceived restrictions of being on the ‘real world’ BPA avoidance diet  
29  
30 263 (“Difficulty eating out, hard to find foods in college or ‘out’ that hadn’t touched BPA. My  
31  
32 264 family had a takeaway on Saturday night and I couldn’t eat it” – participant 56, “Sometimes I  
33  
34 265 can’t eat / drink what I want because of the recycling number” – participant 112). 4) The  
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36 266 impact of eating ‘BPA free’ was the only positive theme emerging (“I feel I have eaten much  
37  
38 267 more healthily this week ... I didn’t eat so much junk food” – participant 74, “I ate more  
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40 268 vegetables and less chocolate” – participant 83). 5) The impact on shopping habits (“You  
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42 269 can’t get it all from supermarkets” – Participant 37; “Had to go to more individual food  
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44 270 shops” – participant 103).  
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### 50 272 **DISCUSSION**

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274 Exposure to the endocrine disrupting chemical Bisphenol A (BPA) is ubiquitous [2], with  
275 growing evidence that it may be associated with adverse health outcomes [4]. Here, 104  
276 researcher participants aged 17-19 years designed and undertook a quantitative and  
277 qualitative engaged research project designed to assess the potential for reduction of personal  
278 exposure to BPA through moderation of diet, which would have utility in a 'real world'  
279 setting.

280

281 Although levels of urinary BPA in our study cohort were slightly lower at the outset of the  
282 study in our cohort than in others [13], measureable levels were present in the vast majority  
283 of our participants. Participants were unable to achieve a reduction in their urinary BPA  
284 levels over the 7 day trial period, despite good compliance to supplied guidelines. Avoidance  
285 of BPA was not easily achieved on an individual level in our study population, with  
286 qualitative analysis indicating that participants experienced feelings of restriction and  
287 difficulties in sourcing BPA-free food due to inadequate labelling of foods and food  
288 packaging. This suggests that the intervention would be difficult to sustain in the longer term.

289

290 This work represents the largest group of unrelated participants in one of the highest exposure  
291 demographics to date, since previous work has focused on families and related individuals  
292 [11] [12], who may share common sources of BPA. Our intervention is a 'real world' diet,  
293 designed to a set of guidelines (such as reduction in the usage of tinned foods or foods with  
294 high levels of processing), rather than the strict, prescribed diets that have been used in other  
295 studies [11], which suggested that it was possible for participants to reduce their urinary BPA  
296 excretion by approximately 60% in a period of just 3 days [11]. In our self-designed, self-  
297 administered study this was unachievable. This may reflect the difficulty in identifying and

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3 298 sourcing foods free of BPA in our commercial environment. Finally, the qualitative thematic  
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5 299 analysis we carried out in our study has given an indication that adherence to even a 'real  
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7 300 world' BPA reduction diet with fewer restrictions and more choice over the longer term was  
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9 301 unlikely in our study population due to difficulties in identifying foodstuffs likely to contain  
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11 302 less BPA.

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17 304 BPA has a terminal half-life of 6 hours [10]. Spot samples may therefore not be as accurate as  
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19 305 continuous sampling strategies (24hr urine collection). However, recent studies suggest that  
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21 306 despite its short half-life, measurable BPA remains present for up to 43 hours post-fasting,  
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23 307 indicating non-food exposures or accumulation in body tissues such as fat [15]. We identified  
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25 308 no impact of time of sample collection on BPA levels in our sample set, in either creatinine-  
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27 309 adjusted or unadjusted data, indicating that our measurements were not influenced by time  
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29 310 since the last meal. Spot sampling as used here may therefore represent an acceptable  
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31 311 compromise and remains a practical option in the community setting of our study.

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38 313 Calculating an accurate BPA risk score is challenging. Data were self-reported, and  
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40 314 foodstuffs are not labelled for BPA content. It is difficult to generalise across food types and  
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42 315 large variations in BPA concentrations occur between different products of the same food  
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44 316 type or even different lots of the same product [1]. Foods that were free of BPA-containing  
45  
46 317 packaging (as far as it was possible to tell) may have been highly processed or contain food  
47  
48 318 items from a variety of sources. Highly processed and 'fast' food has previously been  
49  
50 319 demonstrated to be a source of BPA [16]. A study of the temporal trends seen in composite  
51  
52 320 food samples found no change in the overall BPA content of the food, despite large reduction  
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54 321 in the BPA content of some individual food items, illustrating the difficulties in effectively

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3 322 excluding BPA from a varied diet [17]. Participants may therefore have changed BPA  
4  
5 323 containing foods for other, perceived healthier choices, which may still contain BPA by  
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7 324 virtue of processing.  
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13 326 BPA enters foodstuffs by leaching from polycarbonate or epoxy resin after manufacture, or  
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15 327 by hydrolysis of the polymer itself [18]. The migration rate of BPA increases with higher  
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17 328 temperatures [19], and with time and use, e.g. repeated use of polycarbonate water bottles  
18  
19 329 [20]. Exposure to BPA can also occur through routes other than food, including dust  
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21 330 ingestion and dermal absorption [21] and this was not taken into account in our study. A  
22  
23 331 study of volunteers who purposefully handled thermal receipts showed an increase in urinary  
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25 332 BPA excretion of up to 84%, and their BPA levels took longer to return to pre exposure  
26  
27 333 levels, suggesting a difference in the bio-availability of BPA through skin and oral routes  
28  
29 334 [22]. We may also have been underpowered to detect subtle changes in urinary BPA, given  
30  
31 335 the heterogeneity in food choice; detection of such effects may need thousands of  
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33 336 participants. Finally, our study, like other studies of its type, does not take account of inter-  
34  
35 337 individual differences in the metabolism and excretion of BPA arising from differences in  
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37 338 genetic background between people. BPA is metabolised primarily by UDP-  
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39 339 glucuronosyltransferases, and altered activity polymorphisms of these enzymes have been  
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41 340 reported [23].  
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49 342 Emerging evidence suggests that that BPA may be linked to several chronic human health  
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51 343 conditions [24-28], suggesting that continued study of the human health effects of BPA  
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53 344 exposure is justified. The opinion of the European Food Safety Authority (EFSA), is that  
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55 345 whilst uncertainty over the human health effects of BPA exists, caution should be exercised  
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3 346 in ingestion of BPA [3]. Our data suggests that in our study population, it is unlikely that  
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5 347 participants could moderate their own BPA exposure in the long term by self-directed  
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7 348 modification of diet in a 'real world' setting, and furthermore, participants would have been  
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9 349 reluctant to adopt such a lifestyle change in the longer term due to the restrictions in dietary  
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11 350 choice and the effects on day to day life. Most of these barriers appear to arise from the  
12  
13 351 pervasiveness of BPA in our food chain, and inadequate labelling of foods packaged in BPA-  
14  
15 352 containing substances. We propose that until a definitive assessment of the health risks of  
16  
17 353 BPA is available, informed choice over whether or not to consume BPA and similar  
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19 354 chemicals in foodstuffs should be facilitated by better labelling.  
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## 356 **CONTRIBUTORSHIP STATEMENT**

357 TSG - Contributed to study design and co-wrote the paper

358 NB - Contributed to study design and participant involvement

359 BP - Managed the technical aspects of the project and reviewed the manuscript

360 ALC - Contributed to data entry and interpretation and reviewed the manuscript

361 BPA Schools Study Consortium members - designed and interpreted the study and  
362 contributed to the manuscript.

363 MHS - Carried out the qualitative analysis and reviewed the manuscript

364 AMS - Managed sample collection, contributed to study design and reviewed the manuscript.

365 LWH - PI , managed the study, wrote the manuscript

366

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8 370 collection of the urine samples.  
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## 13 14 372 **COMPETING INTERESTS**

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20 374 The authors have no competing interests to declare.  
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## 25 26 376 **DATA SHARING STATEMENT**

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29 377 Extra data is available upon reasonable request by emailing Lorna Harries  
30  
31 378 (L.W.Harries@exeter.ac.uk).  
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3 462 **FIGURE LEGENDS**  
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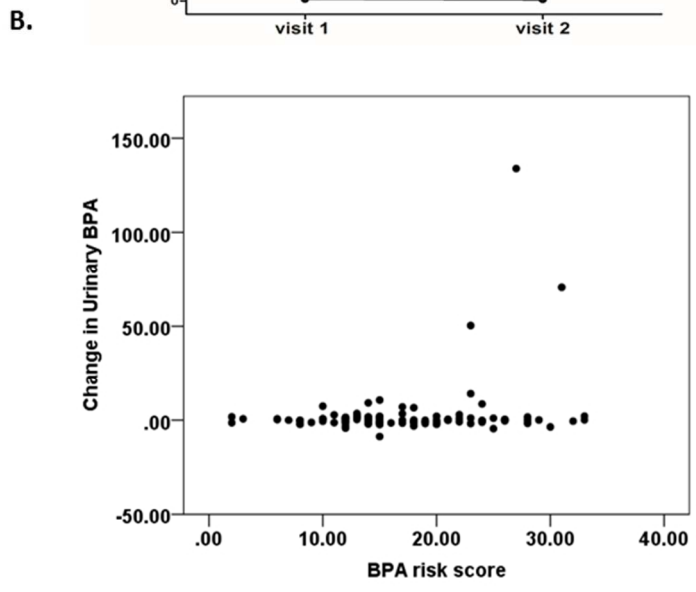
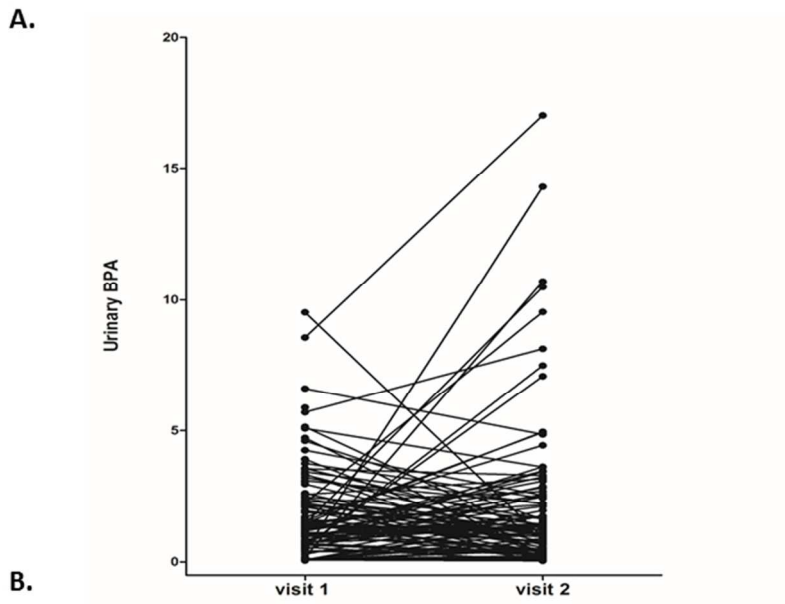
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9 464 **Figure 1. The effect of a ‘real world’ BPA avoidance diet on urinary BPA exposure over**  
10 **a 7 day period.** A. Urinary BPA levels (ng/ml) adjusted for urinary creatinine were plotted at  
11 465 visit 1 before the intervention and at visit 2 after the intervention. The 3 extreme outliers have  
12 466 been removed. The trajectories of individual participant measurements are shown. B. Change  
13 467 in urinary BPA levels in ng/ml following the intervention diet are plotted against the self-  
14 468 reported BPA risk score.  
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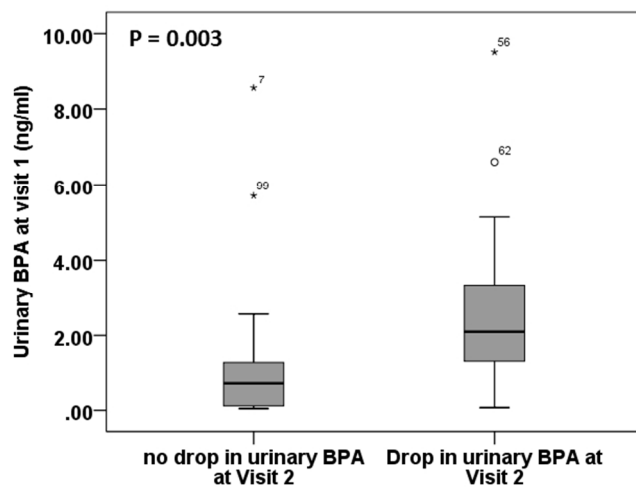
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26 471 **Figure 2. The effect of baseline urinary BPA on the probability of achieving a drop in**  
27 **levels following the intervention.** This graph illustrates the median urinary BPA level  
28 472 adjusted for creatinine at visit 1 prior to the intervention expressed relative to whether or not  
29 473 a reduction in urinary BPA levels was achieved following the 7 day intervention diet at visit  
30 474 2. Error bars refer to the interquartile range of measurement.  
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## BPA Myth and Reality Dietary Intervention Guidelines



### General instructions

The purpose of this dietary intervention trial is to follow a diet designed to minimise routes of exposure to the food packaging chemical bisphenol A (BPA). For the dietary intervention period, please follow as closely as possible the instruction given below. Try to maintain your diet during the intervention period to be as closely similar to your normal diet as possible, in terms of the content, amount and calorific value of the food you eat. Please record details of each meal and the drinks and snacks you consume on the forms provided. Below are some general cooking and eating tips and an indication of which foods are best to avoid and those that are considered a low source of BPA.

### Cooking and eating tips for the intervention period.

The general approach is to replace any food items that fall into the 'avoidance' category with an alternative, chosen to minimise exposure to BPA

- **Switch to stainless steel and glass food storage and drink containers.**
- **Move foods to ceramic or glass food containers before microwaving.**
- **Consider a coffee filter or percolator for coffee – home coffee makers (Such as Nespresso™) may have polycarbonate-based water tanks and phthalate-based tubing.**
- **Eat out less, especially at restaurants that do not use fresh ingredients.**
- **Avoid canned food consumption. Where possible, replace with fresh produce or cardboard or tetrapack packaged alternatives.**
- **Choose fresh fruits and vegetables when possible, and frozen if not.**
- **Soak dried beans for cooking rather than tinned.**

## Foods to avoid

**Tinned foods.** Top ten tinned foods that are reported to be sources of BPA include coconut milk, soup, meat, vegetables, meals (e.g. pasta with sauce), juice, fish, beans, meal replacement drinks, fruit.

**Carbonated/fizzy drinks and juices in cans.** Avoid carbonated drinks in cans and drinks stored for prolonged periods in reusable sports bottles, unless they are labelled 'BPA free' (many commercial sports bottles are).

**Fast food from commercial outlets.** Most processed food has passed through numerous processes, and each additional processing step provides an opportunity for BPA to enter through packaging or tubing. Try to replace fast and processed foods with a freshly prepared and cooked alternative.

**Packaged fruit and vegetables.** Replace these where possible with unpackaged, loose fruit and vegetable items as far as possible.

**Convenience/ready meals.** Plastics types considered safest in terms of chemical migration are recycling numbers 2 and 5. Avoid food prepared in packaging with recycling number 7, which includes many different types of polymer and mixed polymers, including polycarbonate, a source of BPA. Try to avoid foods that are designed to be heated in the microwave in their packaging.

**Chocolate and ice cream.** Individuals who report eating chocolate bars and ice cream on a regular basis have been reported to have higher than average BPA exposure. Try to avoid excessive consumption.

## Non-food or food packaging routes of exposure

Although plastics found in consumer goods such as DVDs, CDs, computer goods and sunglasses do contain BPA, this is not an important route of exposure.

Till receipts often contain high levels of BPA, so wash your hands before eating or drinking if you have been handling them.

Dental sealants may contain BPA, so avoid any pre-planned dental work

## Example daily diet

Food Item	Comments
<b>Breakfast</b>	
Cereal, Fruit	
Milk	Polypropylene or glass packaging
Bread	
Yoghurt	Choose polypropylene container
<b>Lunch</b>	
Meat or fish products	Check packaging and avoid those labelled no. 7. Avoid tinned ingredients
Cheese	
Salad items, Fruit	Choose unpackaged where possible, wash before use
Pasta	
<b>Dinner</b>	
Shepherds pie	Cooked in saucepan and oven rather than microwaved in plastic
Green beans	Fresh or frozen
Bread	
<b>Drinks</b>	
Water	Water direct from tap or use stainless steel or BPA free water bottle
Tea/coffee	Prepare in teapot or cafetiere, avoid commercial coffee makers
Carbonated drinks	Avoid canned drinks and those stored in reusable containers for prolonged periods
Milk	Polypropylene or glass packaging
<b>Snacks</b>	
Fruit	
Potato crisps	

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Place participant barcode here	FOOD - DAY 1		DRINK - DAY 1	
Contents of meal	Was food packaged in plastic known or suspected to contain BPA?	Was food cooked in plastic known or suspected to contain BPA?	Type of Drink	Packaging (please describe) e.g. canned, plastic ( $\Delta$ number), tetrapak
<b>Breakfast:</b>				
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<b>Lunch:</b>				
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<b>Dinner:</b>				
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<b>Snacks:</b>				
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Place participant barcode here	FOOD - DAY 2		DRINK - DAY 2	
Contents of meal	Was food packaged in plastic known or suspected to contain BPA?	Was food cooked in plastic known or suspected to contain BPA?	Type of Drink	Packaging (please describe) e.g. canned, plastic ( $\Delta$ number), tetrapak
<b>Breakfast:</b>				
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<b>Lunch:</b>				
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<b>Dinner:</b>				
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Place participant barcode here	FOOD - DAY 3		DRINK - DAY 3	
Contents of meal	Was food packaged in plastic known or suspected to contain BPA?	Was food cooked in plastic known or suspected to contain BPA?	Type of Drink	Packaging (please describe) e.g. canned, plastic (Δ number), tetrapak
<b>Breakfast:</b>				
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3.				
4.				
5.				
<b>Lunch:</b>				
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2.				
3.				
4.				
5.				
<b>Dinner:</b>				
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4.				
5.				
<b>Snacks:</b>				
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2.				
3.				
4.				

Place participant barcode here	FOOD - DAY 4		DRINK - DAY 4	
Contents of meal	Was food packaged in plastic known or suspected to contain BPA?	Was food cooked in plastic known or suspected to contain BPA?	Type of Drink	Packaging (please describe) e.g. canned, plastic ( $\Delta$ number), tetrapak
<b>Breakfast:</b>				
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3.				
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5.				
<b>Lunch:</b>				
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<b>Dinner:</b>				
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<b>Snacks:</b>				
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Place participant barcode here	FOOD - DAY 5		DRINK - DAY 5	
Contents of meal	Was food packaged in plastic known or suspected to contain BPA?	Was food cooked in plastic known or suspected to contain BPA?	Type of Drink	Packaging (please describe) e.g. canned, plastic ( $\Delta$ number), tetrapak
<b>Breakfast:</b>				
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<b>Lunch:</b>				
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<b>Dinner:</b>				
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<b>Snacks:</b>				
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Place participant barcode here	FOOD - DAY 6		DRINK - DAY 6	
Contents of meal	Was food packaged in plastic known or suspected to contain BPA?	Was food cooked in plastic known or suspected to contain BPA?	Type of Drink	Packaging (please describe) e.g. canned, plastic ( $\Delta$ number), tetrapak
<b>Breakfast:</b>				
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<b>Lunch:</b>				
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<b>Dinner:</b>				
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<b>Snacks:</b>				
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Place participant barcode here	FOOD - DAY 7		DRINK - DAY 7	
Contents of meal	Was food packaged in plastic known or suspected to contain BPA?	Was food cooked in plastic known or suspected to contain BPA?	Type of Drink	Packaging (please describe) e.g. canned, plastic ( $\Delta$ number), tetrapak
<b>Breakfast:</b>				
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<b>Lunch:</b>				
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5.				
<b>Dinner:</b>				
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3.				
4.				
5.				
<b>Snacks:</b>				
1.				
2.				
3.				
4.				

**Participant barcode****Additional study information.**

Please do not feel obliged to answer these questions if you are uncomfortable doing so.

**Gender**

- Female  
 Male  
 Prefer not to say

**Tobacco Usage** – Have you used tobacco over the past week

- Yes  
If so, what type and how much? \_\_\_\_\_  
 No  
 Prefer not to say

**Alcohol Usage** – Have you used alcohol over the past week

- Yes  
If so, what type and how much? \_\_\_\_\_  
 No  
 Prefer not to say

**Medication**- Have you taken any medication over the last week?

- Yes  
 No  
 Prefer not to say

If so, Please name the medication \_\_\_\_\_  Prefer not to say

**Vegetarian/vegan diet** - Have you eaten or drank any soya products over the past week?

- Yes  
 No  
 Prefer not to say

**Your measurements** - leave blank if you prefer not to say

Your height \_\_\_\_\_

Your weight \_\_\_\_\_

Participant Barcode

## BPA: Myth and Reality diet questionnaire

1. Were there any times during the week that you knowingly/unknowingly did not stick to the diet? Please tick any that apply and give indication of frequency.

- School meals  \_\_\_ times
- Restaurants/cafés  \_\_\_ times
- Friends' houses  \_\_\_ times
- Takeaway  \_\_\_ times
- Other \_\_\_\_\_  \_\_\_ times

2. If you heated your food in a microwave, what was the food in? Tick any which apply and give indication of frequency.

- A food storage container or bowl known or suspected to contain BPA  \_\_\_ times

3. When you or your family drank water, where did your water come from? Tick any which apply and give indication of frequency.

- Plastic filter jug known or suspected to contain BPA  \_\_\_ times
- Individual water bottle known or suspected to contain BPA  \_\_\_ times
- Larger water container known or suspected to contain BPA  \_\_\_ times

4. How many times during the week did you eat food that had been stored or transported in plastic containers known or suspected to contain BPA?

\_\_\_\_\_

5. How many times during the week did you eat tinned food or drink from cans?

\_\_\_\_\_

6. Did the BPA reduced diet affect How much you spent on shopping?

- Spent more
- Spent less
- No difference

Participant questionnaire V3 25Jun15

Participant Barcode

1  
2  
3  
4  
5 **7. Did it take longer to source your food than usual?**

6 Yes  No

7  
8 If so, why? \_\_\_\_\_

9  
10  
11 \_\_\_\_\_

12  
13  
14  
15 **8. Did it take longer to prepare food than usual?**

16 Yes  No

17  
18 If so, why? \_\_\_\_\_

19  
20  
21 \_\_\_\_\_

22  
23  
24  
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26  
27 **9. How restricted did you feel by your food choice?**

28  
29  
30  Very  Slightly  No difference

31  
32 If you felt you were restricted by the diet, why was this? \_\_\_\_\_

33  
34  
35  
36  
37 \_\_\_\_\_

38  
39  
40  
41 **10. Did the diet affect your calorific intake?**

42  
43  
44  
45 Yes  No

46  
47 If so, why? \_\_\_\_\_

48  
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56  
57  
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59  
60 \_\_\_\_\_

Participant questionnaire V3 25Jun15

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

Participant Barcode

11. How easy would you find it to sustain this diet over a longer period of time?

- Very easy
- Easy
- Hard
- Very hard
- Not sure

12. Is there anything else about following the diet that you would like to add?



Thank you for reading this leaflet. If you wish to participate in this study, you will be asked to agree to the consent statements below in the presence of a member of the research team.

## CONSENT STATEMENTS

1. I confirm that I have read this information sheet and have discussed participation in this project with my family. I have had opportunity to consider the information, ask questions and have had these questions answered satisfactorily. *You should not give consent until you are happy that you understand what the study involves.*
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my right to participate in the rest of the study being affected. *This means that even if you helped design this study you do not have to be a participant and you should not feel under any pressure to participate.*
3. I agree to participate in this study as a research subject. *This means that you agree to participate in a one-week diet and to provide two blood and urine samples.*
4. I understand that my anonymised blood and urine samples and linked anonymous questionnaire data will be sent to University of Exeter Medical School, Royal Devon & Exeter Hospital and my urine sample only will be sent to the Rolvaintain laboratory, a specialist BPA analysis company. *This means that laboratory staff will not know that samples belong to you, but dedicated staff at the University of Exeter, with training and experience in data protection, will be able to link your sample data to your questionnaire data.*
5. I understand that RNA (genetic material) will be extracted from my blood and will be stored anonymously. *This means that Professor Harries' team will use our RNA to provide data that you will help analyse but may also do further research on the samples to identify reasons for any changes seen.*
6. I understand that data relating to my participation in the study will be returned anonymously to my school to be used for educational purposes. *This means that although you will get to analyse data from your samples there is no way you will know which data relates to your samples and which to other participants.*

### Complaints:

If you have any complaints about the way in which this study has been carried out please contact the Chair of the University of Exeter Medical School Research Ethics Committee Peta Foxall PhD, Chair, UEMS Research Ethics Committee: P.J.D.Foxall@exeter.ac.uk.

This project has been reviewed and approved by the University of Exeter Medical School Research Ethics committee UEMS REC REFERENCE NUMBER: 15/07/074)

## BPA: Myth or Reality?

A research study investigating the effect of chemicals in plastic on gene activity and whether dietary interventions can reduce BPA levels in teenagers.



### Involvement & Engagement

The aim of this year-long project is to involve teenagers in a research study that is relevant to them, by allowing them to help design a research project, analyse non-identifiable participant data and help to present and publish the outcomes.

### Participation

Students will be asked to undertake a one week diet to reduce their intake of BPA, a chemical found in plastics. They will be asked to provide urine and blood samples before and after their diet.

Supported by  
**wellcome**trust

UNIVERSITY OF  
**EXETER** MEDICAL SCHOOL

**NHS**  
National Institute for  
Health Research



## What is BPA?

BPA (Bisphenol A) is a chemical used in the manufacture of plastics. Plastics containing BPA are found in a wide range of products including food and drink containers. BPA in these products can be ingested and there are concerns that high BPA levels in the blood could possibly affect human health. Research is therefore needed to understand its effects on the human body and how we can reduce its consumption by minor changes to our diet.



This project is being run as a student-involvement project to answer two specific questions:

1. Can we see the effects of dietary BPA on our genes?
2. Can we effectively reduce BPA in our diet?

In the past, small-scale experiments have shown that BPA levels in the human body can be reduced by rigid dietary interventions but these interventions would be difficult to implement in the "real world". In this study a one-week dietary intervention designed by teenagers will be used by them to determine whether BPA levels, and the activity of BPA-responsive genes can be effectively reduced in young people by avoiding food packaging that contains this chemical.

## What will I need to do?

### Day 1

- Provide a nurse with a 2.5ml blood sample and a urine sample.

### Day 2 - Day 8

- Follow a diet that you have helped to design.
- The diet will exclude sources of BPA as much as possible but will be nutritionally and calorifically similar to your usual diet.
- You will be asked to complete a food diary and answer a questionnaire about how easy it was to follow this diet.

### Day 8

- Provide a nurse with a 2.5ml blood sample and a urine sample.

**We recommend that you discuss the project with your family and involve them in planning what you eat and how you will prepare it.**



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## What will happen to my samples and data?

When you participate in the study you will be allocated with a numerical study ID. Your samples and data will be labelled with this number so that we can match your 'before' and 'after' diet samples with your food diary data. Once all data has been collated and coded it will be further anonymised by a person external to the project so that no data can be linked to any of the participants.



Urine samples from before and after the diet will be sent to the Royal Devon & Exeter NHS Foundation Trust for creatinine analysis and to the Royal Devon & Exeter Molecular Genetics Laboratory for BPA analysis. RNA will be extracted from blood samples at the Royal Devon & Exeter Molecular Genetics Laboratory and the expression levels of two BPA-responsive genes will be measured in the samples taken before and after the diet. These anonymised RNA samples will be stored and used only by Professor Harries team for further research on the mechanisms behind our findings.

## What are the benefits of taking part?

This project will help you to understand how you might be able to reduce BPA in your diet and your involvement in the design will give you an excellent insight into clinical research, community outreach and scientific practise. Your role as a participant is unlikely to have any direct health benefits.



## Are there any risks intaking part?

Blood samples will be taken by fully qualified and insured NHS personnel. Any potential discomfort or side-effects will be equivalent to that experienced giving a blood sample to your GP. All data will be fully anonymised before analysis. This means that you will not find out anything about your blood or urine samples. Following the diet may minimally increase the cost of your groceries for the week, but since fresh foods are usually less expensive than pre-packaged foods, we do not expect this to be an issue.



## What will happen to the results of the research study?

You will be given the opportunity to help analyse anonymised data from this project and to help disseminate the outcomes of this research. It is hoped that the findings will be published in peer-reviewed journals and the wider media.

## Who is organising this research?

The research is organised by Professors Lorna Harries & Tamara Galloway of the University of Exeter as part of their research program into BPA and part of the University's outreach program to involve schools in academic research.

Version 4 (2/8/2015)

BPA: Myth & Reality

STUDY ID

CONSENT STATEMENTS		Please circle
1. I confirm that I have read information sheet BPA PIS Version 4 and have discussed participation in this project with my family. I have had opportunity to consider the information, ask questions and have had these questions answered satisfactorily. <i>You should not give consent until you are happy that you understand what the study involves.</i>		YES / NO
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without right to participate in the rest of the study being affected. <i>This means that even if you helped design this study you do not have to be a participant and you should not feel under any pressure to participate.</i>		YES / NO
3. I agree to participate in this study as a research subject. <i>This means that you agree to participate in a one-week diet and to provide two blood and urine samples.</i>		YES / NO
4. I understand that my anonymised blood and urine samples and linked anonymous questionnaire data will be sent to University of Exeter Medical School, Royal Devon & Hospital and my urine sample only will be sent to the Rolvaintain laboratory, a specialist BPA analysis company. <i>This means that laboratory staff will not know that samples belong to you, but dedicated staff at the University of Exeter, with training and experience in data protection, will be able to link your sample data to your questionnaire data.</i>		YES / NO
5. I understand that RNA (genetic material) will be extracted from my blood and will be stored anonymously. <i>This means that Professor Harries' team will use our RNA to provide data that you will help analyse but may also do further research on the samples to identify reasons for any changes seen.</i>		YES / NO
6. I understand that data relating to my participation in the study will be returned anonymously to my school to be used for educational purposes. <i>This means that although you will get to analyse data from your samples there is no way you will know which data relates to your samples and which to other participants.</i>		YES / NO
Name of Participant	Signature	Date
Name of Person Obtaining Consent	Signature	Date
I the above signed testify the participant is providing voluntary and fully informed consent to participate in this study. I am on the delegation log to obtain consent for this study and are trained in obtaining consent.		
This project has been reviewed and approved by the University of Exeter Medical School Research Ethics Committee UEMS REC REFERENCE NUMBER: 15/07/074)		

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

	Item No	Recommendation
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found  <b>a) Page 1</b> <b>b) Page 2</b>
<b>Introduction</b>		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported  <b>Page 6, line 82</b>
Objectives	3	State specific objectives, including any prespecified hypotheses  <b>Page 7, line 113</b>
<b>Methods</b>		
Study design	4	Present key elements of study design early in the paper  <b>Page 8, line 140</b>
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection  <b>Page 8, line 152</b>
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up  <b>Page 7, line 123</b>  <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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants <hr/> (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable  Page 7, line 140, Page 8, line 152.

1 2 3 4 5 6 7 8 9	Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group  <b>Page 8, line 140, Page 8, line 152</b>
10 11 12 13 14	Bias	9	Describe any efforts to address potential sources of bias  <b>Page 8, line 154, page 9 line 165</b>
15 16 17 18	Study size	10	Explain how the study size was arrived at  <b>Page 7, line 127</b>
19 20 21 22 23 24	Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why  <b>Page 9, line 157</b>
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	Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding  <b>Page 9, line 170</b>  (b) Describe any methods used to examine subgroups and interactions  <b>Page 9, line 175</b>  (c) Explain how missing data were addressed  <b>Page 9, line 164</b>  (d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed  <b>Page 12, line 206</b>  <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed  <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy  (e) Describe any sensitivity analyses  N/A

Continued on next page

**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>Table 1</b>
		(b) Give reasons for non-participation at each stage
		<b>Page 12, line 206</b>
		(c) Consider use of a flow diagram
		N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		<b>Table 1</b>
		(b) Indicate number of participants with missing data for each variable of interest
		<b>Table 1</b>
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)
		<b>Page 9, line 172</b>
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time
		<b>Table 1</b>
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures
Main results	16	(a) 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
		<b>Page 12, line 213 to page 13 line 229</b>
		(b) Report category boundaries when continuous variables were categorized
		<b>Page 9, line 176</b>
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful

1  
2 time period  
3

4 N/A  
5

---

6 Other analyses 17 Report other analyses done—eg analyses of subgroups and interactions, and sensitivity  
7 analyses  
8

9  
10 **Page 13, line 234**  
11

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## 12 Discussion

13  
14 Key results 18 Summarise key results with reference to study objectives  
15

16 **Page 15, line 276**  
17

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18 Limitations 19 Discuss limitations of the study, taking into account sources of potential bias or imprecision.  
19 Discuss both direction and magnitude of any potential bias  
20

21 **Page 16, line 298**  
22

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23 Interpretation 20 Give a cautious overall interpretation of results considering objectives, limitations, multiplicity  
24 of analyses, results from similar studies, and other relevant evidence  
25

26 **Page 17, line 334**  
27

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28 Generalisability 21 Discuss the generalisability (external validity) of the study results  
29

30 **Page 18, line 344**  
31

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## 32 Other information

33 Funding 22 Give the source of funding and the role of the funders for the present study and, if applicable,  
34 for the original study on which the present article is based  
35

36 **Page 19, line 374**  
37

38 \*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and  
39 unexposed groups in cohort and cross-sectional studies.  
40

41  
42 **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and  
43 published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely  
44 available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at  
45 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is  
46 available at [www.strobe-statement.org](http://www.strobe-statement.org).  
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# BMJ Open

## An engaged research study to assess the effect of a 'real-world' dietary intervention on urinary bisphenol A (BPA) levels in teenagers

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-018742.R1
Article Type:	Research
Date Submitted by the Author:	23-Aug-2017
Complete List of Authors:	Galloway, Tamara; University of Exeter, College of Life and Environmental Sciences Baglin, Nigel; Research Projects Lee, Benjamin; University of Exeter Medical School, Institute of Biomedical and Clinical Studies Kocur, Anna; University of Exeter Medical School, Institute of Biomedical and Clinical Studies Shepherd, Maggie; Royal Devon and Exeter National Health Service Foundation Trust, National Institute for Health Research Exeter Clinical Research Facility Steele, Anna; Royal Devon and Exeter National Health Service Foundation Trust, National Institute for Health Research Exeter Clinical Research Facility BPA Schools, Study Consortium; University of Exeter Medical School, Institute of Biomedical and Clinical Studies Harries, Lorna; University of Exeter Medical School, Institute of Biomedical and Clinical Studies
<b>Primary Subject Heading</b>:	Public health
Secondary Subject Heading:	Communication
Keywords:	Bisphenol A, Dietary intervention, PUBLIC HEALTH, community, Engaged research

SCHOLARONE™  
Manuscripts

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2  
3 1 An engaged research study to assess the effect of a 'real-world' dietary  
4  
5 2 intervention on urinary bisphenol A (BPA) levels in teenagers  
6  
7

8 3 Tamara. S. Galloway<sup>1</sup>, Nigel Baglin<sup>2</sup>, Benjamin P Lee<sup>3</sup>, A.L. Kocur<sup>3</sup>, M.H. Shepherd<sup>4</sup>, A.M.  
9 4 Steele<sup>4</sup>, BPA schools study consortium<sup>#</sup> and L.W. Harries<sup>3</sup>  
10  
11

12  
13  
14 5 <sup>1</sup>College of Life and Environmental Sciences, University of Exeter, Exeter UK EX4 4AS.

15 6 <sup>2</sup>Research Projects, Exeter, UK, EX2 5DQ.

16 7 <sup>3</sup>RNA-Mediated Disease Mechanisms group, Institute of Biomedical and Clinical Sciences,  
17 8 University of Exeter Medical School, University of Exeter, Exeter, UK EX2 5DW.

18 9 <sup>4</sup>National Institute for Health Research Exeter Clinical Research Facility, Royal Devon and  
19 10 Exeter National Health Service Foundation Trust, and University of Exeter Medical School,  
20 11 Exeter, U.K.  
22

23 12 <sup>#</sup> Consortium members listed in supplementary information file 1  
24  
25

26  
27 14 **Word count 3021**  
28  
29

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43 24 **Declaration of competing issues**  
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45

46 25 The authors have no competing interests to declare.  
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## 27 ABSTRACT

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### 29 **Objective**

30 Bisphenol A has been associated adverse human health outcomes and exposure to this  
31 compound is near-ubiquitous in the Western world. We aimed to examine whether self-  
32 moderation of BPA exposure is possible by altering diet in a real-world setting.

### 33 **Design**

34 An Engaged Research dietary intervention study designed, implemented and analysed by  
35 healthy teenagers from 6 schools and undertaken in their own homes.

### 36 **Participants**

37 104 students aged between 17 and 19 years from schools in the South West of the UK  
38 provided diet diaries and urine samples for analysis.

### 39 **Intervention**

40 Researcher participants designed a set of literature-informed guidelines for reduction of  
41 dietary BPA to be followed for 7 days.

### 42 **Main outcome measure**

43 Creatinine-adjusted urinary BPA levels were taken before and after the intervention.  
44 Information on packaging and food/drink ingested was used to calculate a BPA risk score for  
45 anticipated exposure. A qualitative analysis was carried out to identify themes addressing  
46 long term sustainability of the diet.

### 47 **Results**

1  
2  
3 48 BPA was detected in urine of 86% of participants at baseline at a median value of 1.34 ng/ml  
4  
5 49 (IQR 1.82). No effect of the intervention diet on BPA levels was identified overall ( $p = 0.25$ ),  
6  
7 50 but there was a positive association in those participants who showed a drop in urinary BPA  
8  
9 51 concentration post intervention and their initial BPA level ( $p = 0.003$ ). Qualitative analysis  
10  
11 52 identified themes around feelings of lifestyle restriction and the inadequacy of current  
12  
13 53 labelling practices.

## 14 15 16 54 **Conclusions**

17  
18  
19 55 We found no evidence in this self-administered intervention study that it was possible to  
20  
21 56 moderate BPA exposure by diet in a real world setting. Furthermore, our study participants  
22  
23 57 indicated that they would be unlikely to sustain such a diet long term, due to the difficulty in  
24  
25 58 identifying BPA-free foods.

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2  
3 60 **Article Summary**  
4

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7 62 *Strengths of the study*  
8

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- 10  
11 64 • This study represents the largest assessment to date of the potential for moderating  
12 one's own BPA exposure through diet  
13  
14  
15 66 • The study was carried out in a 'real-world' setting rather than a regulated, controlled  
16 environment.  
17  
18  
19  
20 68 • The study was carried out in teenagers, the demographic with amongst the highest  
21 exposure.  
22  
23  
24 70 • Qualitative analysis reveals challenges with sustaining such a diet.  
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27 71 *Limitations of the study*  
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- 29  
30 72 • Calculation of a risk score is challenging due to the pervasive nature of BPA  
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## 75 INTRODUCTION

76

77 Bisphenol A is one of the world's highest production volume chemicals. It is used in the  
78 manufacture of polycarbonate and other plastic consumer products, in heat resistant papers,  
79 dental sealants and in the epoxy resin-based lining of food and drink containers [1]. BPA can  
80 be found above the detection limit in the urine of the majority of people worldwide [2].  
81 Concern has been raised for public health, since BPA is classified as an endocrine disrupting  
82 chemical (EDC) which has been linked with several disorders in cell and animal models [3-  
83 5]. Several epidemiological studies have also linked outcomes such as type 2 diabetes,  
84 cardiovascular disease, obesity and abnormalities of sex hormone levels with BPA levels in  
85 human populations [6-10] Epidemiological data in humans has historically been more  
86 contentious however, due to relatively small sample sizes and issues around causality [11].  
87 The Endocrine Society concluded in 2015 that current evidence suggests that BPA and other  
88 endocrine disrupting chemicals may have effects on several reproductive, cardiovascular and  
89 metabolic traits in humans [12]. The current opinion of food regulatory bodies such as the  
90 European Food Standards Agency (EFSA) is that sufficient uncertainty remains to be able to  
91 exclude effects on the reproductive, immune, nervous, metabolic and cardiovascular systems  
92 and on cancer development [3] whilst the European Chemicals Agency (ECHA) has recently  
93 reclassified BPA as a chemical of very high concern due to its endocrine disrupting properties  
94 [13].

95

96 There has been wide interest in the sources of BPA and the potential for individuals to reduce  
97 their own exposure. Human exposure has been reported from inhalation of dust, uptake  
98 across the skin from thermal papers and till receipts and release from dental sealants. The  
99 main source is the ingestion of food and drink contaminated with BPA leached from

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3 100 packaging materials [1, 14]. BPA is rapidly metabolised in the gut wall and liver and  
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5 101 removed from the blood by the kidneys, with a terminal half-life of 6 hours after oral  
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7 102 ingestion [15]. BPA has been detected in food samples packaged in glass, plastic, paper and  
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9 103 paperboard cartons, with an average concentration of 0.46 ng/g, rising to over 700 ng/g for  
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11 104 certain canned foods. Conversely, in a dietary intervention study in which 22 volunteers  
12  
13 105 consumed a 3 day fresh food diet which excluded canned or packaged foods, there was a 66%  
14  
15 106 reduction in urinary BPA excretion compared to concentrations before the intervention [16].  
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17 107 This latter study involved full dietary replacement of foodstuffs, an approach which is  
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19 108 impractical for the population at large. A follow up study found that households who  
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21 109 followed written recommendations produced by health care professionals showed no  
22  
23 110 significant change in their BPA exposure [17].  
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30 112 We present an alternative, citizen-science based approach, where 104 student volunteers  
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32 113 designed and undertook their own intervention diet, following provision of educational  
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34 114 materials. We questioned whether adherence to a self-designed and self-administered 'real  
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36 115 world' diet over 7 days would lead to significant reductions in excreted urinary BPA, and if  
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38 116 so, whether such a diet was likely to be sustainable in the long term.  
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## 44 118 **METHODS**

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### 46 120 **Participant group**

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48 122 We chose adolescents because they represent a demographic with high BPA exposure  
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50 123 (aggregated exposure of 1.449 µg/kg body weight per day) [3, 18]. 124 students aged 17-19  
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52 124 from local schools were initially invited to participate in this engaged research project, of  
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3 125 which 104 signed up to take part in some form. 94 individuals provided information and  
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5 126 samples at both visit one and visit 2 and comprise the complete dataset. This represents the  
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7 127 largest intervention study in the population demographic with the highest BPA exposure to  
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9 128 date [18]. Study size was arrived upon based on anticipated effect sizes from previous work  
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11 129 of this nature [16], and we allowed for a 10% dropout rate. Students designed all of the  
12  
13 130 materials required for completion of the study (study protocols, food diaries, lifestyle  
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15 131 questionnaires, patient information sheets and consent forms (see Supplementary Information  
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17 132 files 2 to 6).  
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### 134 **Ethical Permission**

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29 136 Ethical permission was granted by the University of Exeter Medical School Ethics  
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31 137 Committee (reference number 15/07/074) and the study was carried out in accordance with  
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33 138 the Declaration of Helsinki.  
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### 140 **The intervention diet**

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43 142 Students designed a “real world” diet designed to reduce consumption of BPA by avoidance  
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45 143 of processed foods and foods packaged in known sources of BPA [1, 14]; supplementary  
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47 144 information file 2). The study was designed at the University of Exeter as a collaboration  
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49 145 between academic staff and participating students and was developed at a series of interactive  
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51 146 workshops attended by all parties.  
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3 148 Students were asked to minimise their intake of known sources of BPA according to a set of  
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5 149 guidelines that had been co-designed with them based on the known literature. We requested  
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7 150 that calorific intake was maintained as near to their usual diet as possible and recorded details  
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9 151 of their daily diet including all food and drink, and its associated packaging, in a self-reported  
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11 152 food diary (Supplementary information file 3). Adherence was assessed using a 'BPA risk  
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13 153 score' based on instances of known or suspected exposure for each participant was then  
14  
15 154 calculated, whereby each individual incidence of potential BPA exposure was given a score  
16  
17 155 of 1. These scores were collated at the end of the 7 day trial to give a final risk score. Risk  
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19 156 scores from the final day of the intervention only were also considered, since the half-life of  
20  
21 157 BPA means that this is most relevant to the sample collected at visit 2. Information on  
22  
23 158 lifestyle factors including sex, BMI and time of urine collection was also collected  
24  
25 159 (Supplementary information file 4). We recognised that there may be a temptation for  
26  
27 160 students to change their diets before the trial based on their new learning. To avoid this,  
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29 161 students were also specifically asked not alter their diet before the intervention.  
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### 163 **Sample collection and measurement of urinary BPA**

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40 165 Urine samples were collected into BPA-free bottles (Vacutest Kima, Italy) immediately  
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42 166 before and after the intervention, and were frozen at -20°C within 4 hours. Each participant  
43  
44 167 was sampled twice, once at visit 1 before the intervention and once at visit 2 after the  
45  
46 168 intervention. Sample collections were staggered to allow for the large number of participants  
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48 169 passing through the facility, but students were sampled during the same time slot at both  
49  
50 170 visits to account for circadian variation in BPA metabolism. The initial samples were  
51  
52 171 collected during the early part of the day just prior to the students commencing the trial. The  
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54 172 second samples were taken over the same time period 7 days later, just prior to the students  
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173 recommencing their usual diet. Samples were transported on dry ice to a commercial  
174 laboratory (Rovaltain Research Company, Aixain, France) where analysis of total BPA was  
175 assessed by gas chromatography-tandem mass spectrometry. Experimental methods were  
176 validated for linearity, detection limit and accuracy and specificity of quantification based on  
177 the Standard NF T 90-201 for determination of xenobiotics. A quality control check of  
178 known standards injected every 6 samples at two levels of concentration (0.5 ng/ml and 5  
179 ng/ml) was quantified with each batch of unknown samples. Water-only samples were  
180 included as negative controls. Urinary creatinine was measured at the Royal Devon and  
181 Exeter Hospital using the Jaffe method on the Roche P800 platform (Roche, Mannheim,  
182 Germany), to allow correction for urine dilution. Results were expressed as a BPA:creatinine  
183 ratio. Samples where BPA was detected but quantifying at or around the limits of  
184 quantification (LoQ) of 0.1ng/ml were scored as  $LoQ/\sqrt{2}$  according to the method of Hornung  
185 and Reed [19].

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### 187 **Statistical Analysis**

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189 The difference between urinary BPA adjusted for creatinine between samples taken at visits 1  
190 and 2 was assessed to generate a  $\Delta$ BPA continuous variable. BPA risk scores were calculated  
191 as a continuous variable. The relationship between urinary BPA levels before and after the 7  
192 day intervention was assessed using a repeated-measure ANOVA, adjusted for sex, time of  
193 sampling and BMI, with and without correction for creatinine. The relationship between  
194 urinary BPA at visit 1 and whether or not the participants had lower BPA at visit 2 was also  
195 examined by binary logistic regression, adjusted for sex, time of sampling and BMI. Here,  
196 samples showing small changes  $< 0.5$ ng/ml in either direction were omitted to avoid natural  
197 stoichiometric variation around zero. The relationship between change in BPA ( $\Delta$ BPA) and

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3 198 BPA risk score was assessed by linear regression, adjusted for sex, time of sampling and BMI  
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5 199 both with and without adjustment for creatinine. Statistical analysis was carried out using  
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7 200 SPSS, v.22 (IBM, USA).  
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## 11 202 **Impact of following reduced BPA diet on lifestyle**

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16 204 We carried out quantitative and qualitative analysis to address long-term sustainability of the  
17  
18 205 diet. Data on the impact of following the diet on feelings of dietary restriction, time spent  
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20 206 sourcing or preparing meals, calorific intake and long term sustainability were collected via a  
21  
22 207 questionnaire (See Supplementary information file 4). The questionnaire also included a  
23  
24 208 freeform section where participants could write about their experiences following the diet in a  
25  
26 209 non-prescribed fashion for qualitative analysis. Qualitative data was assessed for thematic  
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28 210 content by two experienced qualitative researchers. Key themes were independently  
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30 211 identified and coded until agreement was reached.  
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## 34 213 **RESULTS**

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### 36 215 **Participant Characteristics**

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41 217 There were 104 volunteer participants in this engaged research study. A total of 104 students  
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43 218 participated in the intervention, but a small number were absent or unable to produce a urine  
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45 219 sample at both visits. A complete dataset was received from 94 students. Information on the  
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47 220 characteristics of the study cohort are given in table 1.  
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**Table 1: Characteristics of the study population.** A complete dataset was available on 94 out of 104 participants. IQR = interquartile range, SD = Standard deviation. The units of BPA are ng/ml and BMI is defined as Kg/m<sup>2</sup>. LoQ = limit of quantification. Urinary BPA levels are given both as unadjusted data and as a BPA (ng/ml) to creatinine (mg/ml) ratio.

<b>Unadjusted urinary BPA at visit 1 (n = 98)</b>	
median (IQR)	1.37 (2.52)
95% confidence intervals	1.58 to 2.57
mean (SD)	2.07 (2.51)
Number of samples below LoQ (0.1ng/ml)	16
Minimum value (ng/ml)	0.07
Maximum value (ng/ml)	13.55
<b>Creatinine-adjusted urinary BPA at visit 1 (n = 98)</b>	
median (IQR)	1.34 (1.82)
95% confidence intervals	1.38 to 2.13
mean (SD)	1.75 (1.82)
Number of samples below LoQ (0.1ng/ml)	16
Minimum value (ng/ml)	0.05
Maximum value (ng/ml)	9.52
<b>Unadjusted urinary BPA at visit 2 (n = 99)</b>	
median (IQR)	1.91 (2.68)
95% confidence intervals	2.15 to 4.56
mean (SD)	3.35 (6.18)
Number of samples below LoQ (0.1ng/ml)	12
Minimum value (ng/ml)	0.07
Maximum value (ng/ml)	49.6
<b>Creatinine-adjusted urinary BPA at visit 2 (n = 99)</b>	
median (IQR)	1.31 (2.24)
95% confidence intervals	1.46 to 8.34
mean (SD)	4.90 (16.8)
Number of samples below LoQ (0.1ng/ml)	12
Minimum value (ng/ml)	0.04
Maximum value (ng/ml)	139.33
<b>Unadjusted ΔBPA (n = 94)</b>	
median (IQR)	0.14
95% confidence intervals	0.15 to 2.41
mean (SD)	1.28 (5.79)
Minimum value	-8.02
Maximum value	49.5
<b>Adjusted ΔBPA (n = 94)</b>	
median (IQR)	0.02 (2.61)
95% confidence intervals	-0.23 to 6.53
mean (SD)	3.15 (16.5)
Minimum value	-8.6



Maximum value	133.45
<b>BPA risk score (n = 99)</b>	
median (IQR)	15.0 (10.3)
95% confidence intervals	15.5 to 18.4
mean (SD)	17.0 (7.12)
<b>Demographics (n= 99)</b>	
Sex - % male	44
Exposure to estrogens - % of cohort	14
BMI- median (IQR)	20.7 (3.45)
BMI- mean (SD)	21.2 (3.07)

226

227 BPA was detected in the urine of 86% of subjects at visit 1 prior to the intervention. Missing  
 228 samples were due to non-attendance of participants or non-provision of a suitable sample.  
 229 Samples below the limit of quantification were scored as 0.07 ng/ml (LoQ/ $\sqrt{2}$ ).

230

231 **Creatinine-adjusted urinary BPA concentrations do not change significantly after**  
 232 **following an intervention diet designed to reduce BPA exposure for 7 days.**

233

234 The median change in creatinine-adjusted urinary BPA between visits ( $\Delta$ BPA) was 0.02  
 235 ng/ml with an interquartile range of 2.61 ng/ml. We identified no changes in urinary BPA  
 236 between visits ( $p = 0.25$ ; figure 1a). 3 outliers with very high urinary BPA readings at visit 2  
 237 were excluded from the analysis, since these samples lay outside the linear range of analysis,  
 238 so confidence in quantification was poor. No confounding factors included in the analysis  
 239 were associated with change in BPA ( $p = 0.78, 0.43$  and  $0.36$  for sex, time of sample  
 240 collection and BMI respectively). We also identified no change in BPA levels between visits  
 241 using data uncorrected for creatinine ( $p = 0.20$ ). We also assessed whether participants from  
 242 different schools showed variable BPA levels at either visit 1, or change in BPA, but no such  
 243 effects were noted.

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3 245 Similarly, no relationship between change in urinary BPA ( $\Delta$ BPA) and BPA risk score was  
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5 246 identified (beta coefficient 0.08, standard error 0.07,  $p = 0.55$ ; figure 1b). No associations  
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7 247 were noted between change in urinary BPA and BPA risk score in data not adjusted for  
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9 248 creatinine ( $p = 0.27$ ). We found no association between  $\Delta$ BPA and BPA risk score when  
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11 249 considering only the exposure on the day prior to testing, taking into account the short half-  
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13 250 life of BPA ( $p = 0.16$  and  $p = 0.33$  for adjusted and unadjusted data respectively).  
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18 252 **Participants with highest starting urinary BPA levels were more likely to demonstrate**  
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20 253 **lower BPA levels at visit 2.**  
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25 255 We found an inverse relationship between initial BPA levels and whether a participant had  
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27 256 reduced BPA levels at visit 2 ( $p = 0.003$ ). These data indicate that the participants in the  
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29 257 cohort with the highest creatinine-adjusted urinary BPA levels at visit 1 were more likely to  
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31 258 demonstrate a drop in their urinary BPA at visit 2 (figure 2).  
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37 260 **Following the intervention diet has significant effects on participant lifestyle**  
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43 262 Participants indicated that following the diet had no significant cost implications on family  
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45 263 finances, with 50% of participants reporting that it had cost more, and 50% reporting that  
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47 264 costs had decreased or remained the same. Although participants did not spend longer  
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49 265 preparing their food, 78% of participants reported that their shopping took longer. 58% of  
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51 266 participants reported that the diet did not affect their calorific intake. 91% of participants  
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53 267 reported that they felt at least slightly restricted in their food choices. 27% of participants  
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3 268 reported that they felt very restricted. Finally, 66% of participants stated that they would find  
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5 269 it hard or very hard to follow the diet long term.  
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### 10 271 **Qualitative analysis of the effect of following the diet on lifestyle**

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14 273 We identified 5 overriding themes in our qualitative analysis of the effect of following the  
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16 274 diet on lifestyle. These were 1) the widespread use of plastics possibly containing BPA in  
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18 275 food packaging (“almost everything is packaged in plastic” – participant 70, “Literally  
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20 276 everything involved plastic” – participant 28). 2) Lack of clarity in labelling of products and  
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22 277 packaging potentially containing BPA (“I found it really hard to know what foods I could eat  
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24 278 ... there is never a guarantee it is BPA free” – participant 43, “The biggest problem was that  
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26 279 a lot of packaging doesn’t state what type of plastic it is or whether it contains BPA” –  
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28 280 participant 74). 3) The perceived restrictions of being on the ‘real world’ BPA avoidance diet  
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30 281 (“Difficulty eating out, hard to find foods in college or ‘out’ that hadn’t touched BPA. My  
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32 282 family had a takeaway on Saturday night and I couldn’t eat it” – participant 56, “Sometimes I  
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34 283 can’t eat / drink what I want because of the recycling number” – participant 112). 4) The  
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36 284 impact of eating ‘BPA free’ was the only positive theme emerging (“I feel I have eaten much  
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38 285 more healthily this week ... I didn’t eat so much junk food” – participant 74, “I ate more  
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40 286 vegetables and less chocolate” – participant 83). 5) The impact on shopping habits (“You  
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42 287 can’t get it all from supermarkets” – Participant 37; “Had to go to more individual food  
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44 288 shops” – participant 103).  
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### 50 290 **DISCUSSION**

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3 292 Exposure to the endocrine disrupting chemical Bisphenol A (BPA) is ubiquitous [2], with  
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5 293 growing evidence that it may be associated with adverse health outcomes [4]. Here, 104  
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7 294 researcher participants aged 17-19 years designed and undertook a quantitative and  
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9 295 qualitative engaged research project designed to assess the potential for reduction of personal  
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11 296 exposure to BPA through moderation of diet, which would have utility in a ‘real world’  
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13 297 setting. We conclude that the ‘real world’ diet designed to reduce BPA exposure had no  
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15 298 effect on creatinine-adjusted urinary BPA concentrations in our cohort over a period of 7  
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17 299 days in our dataset.  
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23 301 Although levels of urinary BPA in our study cohort were slightly lower at the outset of the  
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25 302 study in our cohort than in others [18], measureable levels were present in the vast majority  
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27 303 of our participants. Participants were unable to achieve a reduction in their urinary BPA  
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29 304 levels over the 7 day trial period, despite good compliance to supplied guidelines. Avoidance  
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31 305 of BPA was not easily achieved on an individual level in our study population, with  
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33 306 qualitative analysis indicating that participants experienced feelings of restriction and  
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35 307 difficulties in sourcing BPA-free food due to inadequate labelling of foods and food  
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37 308 packaging. This suggests that the intervention would be difficult to sustain in the longer term.  
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44 310 This work represents the largest group of unrelated participants in one of the highest exposure  
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46 311 demographics to date, since previous work has focused on families and related individuals  
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48 312 [16] [17], who may share common sources of BPA. Although other population demographics  
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50 313 such as young children may have higher levels of BPA than our chosen study population  
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52 314 [18], it would not have been possible to do the sort of engaged research project that we  
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54 315 envisaged in this group. Our intervention is a ‘real world’ diet, designed to a set of guidelines  
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3 316 (such as reduction in the usage of tinned foods or foods with high levels of processing), rather  
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5 317 than the strict, prescribed diets that have been used in other studies [16], which suggested that  
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7 318 it was possible for participants to reduce their urinary BPA excretion by approximately 60%  
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9 319 in a period of just 3 days [16]. In our self-designed, self-administered study this was  
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11 320 unachievable. This may reflect the difficulty in identifying and sourcing foods free of BPA in  
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13 321 our commercial environment. Finally, the qualitative thematic analysis we carried out in our  
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15 322 study has given an indication that adherence to even a 'real world' BPA reduction diet with  
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17 323 fewer restrictions and more choice over the longer term was unlikely in our study population  
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19 324 due to difficulties in identifying foodstuffs likely to contain less BPA.  
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26 326 BPA has a terminal half-life of 6 hours [15]. Spot samples may therefore not be as accurate as  
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28 327 continuous sampling strategies (24hr urine collection). However, recent studies suggest that  
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30 328 despite its short half-life, measurable BPA remains present for up to 43 hours post-fasting,  
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32 329 indicating non-food exposures or accumulation in body tissues such as fat [20]. We identified  
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34 330 no impact of time of sample collection on BPA levels in our sample set, in either creatinine-  
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36 331 adjusted or unadjusted data, indicating that our measurements were not influenced by time  
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38 332 since the last meal. Spot sampling as used here may therefore represent an acceptable  
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40 333 compromise and remains a practical option in the community setting of our study. The large  
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42 334 variability in urinary BPA levels within an individual sampled at different times may also  
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44 335 have reduced our ability to observe an effect. This could be facilitated by the use of multiple  
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46 336 sampling, or pools of multiple urines, but was not feasible within the confines of our study.  
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53 338 Calculating an accurate BPA risk score is challenging. Data were self-reported, and  
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55 339 foodstuffs are not labelled for BPA content. It is difficult to generalise across food types and  
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3 340 large variations in BPA concentrations occur between different products of the same food  
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5 341 type or even different lots of the same product [1]. Foods that were free of BPA-containing  
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7 342 packaging (as far as it was possible to tell) may have been highly processed or contain food  
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9 343 items from a variety of sources. Highly processed and ‘fast’ food has previously been  
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11 344 demonstrated to be a source of BPA [21]. A study of the temporal trends seen in composite  
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13 345 food samples found no change in the overall BPA content of the food, despite large reduction  
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15 346 in the BPA content of some individual food items, illustrating the difficulties in effectively  
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17 347 excluding BPA from a varied diet [22]. Participants may therefore have changed BPA  
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19 348 containing foods for other, perceived healthier choices, which may still contain BPA by  
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21 349 virtue of processing.  
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28 351 BPA enters foodstuffs by leaching from polycarbonate or epoxy resin after manufacture, or  
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30 352 by hydrolysis of the polymer itself [23]. The migration rate of BPA increases with higher  
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32 353 temperatures [24], and with time and use, e.g. repeated use of polycarbonate water bottles  
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34 354 [25]. Exposure to BPA can also occur through routes other than food, including dust  
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36 355 ingestion and dermal absorption [26] and this was not taken into account in our study. A  
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38 356 study of volunteers who purposefully handled thermal receipts showed an increase in urinary  
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40 357 BPA excretion of up to 84%, and their BPA levels took longer to return to pre exposure  
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42 358 levels, suggesting a difference in the bio-availability of BPA through skin and oral routes  
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44 359 [27]. It is also possible that some manufacturers may have voluntarily reduced the amount of  
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46 360 BPA-containing food packaging compared to their previous usage, given the attention that  
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48 361 endocrine disrupting chemicals have received in the media. However, measurable levels of  
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50 362 BPA were still detected in the majority of participants in our study, which suggests that there  
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52 363 may be other, non-dietary, sources of BPA, and that exposure to BPA remains an issue. We  
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54 364 may also have been underpowered to detect subtle changes in urinary BPA, given the  
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3 365 heterogeneity in food choice; detection of such effects may need thousands of participants.  
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5 366 Finally, our study, like other studies of its type, does not take account of inter-individual  
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7 367 differences in the metabolism and excretion of BPA arising from differences in genetic  
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9 368 background between people. BPA is metabolised primarily by UDP-  
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11 369 glucuronosyltransferases, and altered activity polymorphisms of these enzymes have been  
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13 370 reported [28].  
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19 372 Emerging evidence suggests that that BPA may be linked to several chronic human health  
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21 373 conditions [6-9, 29], suggesting that continued study of the human health effects of BPA  
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23 374 exposure is justified. The opinion of the European Food Safety Authority (EFSA), is that  
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25 375 whilst uncertainty over the human health effects of BPA exists, caution should be exercised  
26  
27 376 in ingestion of BPA [3]. Our data suggests that in our study population, it is unlikely that  
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29 377 participants could moderate their own BPA exposure in the long term by self-directed  
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31 378 modification of diet in a 'real world' setting, and furthermore, participants would have been  
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33 379 reluctant to adopt such a lifestyle change in the longer term due to the restrictions in dietary  
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35 380 choice and the effects on day to day life. Most of these barriers appear to arise from the  
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37 381 pervasiveness of BPA in our food chain, and inadequate labelling of foods packaged in BPA-  
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39 382 containing substances. We propose that until a definitive assessment of the health risks of  
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41 383 BPA is available, informed choice over whether or not to consume BPA and similar  
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43 384 chemicals in foodstuffs should be facilitated by better labelling.  
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51 386 **CONTRIBUTORSHIP STATEMENT**

52  
53  
54  
55 387 TSG - Contributed to study design and co-wrote the paper  
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58  
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1  
2  
3 388 NB - Contributed to study design and participant involvement  
4  
5 389 BP - Managed the technical aspects of the project and reviewed the manuscript  
6  
7 390 ALC - Contributed to data entry and interpretation and reviewed the manuscript  
8  
9 391 BPA Schools Study Consortium members - designed and interpreted the study and  
10  
11 392 contributed to the manuscript.  
12  
13 393 MHS - Carried out the qualitative analysis and reviewed the manuscript  
14  
15 394 AMS - Managed sample collection, contributed to study design and reviewed the manuscript.  
16  
17 395 LWH - PI , managed the study, wrote the manuscript  
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396

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398

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400 collection of the urine samples.  
401

401

#### 402 **COMPETING INTERESTS**

403

404 The authors have no competing interests to declare.  
405

405

#### 406 **DATA SHARING STATEMENT**

407 Extra data is available upon reasonable request by emailing Lorna Harries  
408 (L.W.Harries@exeter.ac.uk).



409

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411

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414

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3 486 **FIGURE LEGENDS**  
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9 488 **Figure 1. The effect of a ‘real world’ BPA avoidance diet on urinary BPA exposure over**  
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11 489 **a 7 day period.** A. Urinary BPA levels (ng/ml) adjusted for urinary creatinine were plotted at  
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13 490 visit 1 before the intervention and at visit 2 after the intervention. The 3 extreme outliers have  
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15 491 been removed. The trajectories of individual participant measurements are shown. B. Change  
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17 492 in urinary BPA levels in ng/ml following the intervention diet are plotted against the self-  
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19 493 reported BPA risk score.  
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26 495 **Figure 2. The effect of baseline urinary BPA on the probability of achieving a drop in**  
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28 496 **levels following the intervention.** This graph illustrates the median urinary BPA level  
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30 497 adjusted for creatinine at visit 1 prior to the intervention expressed relative to whether or not  
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32 498 a reduction in urinary BPA levels was achieved following the 7 day intervention diet at visit  
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34 499 2. Error bars refer to the interquartile range of measurement.  
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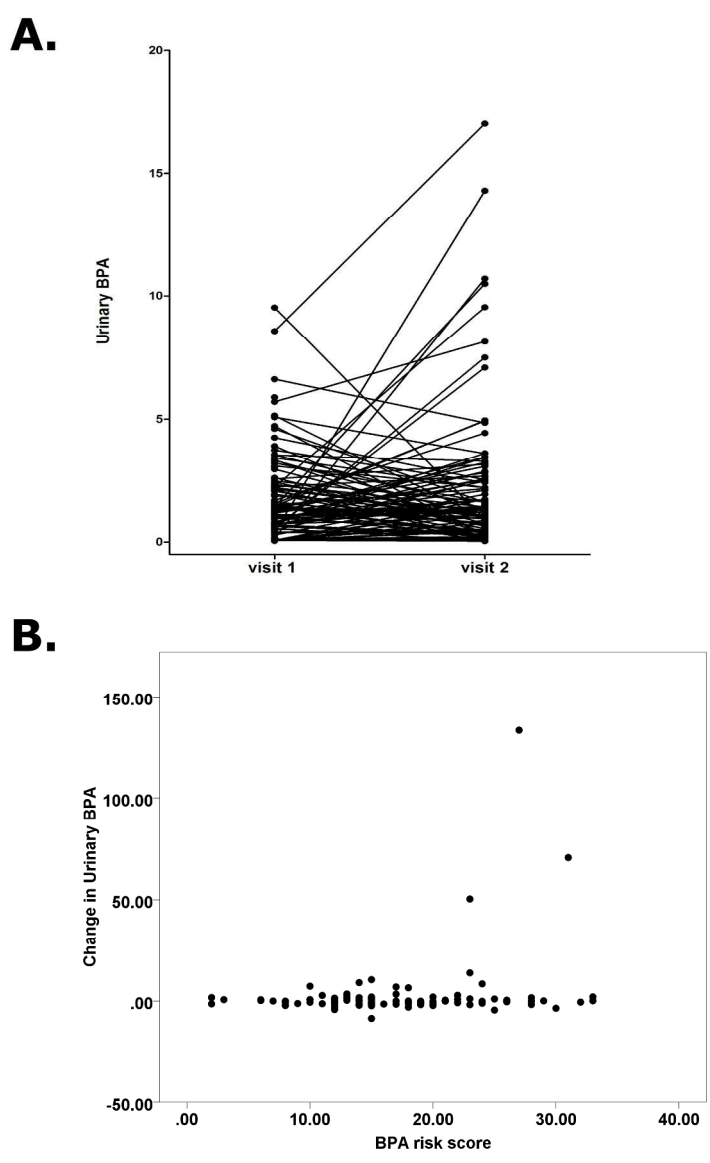


Figure 1

209x297mm (300 x 300 DPI)

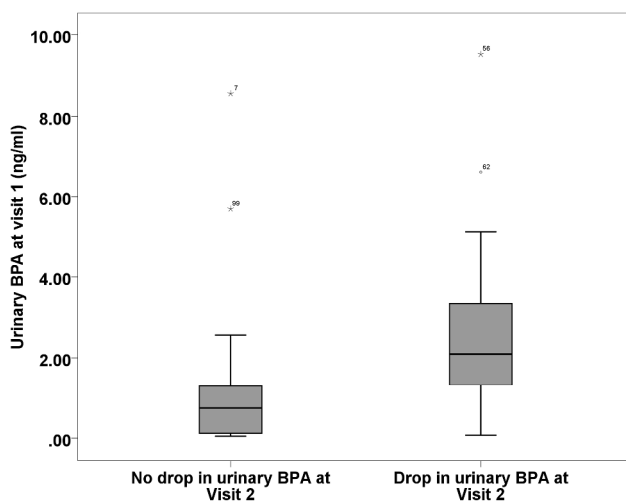


Figure 2

209x297mm (300 x 300 DPI)

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Honour		James	Exeter College
Jalil		Khalil	Exeter College
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Qiaochu		Meng	Exeter College
Rhiannon	I	Morris	Exeter College
Son		Nguyen	Exeter College
Isobella		Perks	Exeter College
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9	Alex	J	Pace	Exeter Mathematics School
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12	Jon	M	Reeves	Exeter Mathematics School
13	Jake	J	Shiel	Exeter Mathematics School
14	Ethan	J	Teague	Exeter Mathematics School
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## BPA Myth and Reality Dietary Intervention Guidelines



### General instructions

The purpose of this dietary intervention trial is to follow a diet designed to minimise routes of exposure to the food packaging chemical bisphenol A (BPA). For the dietary intervention period, please follow as closely as possible the instruction given below. Try to maintain your diet during the intervention period to be as closely similar to your normal diet as possible, in terms of the content, amount and calorific value of the food you eat. Please record details of each meal and the drinks and snacks you consume on the forms provided. Below are some general cooking and eating tips and an indication of which foods are best to avoid and those that are considered a low source of BPA.

### Cooking and eating tips for the intervention period.

The general approach is to replace any food items that fall into the 'avoidance' category with an alternative, chosen to minimise exposure to BPA

- **Switch to stainless steel and glass food storage and drink containers.**
- **Move foods to ceramic or glass food containers before microwaving.**
- **Consider a coffee filter or percolator for coffee – home coffee makers (Such as Nespresso™) may have polycarbonate-based water tanks and phthalate-based tubing.**
- **Eat out less, especially at restaurants that do not use fresh ingredients.**
- **Avoid canned food consumption. Where possible, replace with fresh produce or cardboard or tetrapack packaged alternatives.**
- **Choose fresh fruits and vegetables when possible, and frozen if not.**
- **Soak dried beans for cooking rather than tinned.**

## Foods to avoid

**Tinned foods.** Top ten tinned foods that are reported to be sources of BPA include coconut milk, soup, meat, vegetables, meals (e.g. pasta with sauce), juice, fish, beans, meal replacement drinks, fruit.

**Carbonated/fizzy drinks and juices in cans.** Avoid carbonated drinks in cans and drinks stored for prolonged periods in reusable sports bottles, unless they are labelled 'BPA free' (many commercial sports bottles are).

**Fast food from commercial outlets.** Most processed food has passed through numerous processes, and each additional processing step provides an opportunity for BPA to enter through packaging or tubing. Try to replace fast and processed foods with a freshly prepared and cooked alternative.

**Packaged fruit and vegetables.** Replace these where possible with unpackaged, loose fruit and vegetable items as far as possible.

**Convenience/ready meals.** Plastics types considered safest in terms of chemical migration are recycling numbers 2 and 5. Avoid food prepared in packaging with recycling number 7, which includes many different types of polymer and mixed polymers, including polycarbonate, a source of BPA. Try to avoid foods that are designed to be heated in the microwave in their packaging.

**Chocolate and ice cream.** Individuals who report eating chocolate bars and ice cream on a regular basis have been reported to have higher than average BPA exposure. Try to avoid excessive consumption.

## Non-food or food packaging routes of exposure

Although plastics found in consumer goods such as DVDs, CDs, computer goods and sunglasses do contain BPA, this is not an important route of exposure.

Till receipts often contain high levels of BPA, so wash your hands before eating or drinking if you have been handling them.

Dental sealants may contain BPA, so avoid any pre-planned dental work

## Example daily diet

Food Item	Comments
<b>Breakfast</b>	
Cereal, Fruit	
Milk	Polypropylene or glass packaging
Bread	
Yoghurt	Choose polypropylene container
<b>Lunch</b>	
Meat or fish products	Check packaging and avoid those labelled no. 7. Avoid tinned ingredients
Cheese	
Salad items, Fruit	Choose unpackaged where possible, wash before use
Pasta	
<b>Dinner</b>	
Shepherds pie	Cooked in saucepan and oven rather than microwaved in plastic
Green beans	Fresh or frozen
Bread	
<b>Drinks</b>	
Water	Water direct from tap or use stainless steel or BPA free water bottle
Tea/coffee	Prepare in teapot or cafetiere, avoid commercial coffee makers
Carbonated drinks	Avoid canned drinks and those stored in reusable containers for prolonged periods
Milk	Polypropylene or glass packaging
<b>Snacks</b>	
Fruit	
Potato crisps	

Place participant barcode here	FOOD - DAY 1		DRINK - DAY 1	
Contents of meal	Was food packaged in plastic known or suspected to contain BPA?	Was food cooked in plastic known or suspected to contain BPA?	Type of Drink	Packaging (please describe) e.g. canned, plastic (Δ number), tetrapak
<b>Breakfast:</b>				
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<b>Dinner:</b>				
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Place participant barcode here	FOOD - DAY 2		DRINK - DAY 2	
Contents of meal	Was food packaged in plastic known or suspected to contain BPA?	Was food cooked in plastic known or suspected to contain BPA?	Type of Drink	Packaging (please describe) e.g. canned, plastic (Δ number), tetrapak
<b>Breakfast:</b>				
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<b>Lunch:</b>				
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<b>Dinner:</b>				
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<b>Snacks:</b>				
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Place participant barcode here	FOOD - DAY 3		DRINK - DAY 3	
Contents of meal	Was food packaged in plastic known or suspected to contain BPA?	Was food cooked in plastic known or suspected to contain BPA?	Type of Drink	Packaging (please describe) e.g. canned, plastic (Δ number), tetrapak
<b>Breakfast:</b>				
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Place participant barcode here	FOOD - DAY 4		DRINK - DAY 4	
Contents of meal	Was food packaged in plastic known or suspected to contain BPA?	Was food cooked in plastic known or suspected to contain BPA?	Type of Drink	Packaging (please describe) e.g. canned, plastic (Δ number), tetrapak
<b>Breakfast:</b>				
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Place participant barcode here	FOOD - DAY 5		DRINK - DAY 5	
Contents of meal	Was food packaged in plastic known or suspected to contain BPA?	Was food cooked in plastic known or suspected to contain BPA?	Type of Drink	Packaging (please describe) e.g. canned, plastic (Δ number), tetrapak
<b>Breakfast:</b>				
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<b>Lunch:</b>				
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<b>Dinner:</b>				
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Place participant barcode here	FOOD - DAY 6		DRINK - DAY 6	
Contents of meal	Was food packaged in plastic known or suspected to contain BPA?	Was food cooked in plastic known or suspected to contain BPA?	Type of Drink	Packaging (please describe) e.g. canned, plastic (Δ number), tetrapak
<b>Breakfast:</b>				
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5.				
<b>Snacks:</b>				
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2.				
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Place participant barcode here	FOOD - DAY 7		DRINK - DAY 7	
Contents of meal	Was food packaged in plastic known or suspected to contain BPA?	Was food cooked in plastic known or suspected to contain BPA?	Type of Drink	Packaging (please describe) e.g. canned, plastic (Δ number), tetrapak
<b>Breakfast:</b>				
1.				
2.				
3.				
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5.				
<b>Lunch:</b>				
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<b>Dinner:</b>				
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5.				
<b>Snacks:</b>				
1.				
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**Participant barcode****Additional study information.**

Please do not feel obliged to answer these questions if you are uncomfortable doing so.

**Gender**

- Female  
 Male  
 Prefer not to say

**Tobacco Usage** – Have you used tobacco over the past week

- Yes  
If so, what type and how much? \_\_\_\_\_  
 No  
 Prefer not to say

**Alcohol Usage** – Have you used alcohol over the past week

- Yes  
If so, what type and how much? \_\_\_\_\_  
 No  
 Prefer not to say

**Medication**- Have you taken any medication over the last week?

- Yes  
 No  
 Prefer not to say
- If so, Please name the medication \_\_\_\_\_  Prefer not to say

**Vegetarian/vegan diet** - Have you eaten or drank any soya products over the past week?

- Yes  
 No  
 Prefer not to say

**Your measurements** - leave blank if you prefer not to say

Your height \_\_\_\_\_

Your weight \_\_\_\_\_

Participant Barcode

## BPA: Myth and Reality diet questionnaire

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1. Were there any times during the week that you knowingly/unknowingly did not stick to the diet? Please tick any that apply and give indication of frequency.

- School meals  \_\_\_ times
- Restaurants/cafés  \_\_\_ times
- Friends' houses  \_\_\_ times
- Takeaway  \_\_\_ times
- Other \_\_\_\_\_  \_\_\_ times

2. If you heated your food in a microwave, what was the food in? Tick any which apply and give indication of frequency.

- A food storage container or bowl known or suspected to contain BPA  \_\_\_ times

3. When you or your family drank water, where did your water come from? Tick any which apply and give indication of frequency.

- Plastic filter jug known or suspected to contain BPA  \_\_\_ times
- Individual water bottle known or suspected to contain BPA  \_\_\_ times
- Larger water container known or suspected to contain BPA  \_\_\_ times

4. How many times during the week did you eat food that had been stored or transported in plastic containers known or suspected to contain BPA?

\_\_\_\_\_

5. How many times during the week did you eat tinned food or drink from cans?

\_\_\_\_\_

6. Did the BPA reduced diet affect How much you spent on shopping?

- Spent more
- Spent less
- No difference

Participant questionnaire V3 25Jun15

Participant Barcode

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5 **7. Did it take longer to source your food than usual?**  
6

7 Yes  No

8  
9 If so, why? \_\_\_\_\_  
10  
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16 **8. Did it take longer to prepare food than usual?**  
17

18 Yes  No

19  
20  
21  
22 If so, why? \_\_\_\_\_  
23  
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26  
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28  
29 **9. How restricted did you feel by your food choice?**  
30

31  
32  
33  Very  Slightly  No difference  
34  
35

36  
37 If you felt you were restricted by the diet, why was this? \_\_\_\_\_  
38  
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42  
43  
44 **10. Did the diet affect your calorific intake?**  
45

46  
47  
48 Yes  No

49  
50 If so, why? \_\_\_\_\_  
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Participant questionnaire V3 25Jun15

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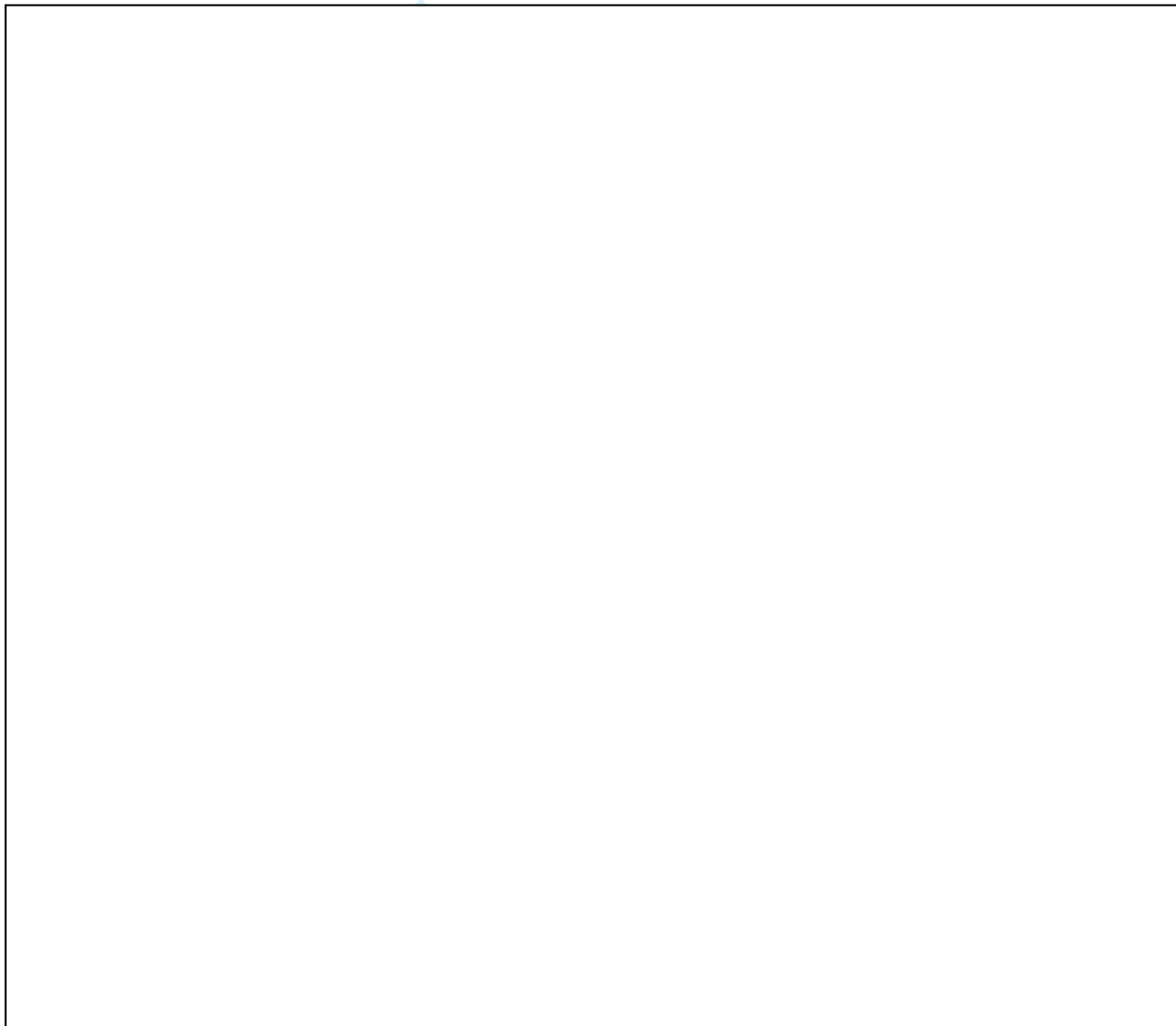
Participant Barcode

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3 **11. How easy would you find it to sustain this diet over a longer period of time?**  
4  
5

- 6  
7 Very easy   
8  
9 Easy   
10  
11 Hard   
12  
13 Very hard   
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15 Not sure   
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17  
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19 **12. Is there anything else about following the diet that you would like to add?**  
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Thank you for reading this leaflet. If you wish to participate in this study, you will be asked to agree to the consent statements below in the presence of a member of the research team.

### CONSENT STATEMENTS

1. I confirm that I have read this information sheet and have discussed participation in this project with my family. I have had opportunity to consider the information, ask questions and have had these questions answered satisfactorily. *You should not give consent until you are happy that you understand what the study involves.*
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my right to participate in the rest of the study being affected. *This means that even if you helped design this study you do not have to be a participant and you should not feel under any pressure to participate.*
3. I agree to participate in this study as a research subject. *This means that you agree to participate in a one-week diet and to provide two blood and urine samples.*
4. I understand that my anonymised blood and urine samples and linked anonymous questionnaire data will be sent to University of Exeter Medical School, Royal Devon & Exeter Hospital and my urine sample only will be sent to the Rolvaintain laboratory, a specialist BPA analysis company. *This means that laboratory staff will not know that samples belong to you, but dedicated staff at the University of Exeter, with training and experience in data protection, will be able to link your sample data to your questionnaire data.*
5. I understand that RNA (genetic material) will be extracted from my blood and will be stored anonymously. *This means that Professor Harries' team will use our RNA to provide data that you will help analyse but may also do further research on the samples to identify reasons for any changes seen.*
6. I understand that data relating to my participation in the study will be returned anonymously to my school to be used for educational purposes. *This means that although you will get to analyse data from your samples there is no way you will know which data relates to your samples and which to other participants.*

#### Complaints:

If you have any complaints about the way in which this study has been carried out please contact the Chair of the University of Exeter Medical School Research Ethics Committee Peta Foxall PhD, Chair, UEMS Research Ethics Committee: P.J.D.Foxall@exeter.ac.uk.

This project has been reviewed and approved by the University of Exeter Medical School Research Ethics committee UEMS REC REFERENCE NUMBER: 15/07/074)

## BPA: Myth or Reality?

A research study investigating the effect of chemicals in plastic on gene activity and whether dietary interventions can reduce BPA levels in teenagers.



### Involvement & Engagement

The aim of this year-long project is to involve teenagers in a research study that is relevant to them, by allowing them to help design a research project, analyse non-identifiable participant data and help to present and publish the outcomes.

### Participation

Students will be asked to undertake a one week diet to reduce their intake of BPA, a chemical found in plastics. They will be asked to provide urine and blood samples before and after their diet.

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## What is BPA?

BPA (Bisphenol A) is a chemical used in the manufacture of plastics. Plastics containing BPA are found in a wide range of products including food and drink containers. BPA in these products can be ingested and there are concerns that high BPA levels in the blood could possibly affect human health. Research is therefore needed to understand its effects on the human body and how we can reduce its consumption by minor changes to our diet.



This project is being run as a student-involvement project to answer two specific questions:

1. Can we see the effects of dietary BPA on our genes?
2. Can we effectively reduce BPA in our diet?

In the past, small-scale experiments have shown that BPA levels in the human body can be reduced by rigid dietary interventions but these interventions would be difficult to implement in the “real world”. In this study a one-week dietary intervention designed by teenagers will be used by them to determine whether BPA levels, and the activity of BPA-responsive genes can be effectively reduced in young people by avoiding food packaging that contains this chemical.

## What will I need to do?

### Day 1

- Provide a nurse with a 2.5ml blood sample and a urine sample.

### Day 2 - Day 8

- Follow a diet that you have helped to design .
- The diet will exclude sources of BPA as much as possible but will be nutritionally and calorifically similar to your usual diet.
- You will be asked to complete a food diary and answer a questionnaire about how easy it was to follow this diet.

### Day 8

- Provide a nurse with a 2.5ml blood sample and a urine sample.

**We recommend that you discuss the project with your family and involve them in planning what you eat and how you will prepare it.**



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## What will happen to my samples and data?

When you participate in the study you will be allocated with a numerical study ID. Your samples and data will be labelled with this number so that we can match your ‘before’ and ‘after’ diet samples with your food diary data. Once all data has been collated and coded it will be further anonymised by a person external to the project so that no data can be linked to any of the participants.



Urine samples from before and after the diet will be sent to the Royal Devon & Exeter NHS Foundation Trust for creatinine analysis and to the Royal Devon & Exeter Molecular Genetics Laboratory for BPA analysis. RNA will be extracted from blood samples at the Royal Devon & Exeter Molecular Genetics Laboratory and the expression levels of two BPA-responsive genes will be measured in the samples taken before and after the diet. These anonymised RNA samples will be stored and used only by Professor Harries team for further research on the mechanisms behind our findings.

## What are the benefits of taking part?



This project will help you to understand how you might be able to reduce BPA in your diet and your involvement in the design will give you an excellent insight into clinical research, community outreach and scientific practise. Your role as a participant is unlikely to have any direct health benefits.

## Are there any risks intaking part?



Blood samples will be taken by fully qualified and insured NHS personnel. Any potential discomfort or side-effects will be equivalent to that experienced giving a blood sample to your GP. All data will be fully anonymised before analysis. This means that you will not find out anything about your blood or urine samples. Following the diet may minimally increase the cost of your groceries for the week, but since fresh foods are usually less expensive than pre-packaged foods, we do not expect this to be an issue.

## What will happen to the results of the research study?

You will be given the opportunity to help analyse anonymised data from this project and to help disseminate the outcomes of this research. It is hoped that the findings will be published in peer-reviewed journals and the wider media.

## Who is organising this research?

The research is organised by Professors Lorna Harries & Tamara Galloway of the University of Exeter as part of their research program into BPA and part of the University's outreach program to involve schools in academic research.

2019-2020  
 February 21st  
 11:28 AM  
 http://bmjopen.bmj.com/

## Version 4 (2/8/2015)

## BPA: Myth &amp; Reality

## STUDY ID

CONSENT STATEMENTS		Please circle
1. I confirm that I have read information sheet BPA PIS Version 4 and have discussed participation in this project with my family. I have had opportunity to consider the information, ask questions and have had these questions answered satisfactorily. <i>You should not give consent until you are happy that you understand what the study involves.</i>		YES / NO
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without right to participate in the rest of the study being affected. <i>This means that even if you helped design this study you do not have to be a participant and you should not feel under any pressure to participate.</i>		YES / NO
3. I agree to participate in this study as a research subject. <i>This means that you agree to participate in a one-week diet and to provide two blood and urine samples.</i>		YES / NO
4. I understand that my anonymised blood and urine samples and linked anonymous questionnaire data will be sent to University of Exeter Medical School, Royal Devon & Hospital and my urine sample only will be sent to the Rolvaintain laboratory, a specialist BPA analysis company. <i>This means that laboratory staff will not know that samples belong to you, but dedicated staff at the University of Exeter, with training and experience in data protection, will be able to link your sample data to your questionnaire data.</i>		YES / NO
5. I understand that RNA (genetic material) will be extracted from my blood and will be stored anonymously. <i>This means that Professor Harries' team will use our RNA to provide data that you will help analyse but may also do further research on the samples to identify reasons for any changes seen.</i>		YES / NO
6. I understand that data relating to my participation in the study will be returned anonymously to my school to be used for educational purposes. <i>This means that although you will get to analyse data from your samples there is no way you will know which data relates to your samples and which to other participants.</i>		YES / NO
Name of Participant	Signature	Date
Name of Person Obtaining Consent	Signature	Date
I the above signed testify the participant is providing voluntary and fully informed consent to participate in this study. I am on the delegation log to obtain consent for this study and are trained in obtaining consent.		
This project has been reviewed and approved by the University of Exeter Medical School Research Ethics Committee UEMS REC REFERENCE NUMBER: 15/07/074)		

Version 4 (2/8/2015)

BPA: Myth & Reality

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

	Item No	Recommendation
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found  <b>a) Page 1</b> <b>b) Page 2</b>
<b>Introduction</b>		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported  <b>Page 6, line 82</b>
Objectives	3	State specific objectives, including any prespecified hypotheses  <b>Page 7, line 113</b>
<b>Methods</b>		
Study design	4	Present key elements of study design early in the paper  <b>Page 8, line 140</b>
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection  <b>Page 8, line 152</b>
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up  <b>Page 7, line 123</b>  <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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants <hr/> (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable  Page 7, line 140, Page 8, line 152.

1  
2 Data sources/  
3 measurement 8\* For each variable of interest, give sources of data and details of methods of  
4 assessment (measurement). Describe comparability of assessment methods if there  
5 is more than one group

6  
7 **Page 8, line 140, Page 8, line 152**

8  
9  
10 Bias 9 Describe any efforts to address potential sources of bias

11  
12 **Page 8, line 154, page 9 line 165**

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14  
15 Study size 10 Explain how the study size was arrived at

16  
17 **Page 7, line 127**

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19 Quantitative variables 11 Explain how quantitative variables were handled in the analyses. If applicable,  
20 describe which groupings were chosen and why

21  
22 **Page 9, line 157**

23  
24  
25 Statistical methods 12 (a) Describe all statistical methods, including those used to control for confounding

26  
27 **Page 9, line 170**

28  
29 (b) Describe any methods used to examine subgroups and interactions

30  
31 **Page 9, line 175**

32  
33 (c) Explain how missing data were addressed

34  
35 **Page 9, line 164**

36  
37 (d) *Cohort study*—If applicable, explain how loss to follow-up was addressed

38  
39 **Page 12, line 206**

40  
41 *Case-control study*—If applicable, explain how matching of cases and controls was  
42 addressed

43  
44 *Cross-sectional study*—If applicable, describe analytical methods taking account of  
45 sampling strategy

46  
47 (e) Describe any sensitivity analyses

48  
49  
50  
51 N/A

52  
53 Continued on next page

**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>Table 1</b>
		(b) Give reasons for non-participation at each stage
		<b>Page 12, line 206</b>
		(c) Consider use of a flow diagram
		N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		<b>Table 1</b>
		(b) Indicate number of participants with missing data for each variable of interest
		<b>Table 1</b>
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)
		<b>Page 9, line 172</b>
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time
		<b>Table 1</b>
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures
Main results	16	(a) 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
		<b>Page 12, line 213 to page 13 line 229</b>
		(b) Report category boundaries when continuous variables were categorized
		<b>Page 9, line 176</b>
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful

1  
2 time period  
3

4 N/A  
5

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6 Other analyses 17 Report other analyses done—eg analyses of subgroups and interactions, and sensitivity  
7 analyses  
8

9  
10 **Page 13, line 234**  
11

---

## 12 Discussion

13  
14 Key results 18 Summarise key results with reference to study objectives  
15

16 **Page 15, line 276**  
17

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18 Limitations 19 Discuss limitations of the study, taking into account sources of potential bias or imprecision.  
19 Discuss both direction and magnitude of any potential bias  
20

21 **Page 16, line 298**  
22

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23 Interpretation 20 Give a cautious overall interpretation of results considering objectives, limitations, multiplicity  
24 of analyses, results from similar studies, and other relevant evidence  
25

26 **Page 17, line 334**  
27

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28 Generalisability 21 Discuss the generalisability (external validity) of the study results  
29

30 **Page 18, line 344**  
31

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## 32 Other information

33 Funding 22 Give the source of funding and the role of the funders for the present study and, if applicable,  
34 for the original study on which the present article is based  
35

36 **Page 19, line 374**  
37

38 \*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and  
39 unexposed groups in cohort and cross-sectional studies.  
40

41  
42 **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and  
43 published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely  
44 available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at  
45 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is  
46 available at [www.strobe-statement.org](http://www.strobe-statement.org).  
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# BMJ Open

## An engaged research study to assess the effect of a 'real-world' dietary intervention on urinary bisphenol A (BPA) levels in teenagers

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-018742.R2
Article Type:	Research
Date Submitted by the Author:	07-Nov-2017
Complete List of Authors:	Galloway, Tamara; University of Exeter, College of Life and Environmental Sciences Baglin, Nigel; Research Projects Lee, Benjamin; University of Exeter Medical School, Institute of Biomedical and Clinical Studies Kocur, Anna; University of Exeter Medical School, Institute of Biomedical and Clinical Studies Shepherd, Maggie; Royal Devon and Exeter National Health Service Foundation Trust, National Institute for Health Research Exeter Clinical Research Facility Steele, Anna; Royal Devon and Exeter National Health Service Foundation Trust, National Institute for Health Research Exeter Clinical Research Facility BPA Schools, Study Consortium; University of Exeter Medical School, Institute of Biomedical and Clinical Studies Harries, Lorna; University of Exeter Medical School, Institute of Biomedical and Clinical Studies
<b>Primary Subject Heading</b>:	Public health
Secondary Subject Heading:	Communication
Keywords:	Bisphenol A, Dietary intervention, PUBLIC HEALTH, community, Engaged research

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Manuscripts



1 **An engaged research study to assess the effect of a ‘real-world’ dietary**  
2 **intervention on urinary bisphenol A (BPA) levels in teenagers**

3 Tamara. S. Galloway<sup>1</sup>, Nigel Baglin<sup>2</sup>, Benjamin P Lee<sup>3</sup>, A.L. Kocur<sup>3</sup>, M.H. Shepherd<sup>4</sup>, A.M.  
4 Steele<sup>4</sup>, BPA schools study consortium<sup>5,6,7,8,9,10</sup> and L.W. Harries<sup>3</sup>

5 <sup>1</sup>*College of Life and Environmental Sciences, University of Exeter, Exeter UK EX4 4AS.*

6 <sup>2</sup>*Research Projects, Exeter, UK, EX2 5DQ.*

7 <sup>3</sup>*RNA-Mediated Disease Mechanisms group, Institute of Biomedical and Clinical Sciences,*  
8 *University of Exeter Medical School, University of Exeter, Exeter, UK EX2 5DW.*

9 <sup>4</sup>*National Institute for Health Research Exeter Clinical Research Facility, Royal Devon and*  
10 *Exeter National Health Service Foundation Trust, and University of Exeter Medical School,*  
11 *Exeter, U.K.*

12 <sup>5</sup>*Clyst Vale Community College, Broadclyst, Exeter Ex5 3AJ*

13 <sup>6</sup>*Exeter School, Exeter, Devon, EX2 4NS*

14 <sup>7</sup>*South Dartmoor Community College, Ashburton, Devon, TQ13 7EW*

15 <sup>8</sup>*Honiton Community College, Honiton, Devon, EX14 1QT*

16 <sup>9</sup>*Exeter College, Exeter, Devon, EX4 4JS*

17 <sup>10</sup>*Exeter Mathematics School, Exeter, Devon, EX4 3PU*

18  
19 **Word count 3021**

20  
21 Correspondence to:

22 Prof Lorna Harries  
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24 Barrack Road,  
25 Exeter, EX2 5DW  
26 Tel =44 1392 406773  
27 Email: [L.W.Harries@exeter.ac.uk](mailto:L.W.Harries@exeter.ac.uk)

28  
29 **Declaration of competing issues**

30 The authors have no competing interests to declare.

31

## 32 ABSTRACT

33

### 34 Objective

35 Bisphenol A has been associated adverse human health outcomes and exposure to this  
36 compound is near-ubiquitous in the Western world. We aimed to examine whether self-  
37 moderation of BPA exposure is possible by altering diet in a real-world setting.

### 38 Design

39 An Engaged Research dietary intervention study designed, implemented and analysed by  
40 healthy teenagers from 6 schools and undertaken in their own homes.

### 41 Participants

42 A total of 94 students aged between 17 and 19 years from schools in the South West of the  
43 UK provided diet diaries and urine samples for analysis.

### 44 Intervention

45 Researcher participants designed a set of literature-informed guidelines for reduction of  
46 dietary BPA to be followed for 7 days.

### 47 Main outcome measure

48 Creatinine-adjusted urinary BPA levels were taken before and after the intervention.  
49 Information on packaging and food/drink ingested was used to calculate a BPA risk score for  
50 anticipated exposure. A qualitative analysis was carried out to identify themes addressing  
51 long term sustainability of the diet.

### 52 Results

1  
2  
3 53 BPA was detected in urine of 86% of participants at baseline at a median value of 1.34 ng/ml  
4  
5 54 (IQR 1.82). No effect of the intervention diet on BPA levels was identified overall ( $p = 0.25$ ),  
6  
7 55 but there was a positive association in those participants who showed a drop in urinary BPA  
8  
9 56 concentration post intervention and their initial BPA level ( $p = 0.003$ ). Qualitative analysis  
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11 57 identified themes around feelings of lifestyle restriction and the inadequacy of current  
12  
13 58 labelling practices.

## 15 16 59 **Conclusions**

17  
18  
19 60 We found no evidence in this self-administered intervention study that it was possible to  
20  
21 61 moderate BPA exposure by diet in a real world setting. Furthermore, our study participants  
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23 62 indicated that they would be unlikely to sustain such a diet long term, due to the difficulty in  
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25 63 identifying BPA-free foods.

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3 65 **Article Summary**  
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7 67 *Strengths of the study*  
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- 11 69 • This study represents the largest assessment to date of the potential for moderating  
12 one's own BPA exposure through diet  
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14  
15 71 • The study was carried out in a 'real-world' setting rather than a regulated, controlled  
16 environment.  
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19 73 • The study was carried out in teenagers, the demographic with amongst the highest  
20 exposure.  
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24 75 • Qualitative analysis reveals challenges with sustaining such a diet.  
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27 76 *Limitations of the study*  
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- 30 77 • Calculation of a risk score is challenging due to the pervasive nature of BPA  
31 contamination  
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## 80 INTRODUCTION

81

82 Bisphenol A is one of the world's highest production volume chemicals. It is used in the  
83 manufacture of polycarbonate and other plastic consumer products, in heat resistant papers,  
84 dental sealants and in the epoxy resin-based lining of food and drink containers [1]. BPA can  
85 be found above the detection limit in the urine of the majority of people worldwide [2].  
86 Concern has been raised for public health, since BPA is classified as an endocrine disrupting  
87 chemical (EDC) which has been linked with several disorders in cell and animal models [3-  
88 5]. Several epidemiological studies have also linked outcomes such as type 2 diabetes,  
89 cardiovascular disease, obesity and abnormalities of sex hormone levels with BPA levels in  
90 human populations [6-10] Epidemiological data in humans has historically been more  
91 contentious however, due to relatively small sample sizes and issues around causality [11].  
92 The Endocrine Society concluded in 2015 that current evidence suggests that BPA and other  
93 endocrine disrupting chemicals may have effects on several reproductive, cardiovascular and  
94 metabolic traits in humans [12]. The current opinion of food regulatory bodies such as the  
95 European Food Standards Agency (EFSA) is that sufficient uncertainty remains to be able to  
96 exclude effects on the reproductive, immune, nervous, metabolic and cardiovascular systems  
97 and on cancer development [3] whilst the European Chemicals Agency (ECHA) has recently  
98 reclassified BPA as a chemical of very high concern due to its endocrine disrupting properties  
99 [13].

100

101 There has been wide interest in the sources of BPA and the potential for individuals to reduce  
102 their own exposure. Human exposure has been reported from inhalation of dust, uptake  
103 across the skin from thermal papers and till receipts and release from dental sealants. The  
104 main source is the ingestion of food and drink contaminated with BPA leached from

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3 105 packaging materials [1, 14]. BPA is rapidly metabolised in the gut wall and liver and  
4  
5 106 removed from the blood by the kidneys, with a terminal half-life of 6 hours after oral  
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7 107 ingestion [15]. BPA has been detected in food samples packaged in glass, plastic, paper and  
8  
9 108 paperboard cartons, with an average concentration of 0.46 ng/g, rising to over 700 ng/g for  
10  
11 109 certain canned foods. Conversely, in a dietary intervention study in which 22 volunteers  
12  
13 110 consumed a 3 day fresh food diet which excluded canned or packaged foods, there was a 66%  
14  
15 111 reduction in urinary BPA excretion compared to concentrations before the intervention [16].  
16  
17 112 This latter study involved full dietary replacement of foodstuffs, an approach which is  
18  
19 113 impractical for the population at large. A follow up study found that households who  
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21 114 followed written recommendations produced by health care professionals showed no  
22  
23 115 significant change in their BPA exposure [17].  
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30 117 We present an alternative, citizen-science based approach, where 108 student volunteers  
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32 118 designed and undertook their own intervention diet, following provision of educational  
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34 119 materials. We questioned whether adherence to a self-designed and self-administered 'real  
35  
36 120 world' diet over 7 days would lead to significant reductions in excreted urinary BPA, and if  
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38 121 so, whether such a diet was likely to be sustainable in the long term.  
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## 44 123 **METHODS**

### 45 124

#### 46 125 **Participant group**

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48 127 We chose adolescents because it has been shown that they have higher concentrations of BPA  
49  
50 128 than adults (aggregated exposure of 1.449 µg/kg body weight per day) [3, 18]. A total of 108  
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52 129 students aged 17-19 from local schools were initially invited to participate in this engaged  
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3 130 research project. Six schools participated in this project (Clyst Vale Community College - 14  
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5 131 students; Exeter School - 12 students; South Dartmoor Community College - 13 students;  
6  
7 132 Honiton Community College - 11 students; Exeter College – 29 students and Exeter  
8  
9 133 Mathematics School – 29 students). Information and samples were available from 94  
10  
11 134 individuals at both visit one and visit 2 and comprise the complete dataset. This represents the  
12  
13 135 largest intervention study in the population demographic with the one of the highest BPA  
14  
15 136 exposures to date [18]. The number of students invited to participate was based on anticipated  
16  
17 137 effect sizes from previous work of this nature [16], and we allowed for a 10% dropout rate.  
18  
19 138 Students designed all of the materials required for completion of the study (study protocols,  
20  
21 139 food diaries, lifestyle questionnaires, patient information sheets and consent forms (see  
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23 140 Supplementary Information files 1 to 6).  
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### 30 142 **Ethical Permission**

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36 144 Ethical permission was granted by the University of Exeter Medical School Ethics  
37  
38 145 Committee (reference number 15/07/074) and the study was carried out in accordance with  
39  
40 146 the Declaration of Helsinki.  
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### 46 148 **The intervention diet**

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50 150 Students designed a “real world” diet designed to reduce consumption of BPA by avoidance  
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52 151 of processed foods and foods packaged in known sources of BPA [1, 14]; supplementary  
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54 152 information file 1). The study was designed at the University of Exeter as a collaboration  
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3 153 between academic staff and participating students and was developed at a series of interactive  
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5 154 workshops attended by all parties.  
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11 156 Students were asked to minimise their intake of known sources of BPA according to a set of  
12  
13 157 guidelines that had been co-designed with them based on the known literature. We requested  
14  
15 158 that calorific intake was maintained as near to their usual diet as possible and recorded details  
16  
17 159 of their daily diet including all food and drink, and its associated packaging, in a self-reported  
18  
19 160 food diary (Supplementary information file 2). Adherence was assessed using a 'BPA risk  
20  
21 161 score'; each individual dietary item potentially containing BPA was given a score of 1.  
22  
23 162 Heavily processed items were also scored 1 per item. These scores were collated at the end of  
24  
25 163 the 7 day trial to give a final risk score. An example of scores for a single participant on a  
26  
27 164 single day is given in supplementary information file 3. Given the short half-life of BPA, we  
28  
29 165 also carried out a secondary analysis considering only the BPA risk score from the 24 hours  
30  
31 166 immediately preceding the second sample. Information on lifestyle factors including sex,  
32  
33 167 BMI and time of urine collection was also collected (Supplementary information file 4). We  
34  
35 168 recognised that there may be a temptation for students to change their diets before the trial  
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37 169 based on their new learning. To avoid this, students were also specifically asked not alter  
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39 170 their diet before the intervention.  
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#### 45 172 **Sample collection and measurement of urinary BPA**

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49 174 Urine samples were collected into BPA-free bottles (Vacutest Kima, Italy) immediately  
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51 175 before and after the intervention, and were frozen at -20°C within 4 hours. Each participant  
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53 176 was sampled twice, once at visit 1 before the intervention and once at visit 2 after the  
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177 intervention. Sample collections were staggered to allow for the large number of participants  
178 passing through the facility, but students were sampled during the same time slot at both  
179 visits to account for circadian variation in BPA metabolism. The initial samples were  
180 collected during the early part of the day just prior to the students commencing the trial. The  
181 second samples were taken over the same time period 7 days later, just prior to the students  
182 recommencing their usual diet. Samples were transported on dry ice to a commercial  
183 laboratory (Rovaltain Research Company, Aixain, France) where analysis of total BPA was  
184 assessed by gas chromatography-tandem mass spectrometry. Experimental methods were  
185 validated for linearity, detection limit and accuracy and specificity of quantification based on  
186 the Standard NF T 90-201 for determination of xenobiotics. A quality control check of  
187 known standards injected every 6 samples at two levels of concentration (0.5 ng/ml and 5  
188 ng/ml) was quantified with each batch of unknown samples. Water-only samples were  
189 included as negative controls. Urinary creatinine was measured at the Royal Devon and  
190 Exeter Hospital using the Jaffe method on the Roche P800 platform (Roche, Mannheim,  
191 Germany), to allow correction for urine dilution. Results were expressed as a BPA:creatinine  
192 ratio. Samples where BPA was detected but quantifying at or around the limits of  
193 quantification (LoQ) of 0.1ng/ml were scored as  $LoQ/\sqrt{2}$  according to the method of Hornung  
194 and Reed [19].

195

### 196 **Statistical Analysis**

197

198 The difference between urinary BPA adjusted for creatinine between samples taken at visits 1  
199 and 2 was assessed to generate a  $\Delta$ BPA continuous variable. BPA risk scores were calculated  
200 as a continuous variable. The relationship between urinary BPA levels before and after the 7  
201 day intervention was assessed using a repeated-measure ANOVA, adjusted for sex, time of

202 sampling and BMI, with and without correction for creatinine. The relationship between  
203 urinary BPA at visit 1 and whether or not the participants had lower BPA at visit 2 was also  
204 examined by binary logistic regression, adjusted for sex, time of sampling and BMI. Here,  
205 samples showing small changes  $< 0.5\text{ng/ml}$  in either direction were omitted to avoid natural  
206 stoichiometric variation around zero. The relationship between change in BPA ( $\Delta\text{BPA}$ ) and  
207 BPA risk score was assessed by linear regression, adjusted for sex, time of sampling and BMI  
208 both with and without adjustment for creatinine. Statistical analysis was carried out using  
209 SPSS, v.22 (IBM, USA).

210

### 211 **Impact of following reduced BPA diet on lifestyle**

212

213 We carried out quantitative and qualitative analysis to address long-term sustainability of the  
214 diet. Data on the impact of following the diet on feelings of dietary restriction, time spent  
215 sourcing or preparing meals, calorific intake and long term sustainability were collected via a  
216 questionnaire (See Supplementary information file 4). The questionnaire also included a  
217 freeform section where participants could write about their experiences following the diet in a  
218 non-prescribed fashion for qualitative analysis. Qualitative data was assessed for thematic  
219 content by two experienced qualitative researchers. Key themes were independently  
220 identified and coded until agreement was reached.

221

## 222 **RESULTS**

223

### 224 **Participant Characteristics**

225

226 There were 108 volunteer participants invited to participate in this engaged research study. A  
 227 small number were absent or unable to produce a urine sample at both visits. A complete  
 228 dataset was thus received from 94 students. Information on the characteristics of the study  
 229 cohort are given in table 1.

230

231 **Table 1: Characteristics of the study population.** A complete dataset was available on 94  
 232 out of 108 participants. IQR = interquartile range, SD = Standard deviation. The units of BPA  
 233 are ng/ml and BMI is defined as Kg/m<sup>2</sup>. LoQ = limit of quantification. Urinary BPA levels  
 234 are given both as unadjusted data and as a BPA (ng/ml) to creatinine (mg/ml) ratio.

Unadjusted urinary BPA at visit 1 (n = 98)	
median (IQR)	1.37 (2.52)
95% confidence intervals	1.58 to 2.57
mean (SD)	2.07 (2.51)
Number of samples below LoQ (0.1ng/ml)	16
Minimum value (ng/ml)	0.07
Maximum value (ng/ml)	13.55
Creatinine-adjusted urinary BPA at visit 1 (n = 98)	
median (IQR)	1.34 (1.82)
95% confidence intervals	1.38 to 2.13
mean (SD)	1.75 (1.82)
Number of samples below LoQ (0.1ng/ml)	16
Minimum value (ng/ml)	0.05
Maximum value (ng/ml)	9.52
Unadjusted urinary BPA at visit 2 (n = 99)	
median (IQR)	1.91 (2.68)
95% confidence intervals	2.15 to 4.56
mean (SD)	3.35 (6.18)
Number of samples below LoQ (0.1ng/ml)	12
Minimum value (ng/ml)	0.07
Maximum value (ng/ml)	49.6
Creatinine-adjusted urinary BPA at visit 2 (n = 99)	
median (IQR)	1.31 (2.24)
95% confidence intervals	1.46 to 8.34
mean (SD)	4.90 (16.8)
Number of samples below LoQ (0.1ng/ml)	12
Minimum value (ng/ml)	0.04
Maximum value (ng/ml)	139.33
Unadjusted ΔBPA (n = 94)	

median (IQR)	0.14
95% confidence intervals	0.15 to 2.41
mean (SD)	1.28 (5.79)
Minimum value	-8.02
Maximum value	49.5
<b>Adjusted <math>\Delta</math>BPA (n = 94)</b>	
median (IQR)	0.02 (2.61)
95% confidence intervals	-0.23 to 6.53
mean (SD)	3.15 (16.5)
Minimum value	-8.6
Maximum value	133.45
<b>BPA risk score (n = 99)</b>	
median (IQR)	15.0 (10.3)
95% confidence intervals	15.5 to 18.4
mean (SD)	17.0 (7.12)
<b>Demographics (n= 99)</b>	
Sex - % male	44
Exposure to estrogens - % of cohort	14
BMI- median (IQR)	20.7 (3.45)
BMI- mean (SD)	21.2 (3.07)

235

236 BPA was detected in the urine of 86% of subjects at visit 1 prior to the intervention. Missing  
 237 samples were due to non-attendance of participants or non-provision of a suitable sample.  
 238 Samples below the limit of quantification were scored as 0.07 ng/ml (LoQ/ $\sqrt{2}$ ).

239

240 **Creatinine-adjusted urinary BPA concentrations do not change significantly after**  
 241 **following an intervention diet designed to reduce BPA exposure for 7 days.**

242

243 The median change in creatinine-adjusted urinary BPA between visits ( $\Delta$ BPA) was 0.02  
 244 ng/ml with an interquartile range of 2.61 ng/ml. We identified no changes in urinary BPA  
 245 between visits ( $p = 0.25$ ; figure 1a). Three outliers with very high urinary BPA readings at  
 246 visit 2 were excluded from the analysis, since these samples lay outside the linear range of  
 247 analysis, so confidence in quantification was poor. No confounding factors included in the  
 248 analysis were associated with change in BPA ( $p = 0.78, 0.43$  and  $0.36$  for sex, time of sample  
 249 collection and BMI respectively). We also identified no change in BPA levels between visits

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3 250 using data uncorrected for creatinine ( $p = 0.20$ ). We also assessed whether participants from  
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5 251 different schools showed variable BPA levels at either visit 1, or change in BPA, but no such  
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7 252 effects were noted.  
8

9 253

10  
11 254 Similarly, no relationship between change in urinary BPA ( $\Delta$ BPA) and BPA risk score was  
12  
13 255 identified (beta coefficient 0.08, standard error 0.07,  $p = 0.55$ ; figure 1b). No associations  
14  
15 256 were noted between change in urinary BPA and BPA risk score in data not adjusted for  
16  
17 257 creatinine ( $p = 0.27$ ). We found no association between  $\Delta$ BPA and BPA risk score when  
18  
19 258 considering only the exposure on the day prior to testing, taking into account the short half-  
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21 259 life of BPA ( $p = 0.16$  and  $p = 0.33$  for adjusted and unadjusted data respectively).  
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25 260

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27 261 **Participants with highest starting urinary BPA levels were more likely to demonstrate**  
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29 262 **lower BPA levels at visit 2.**  
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31 263

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34 264 We found an inverse relationship between initial BPA levels and whether a participant had  
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36 265 reduced BPA levels at visit 2 ( $p = 0.003$ ). These data indicate that the participants in the  
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38 266 cohort with the highest creatinine-adjusted urinary BPA levels at visit 1 were more likely to  
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40 267 demonstrate a drop in their urinary BPA at visit 2 (figure 2).  
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46 269 **Following the intervention diet has significant effects on participant lifestyle**  
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52 271 Participants indicated that following the diet had no significant cost implications on family  
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54 272 finances, with 50% of participants reporting that it had cost more, and 50% reporting that  
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3 273 costs had decreased or remained the same. Although participants did not spend longer  
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5 274 preparing their food, 78% of participants reported that their shopping took longer. Calorific  
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7 275 intake was not affected for the majority of participants (58%) of participants. A large  
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9 276 percentage of the cohort (91%) reported that they felt at least slightly restricted in their food  
10  
11 277 choices and 27% of participants reported that they felt very restricted. Finally, 66% of  
12  
13 278 participants stated that they would find it hard or very hard to follow the diet long term.

279

### 280 **Qualitative analysis of the effect of following the diet on lifestyle**

281

282 We identified 5 overriding themes in our qualitative analysis of the effect of following the  
283 diet on lifestyle. These were 1) the widespread use of plastics possibly containing BPA in  
284 food packaging (“almost everything is packaged in plastic” – participant 70, “Literally  
285 everything involved plastic” – participant 28). 2) Lack of clarity in labelling of products and  
286 packaging potentially containing BPA (“I found it really hard to know what foods I could eat  
287 ... there is never a guarantee it is BPA free” – participant 43, “The biggest problem was that  
288 a lot of packaging doesn’t state what type of plastic it is or whether it contains BPA” –  
289 participant 74). 3) The perceived restrictions of being on the ‘real world’ BPA avoidance diet  
290 (“Difficulty eating out, hard to find foods in college or ‘out’ that hadn’t touched BPA. My  
291 family had a takeaway on Saturday night and I couldn’t eat it” – participant 56, “Sometimes I  
292 can’t eat / drink what I want because of the recycling number” – participant 112). 4) The  
293 impact of eating ‘BPA free’ was the only positive theme emerging (“I feel I have eaten much  
294 more healthily this week ... I didn’t eat so much junk food” – participant 74, “I ate more  
295 vegetables and less chocolate” – participant 83). 5) The impact on shopping habits (“You  
296 can’t get it all from supermarkets” – Participant 37; “Had to go to more individual food  
297 shops” – participant 103).

298

299 **DISCUSSION**

300

301 Exposure to the endocrine disrupting chemical Bisphenol A (BPA) is ubiquitous [2], with  
302 growing evidence that it may be associated with adverse health outcomes [4]. Here, 94  
303 researcher participants aged 17-19 years designed and undertook a quantitative and  
304 qualitative engaged research project designed to assess the potential for reduction of personal  
305 exposure to BPA through moderation of diet, which would have utility in a 'real world'  
306 setting. We conclude that the 'real world' diet designed to reduce BPA exposure had no  
307 effect on creatinine-adjusted urinary BPA concentrations in our cohort over a period of 7  
308 days in our dataset.

309

310 Although levels of urinary BPA in our study cohort were slightly lower at the outset of the  
311 study in our cohort than in others [18], measureable levels were present in the vast majority  
312 of our participants. Participants were unable to achieve a reduction in their urinary BPA  
313 levels over the 7 day trial period, despite good compliance to supplied guidelines. Avoidance  
314 of BPA was not easily achieved on an individual level in our study population, with  
315 qualitative analysis indicating that participants experienced feelings of restriction and  
316 difficulties in sourcing BPA-free food due to inadequate labelling of foods and food  
317 packaging. This suggests that the intervention would be difficult to sustain in the longer term.

318

319 This work represents the largest group of unrelated participants in a high exposure  
320 demographic to date, since previous work has focused on families and related individuals  
321 [16][17], who may share common sources of BPA. Although other population demographics



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3 322 such as young children may have higher levels of BPA than our chosen study population  
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5 323 [18], it would not have been possible to do the sort of engaged research project that we  
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7 324 envisaged in this group. Our intervention is a 'real world' diet, designed to a set of guidelines  
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9 325 (such as reduction in the usage of tinned foods or foods with high levels of processing), rather  
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11 326 than the strict, prescribed diets that have been used in other studies [16], which suggested that  
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13 327 it was possible for participants to reduce their urinary BPA excretion by approximately 60%  
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15 328 in a period of just 3 days [16]. In our self-designed, self-administered study this was  
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17 329 unachievable. This may reflect the difficulty in identifying and sourcing foods free of BPA in  
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19 330 our commercial environment. Finally, the qualitative thematic analysis we carried out in our  
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21 331 study has given an indication that adherence to even a 'real world' BPA reduction diet with  
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23 332 fewer restrictions and more choice over the longer term was unlikely in our study population  
24  
25 333 due to difficulties in identifying foodstuffs likely to contain less BPA.  
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32 335 BPA has a terminal half-life of 6 hours [15]. Spot samples may therefore not be as accurate as  
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34 336 continuous sampling strategies (24hr urine collection). However, recent studies suggest that  
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36 337 despite its short half-life, measureable BPA remains present for up to 43 hours post-fasting,  
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38 338 indicating non-food exposures or accumulation in body tissues such as fat [20]. We identified  
39  
40 339 no impact of time of sample collection on BPA levels in our sample set, in either creatinine-  
41  
42 340 adjusted or unadjusted data, indicating that our measurements were not influenced by time  
43  
44 341 since the last meal. Spot sampling as used here may therefore represent an acceptable  
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46 342 compromise and remains a practical option in the community setting of our study. The large  
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48 343 variability in urinary BPA levels within an individual sampled at different times may also  
49  
50 344 have reduced our ability to observe an effect. This could be facilitated by the use of multiple  
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52 345 sampling, or pools of multiple urines, but was not feasible within the confines of our study.  
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346

347 Calculating an accurate BPA risk score is challenging. Data were self-reported, and  
348 foodstuffs are not labelled for BPA content. It is difficult to generalise across food types and  
349 large variations in BPA concentrations occur between different products of the same food  
350 type or even different lots of the same product [1]. Foods that were free of BPA-containing  
351 packaging (as far as it was possible to tell) may have been highly processed or contain food  
352 items from a variety of sources. Highly processed and 'fast' food has previously been  
353 demonstrated to be a source of BPA [21]. A study of the temporal trends seen in composite  
354 food samples found no change in the overall BPA content of the food, despite large reduction  
355 in the BPA content of some individual food items, illustrating the difficulties in effectively  
356 excluding BPA from a varied diet [22]. Participants may therefore have changed BPA  
357 containing foods for other, perceived healthier choices, which may still contain BPA by  
358 virtue of processing.

359

360 BPA enters foodstuffs by leaching from polycarbonate or epoxy resin after manufacture, or  
361 by hydrolysis of the polymer itself [23]. The migration rate of BPA increases with higher  
362 temperatures [24], and with time and use, e.g. repeated use of polycarbonate water bottles  
363 [25]. Exposure to BPA can also occur through routes other than food, including dust  
364 ingestion and dermal absorption [26] and this was not taken into account in our study. A  
365 study of volunteers who purposefully handled thermal receipts showed an increase in urinary  
366 BPA excretion of up to 84%, and their BPA levels took longer to return to pre exposure  
367 levels, suggesting a difference in the bio-availability of BPA through skin and oral routes  
368 [27]. It is also possible that some manufacturers may have voluntarily reduced the amount of  
369 BPA-containing food packaging compared to their previous usage, given the attention that

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3 370 endocrine disrupting chemicals have received in the media. However, measurable levels of  
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5 371 BPA were still detected in the majority of participants in our study, which suggests that there  
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7 372 may be other, non-dietary, sources of BPA, and that exposure to BPA remains an issue. We  
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9 373 may also have been underpowered to detect subtle changes in urinary BPA, given the  
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11 374 heterogeneity in food choice; detection of such effects may need thousands of participants.  
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13 375 Finally, our study, like other studies of its type, does not take account of inter-individual  
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15 376 differences in the metabolism and excretion of BPA arising from differences in genetic  
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17 377 background between people. BPA is metabolised primarily by UDP-  
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19 378 glucuronosyltransferases, and altered activity polymorphisms of these enzymes have been  
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21 379 reported [28].  
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28 381 Emerging evidence suggests that that BPA may be linked to several chronic human health  
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30 382 conditions [6-9, 29], suggesting that continued study of the human health effects of BPA  
31  
32 383 exposure is justified. The opinion of the European Food Safety Authority (EFSA), is that  
33  
34 384 whilst uncertainty over the human health effects of BPA exists, caution should be exercised  
35  
36 385 in ingestion of BPA [3]. Our data suggests that in our study population, it is unlikely that  
37  
38 386 participants could moderate their own BPA exposure in the long term by self-directed  
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40 387 modification of diet in a 'real world' setting, and furthermore, participants would have been  
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42 388 reluctant to adopt such a lifestyle change in the longer term due to the restrictions in dietary  
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44 389 choice and the effects on day to day life. Most of these barriers appear to arise from the  
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46 390 pervasiveness of BPA in our food chain, and inadequate labelling of foods packaged in BPA-  
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48 391 containing substances. We propose that until a definitive assessment of the health risks of  
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50 392 BPA is available, informed choice over whether or not to consume BPA and similar  
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52 393 chemicals in foodstuffs should be facilitated by better labelling.  
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6 395 **CONTRIBUTORSHIP STATEMENT**  
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8  
9 396 TSG - Contributed to study design and co-wrote the paper  
10

11 397 NB - Contributed to study design and participant involvement  
12

13 398 BP - Managed the technical aspects of the project and reviewed the manuscript  
14

15 399 ALK - Contributed to data entry and interpretation and reviewed the manuscript  
16

17  
18 400 BPA Schools Study Consortium members - designed and interpreted the study and  
19  
20 401 contributed to the manuscript.  
21

22 402 MHS - Carried out the qualitative analysis and reviewed the manuscript  
23

24 403 AMS - Managed sample collection, contributed to study design and reviewed the manuscript.  
25

26 404 LWH - PI , managed the study, wrote the manuscript  
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48 411 **COMPETING INTERESTS**  
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54 413 The authors have no competing interests to declare.  
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6 415 **DATA SHARING STATEMENT**7  
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9 416 Data are available upon reasonable request by emailing Lorna Harries  
10  
11 417 (L.W.Harries@exeter.ac.uk).  
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3 503 **FIGURE LEGENDS**  
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9 505 **Figure 1. The effect of a ‘real world’ BPA avoidance diet on urinary BPA exposure over**  
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11 506 **a 7 day period.** A. Urinary BPA levels (ng/ml) adjusted for urinary creatinine were plotted at  
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13 507 visit 1 before the intervention and at visit 2 after the intervention. The 3 extreme outliers have  
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15 508 been removed. The trajectories of individual participant measurements are shown. B. Change  
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17 509 in urinary BPA levels in ng/ml following the intervention diet are plotted against the self-  
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19 510 reported BPA risk score.  
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26 512 **Figure 2. The effect of baseline urinary BPA on the probability of achieving a drop in**  
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28 513 **levels following the intervention.** This graph illustrates the median urinary BPA level  
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30 514 adjusted for creatinine at visit 1 prior to the intervention expressed relative to whether or not  
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32 515 a reduction in urinary BPA levels was achieved following the 7 day intervention diet at visit  
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34 516 2. Error bars refer to the interquartile range of measurement.  
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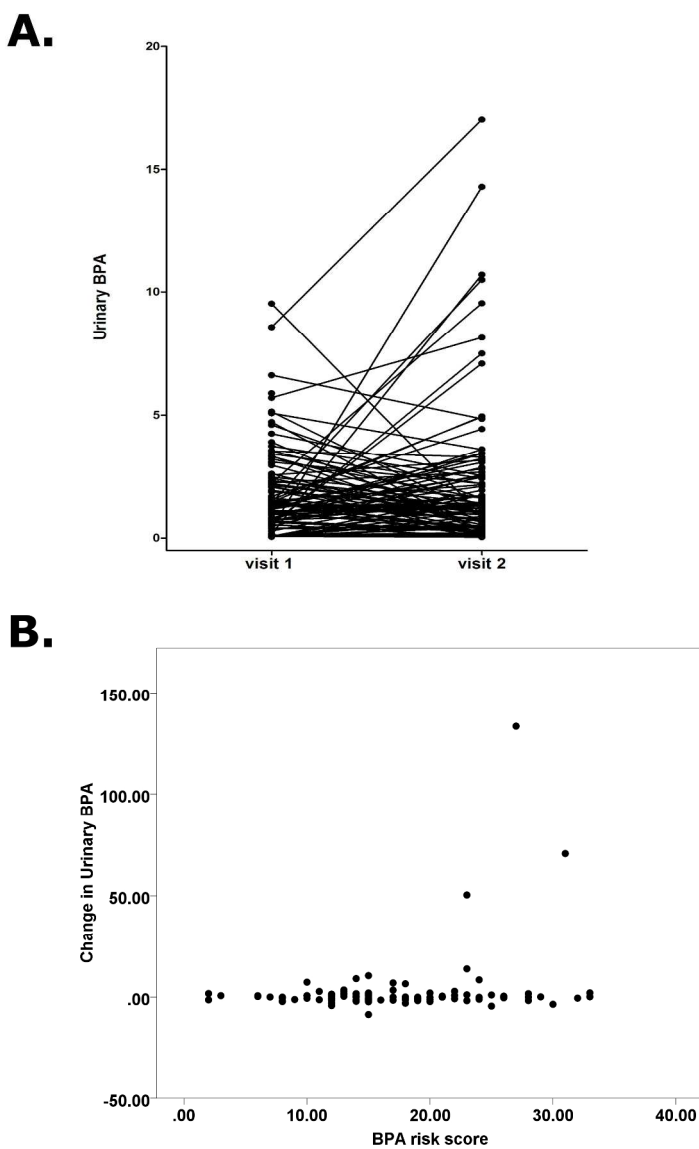


Figure 1

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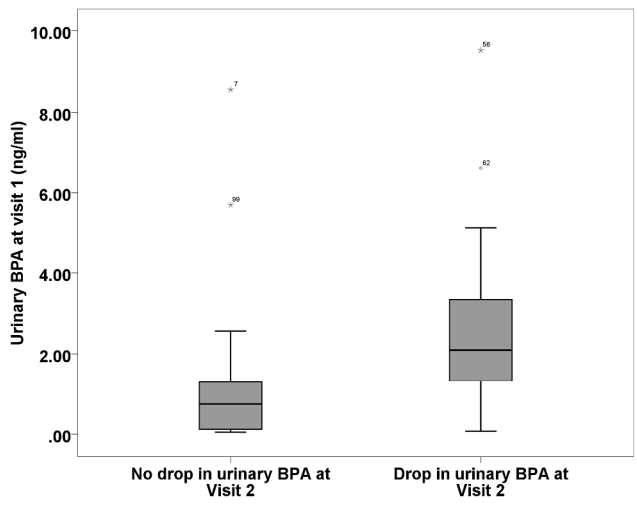


Figure 2

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## BPA Myth and Reality Dietary Intervention Guidelines



### General instructions

The purpose of this dietary intervention trial is to follow a diet designed to minimise routes of exposure to the food packaging chemical bisphenol A (BPA). For the dietary intervention period, please follow as closely as possible the instruction given below. Try to maintain your diet during the intervention period to be as closely similar to your normal diet as possible, in terms of the content, amount and calorific value of the food you eat. Please record details of each meal and the drinks and snacks you consume on the forms provided. Below are some general cooking and eating tips and an indication of which foods are best to avoid and those that are considered a low source of BPA.

### Cooking and eating tips for the intervention period.

The general approach is to replace any food items that fall into the 'avoidance' category with an alternative, chosen to minimise exposure to BPA

- **Switch to stainless steel and glass food storage and drink containers.**
- **Move foods to ceramic or glass food containers before microwaving.**
- **Consider a coffee filter or percolator for coffee – home coffee makers (Such as Nespresso™) may have polycarbonate-based water tanks and phthalate-based tubing.**
- **Eat out less, especially at restaurants that do not use fresh ingredients.**
- **Avoid canned food consumption. Where possible, replace with fresh produce or cardboard or tetrapack packaged alternatives.**
- **Choose fresh fruits and vegetables when possible, and frozen if not.**
- **Soak dried beans for cooking rather than tinned.**

## Foods to avoid

**Tinned foods.** Top ten tinned foods that are reported to be sources of BPA include coconut milk, soup, meat, vegetables, meals (e.g. pasta with sauce), juice, fish, beans, meal replacement drinks, fruit.

**Carbonated/fizzy drinks and juices in cans.** Avoid carbonated drinks in cans and drinks stored for prolonged periods in reusable sports bottles, unless they are labelled 'BPA free' (many commercial sports bottles are).

**Fast food from commercial outlets.** Most processed food has passed through numerous processes, and each additional processing step provides an opportunity for BPA to enter through packaging or tubing. Try to replace fast and processed foods with a freshly prepared and cooked alternative.

**Packaged fruit and vegetables.** Replace these where possible with unpackaged, loose fruit and vegetable items as far as possible.

**Convenience/ready meals.** Plastics types considered safest in terms of chemical migration are recycling numbers 2 and 5. Avoid food prepared in packaging with recycling number 7, which includes many different types of polymer and mixed polymers, including polycarbonate, a source of BPA. Try to avoid foods that are designed to be heated in the microwave in their packaging.

**Chocolate and ice cream.** Individuals who report eating chocolate bars and ice cream on a regular basis have been reported to have higher than average BPA exposure. Try to avoid excessive consumption.

## Non-food or food packaging routes of exposure

Although plastics found in consumer goods such as DVDs, CDs, computer goods and sunglasses do contain BPA, this is not an important route of exposure.

Till receipts often contain high levels of BPA, so wash your hands before eating or drinking if you have been handling them.

Dental sealants may contain BPA, so avoid any pre-planned dental work

## Example daily diet

Food Item	Comments
<b>Breakfast</b>	
Cereal, Fruit	
Milk	Polypropylene or glass packaging
Bread	
Yoghurt	Choose polypropylene container
<b>Lunch</b>	
Meat or fish products	Check packaging and avoid those labelled no. 7. Avoid tinned ingredients
Cheese	
Salad items, Fruit	Choose unpackaged where possible, wash before use
Pasta	
<b>Dinner</b>	
Shepherds pie	Cooked in saucepan and oven rather than microwaved in plastic
Green beans	Fresh or frozen
Bread	
<b>Drinks</b>	
Water	Water direct from tap or use stainless steel or BPA free water bottle
Tea/coffee	Prepare in teapot or cafetiere, avoid commercial coffee makers
Carbonated drinks	Avoid canned drinks and those stored in reusable containers for prolonged periods
Milk	Polypropylene or glass packaging
<b>Snacks</b>	
Fruit	
Potato crisps	

Place participant barcode here	FOOD - DAY 1		DRINK - DAY 1	
Contents of meal	Was food packaged in plastic known or suspected to contain BPA?	Was food cooked in plastic known or suspected to contain BPA?	Type of Drink	Packaging (please describe) e.g. canned, plastic (Δ number), tetrapak
<b>Breakfast:</b>				
1.				
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<b>Lunch:</b>				
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<b>Dinner:</b>				
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<b>Snacks:</b>				
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Place participant barcode here	FOOD - DAY 2		DRINK - DAY 2	
Contents of meal	Was food packaged in plastic known or suspected to contain BPA?	Was food cooked in plastic known or suspected to contain BPA?	Type of Drink	Packaging (please describe) e.g. canned, plastic (Δ number), tetrapak
<b>Breakfast:</b>				
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<b>Lunch:</b>				
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<b>Dinner:</b>				
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<b>Snacks:</b>				
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Place participant barcode here	FOOD - DAY 3		DRINK - DAY 3	
Contents of meal	Was food packaged in plastic known or suspected to contain BPA?	Was food cooked in plastic known or suspected to contain BPA?	Type of Drink	Packaging (please describe) e.g. canned, plastic (Δ number), tetrapak
<b>Breakfast:</b>				
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<b>Lunch:</b>				
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<b>Dinner:</b>				
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<b>Snacks:</b>				
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Place participant barcode here	FOOD - DAY 4		DRINK - DAY 4	
Contents of meal	Was food packaged in plastic known or suspected to contain BPA?	Was food cooked in plastic known or suspected to contain BPA?	Type of Drink	Packaging (please describe) e.g. canned, plastic (Δ number), tetrapak
<b>Breakfast:</b>				
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<b>Lunch:</b>				
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<b>Dinner:</b>				
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<b>Snacks:</b>				
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Place participant barcode here	FOOD - DAY 5		DRINK - DAY 5	
Contents of meal	Was food packaged in plastic known or suspected to contain BPA?	Was food cooked in plastic known or suspected to contain BPA?	Type of Drink	Packaging (please describe) e.g. canned, plastic (Δ number), tetrapak
<b>Breakfast:</b>				
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<b>Lunch:</b>				
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<b>Dinner:</b>				
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Place participant barcode here	FOOD - DAY 6		DRINK - DAY 6	
Contents of meal	Was food packaged in plastic known or suspected to contain BPA?	Was food cooked in plastic known or suspected to contain BPA?	Type of Drink	Packaging (please describe) e.g. canned, plastic (Δ number), tetrapak
<b>Breakfast:</b>				
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<b>Lunch:</b>				
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<b>Dinner:</b>				
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<b>Snacks:</b>				
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Place participant barcode here	FOOD - DAY 7		DRINK - DAY 7	
Contents of meal	Was food packaged in plastic known or suspected to contain BPA?	Was food cooked in plastic known or suspected to contain BPA?	Type of Drink	Packaging (please describe) e.g. canned, plastic (Δ number), tetrapak
<b>Breakfast:</b>				
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<b>Lunch:</b>				
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<b>Dinner:</b>				
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**Participant barcode****Additional study information.**

Please do not feel obliged to answer these questions if you are uncomfortable doing so.

**Gender**

- Female  
 Male  
 Prefer not to say

**Tobacco Usage** – Have you used tobacco over the past week

- Yes

If so, what type and how much? \_\_\_\_\_

- No  
 Prefer not to say

**Alcohol Usage** – Have you used alcohol over the past week

- Yes

If so, what type and how much? \_\_\_\_\_

- No  
 Prefer not to say

**Medication** - Have you taken any medication over the last week?

- Yes  
 No  
 Prefer not to say

If so, Please name the medication \_\_\_\_\_  Prefer not to say

**Vegetarian/vegan diet** - Have you eaten or drank any soya products over the past week?

- Yes  
 No  
 Prefer not to say

**Your measurements** - leave blank if you prefer not to say

Your height \_\_\_\_\_

Your weight \_\_\_\_\_

**Supplementary information file 3. Example daily diet diary.** A score of 1 is given to each item containing suspected to contain BPA or be packaged in BPA-containing materials. Highly processed foods are also scored as 1, due to uncertainties in the processing procedures. The daily totals are summed to produce a BPA risk score for the 7 day intervention.

	Item	Packaging	Score
<b>Breakfast</b>			
	Homemade pancakes	None	0
	Sugar	None	0
	lemon	None	0
	milk	HDPE	0
<b>Lunch</b>			
	Homemade Cheese sandwich	none	0
	Homemade sultana cake	none	0
	water	glass	0
<b>Dinner</b>			
	Homemade omelette	none	0
	Sweetcorn	Can	1
	Rice	Cellophane	0
	Tomatoes	none	0
	water	glass	0
<b>Snacks</b>			
	Crisps (processed)	Cellophane	1
	Apple	none	0
	milk	HDPE	0
		<b>Total for day</b>	<b>2</b>

Participant Barcode

## BPA: Myth and Reality diet questionnaire

1. Were there any times during the week that you knowingly/unknowingly did not stick to the diet? Please tick any that apply and give indication of frequency.

School meals  \_\_\_ times

Restaurants/cafés  \_\_\_ times

Friends' houses  \_\_\_ times

Takeaway  \_\_\_ times

Other \_\_\_\_\_  \_\_\_ times

2. If you heated your food in a microwave, what was the food in? Tick any which apply and give indication of frequency.

A food storage container or bowl known or suspected to contain BPA  \_\_\_ times

3. When you or your family drank water, where did your water come from? Tick any which apply and give indication of frequency.

Plastic filter jug known or suspected to contain BPA  \_\_\_ times

Individual water bottle known or suspected to contain BPA  \_\_\_ times

Larger water container known or suspected to contain BPA  \_\_\_ times

4. How many times during the week did you eat food that had been stored or transported in plastic containers known or suspected to contain BPA?

\_\_\_\_\_

5. How many times during the week did you eat tinned food or drink from cans?

\_\_\_\_\_

6. Did the BPA reduced diet affect How much you spent on shopping?

Spent more

Spent less

No difference

Participant questionnaire V3 25Jun15

Participant Barcode

1  
2  
3  
4  
5 **7. Did it take longer to source your food than usual?**  
6

7 Yes  No

8  
9 If so, why? \_\_\_\_\_  
10  
11  
12

13  
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15  
16 **8. Did it take longer to prepare food than usual?**  
17

18 Yes  No

19  
20  
21  
22 If so, why? \_\_\_\_\_  
23  
24  
25

26  
27  
28  
29 **9. How restricted did you feel by your food choice?**  
30

31  
32  
33  Very  Slightly  No difference  
34  
35

36  
37 If you felt you were restricted by the diet, why was this? \_\_\_\_\_  
38  
39  
40

41  
42  
43  
44 **10. Did the diet affect your calorific intake?**  
45

46  
47  
48 Yes  No

49  
50 If so, why? \_\_\_\_\_  
51  
52  
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Participant questionnaire V3 25Jun15

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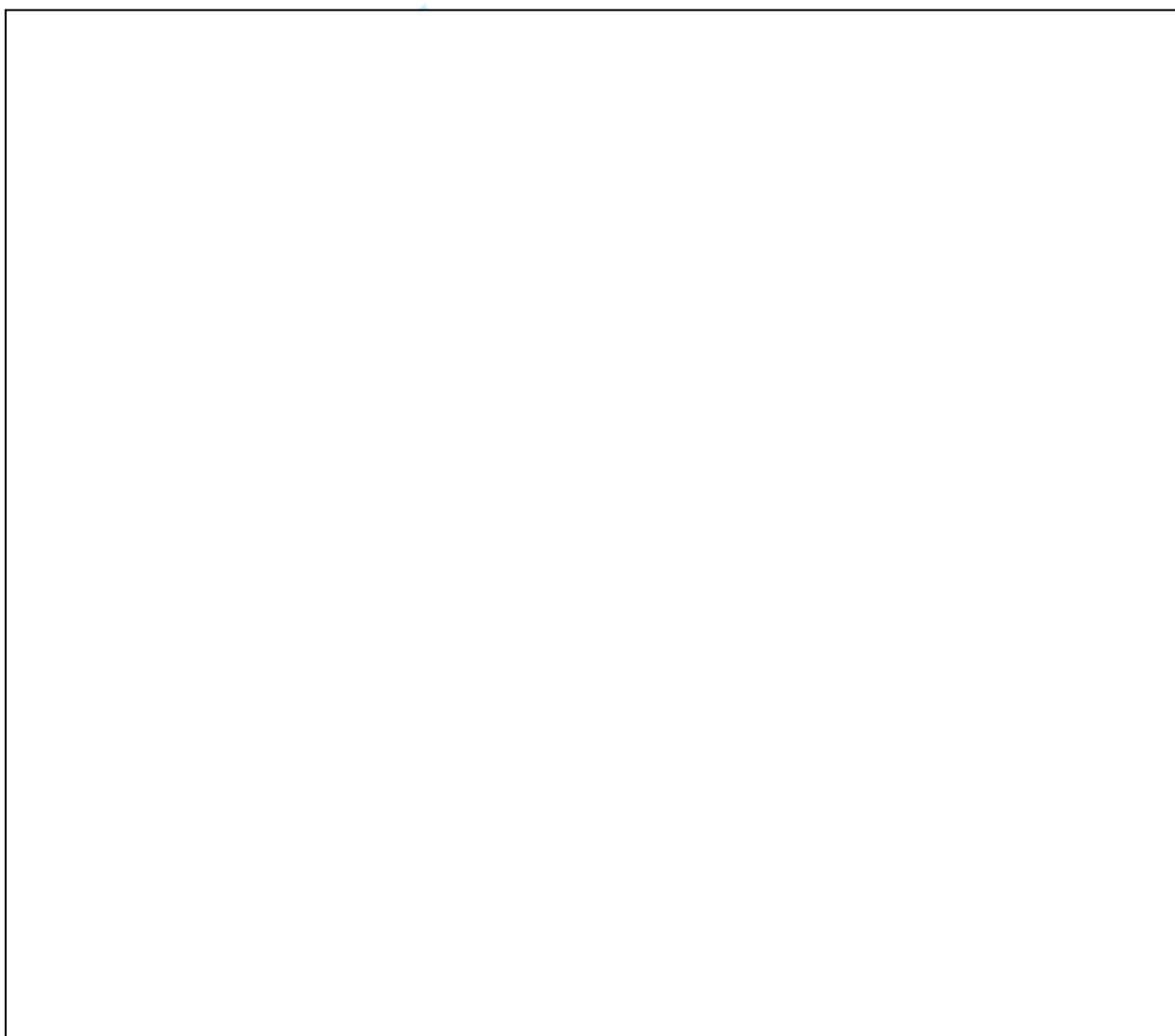
Participant Barcode

1  
2  
3 **11. How easy would you find it to sustain this diet over a longer period of time?**  
4  
5

- 6  
7 Very easy   
8  
9 Easy   
10  
11 Hard   
12  
13 Very hard   
14  
15 Not sure   
16

17  
18  
19 **12. Is there anything else about following the diet that you would like to add?**  
20  
21

22  
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Thank you for reading this leaflet. If you wish to participate in this study, you will be asked to agree to the consent statements below in the presence of a member of the research team.

## CONSENT STATEMENTS

1. I confirm that I have read this information sheet and have discussed participation in this project with my family. I have had opportunity to consider the information, ask questions and have had these questions answered satisfactorily. *You should not give consent until you are happy that you understand what the study involves.*
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my right to participate in the rest of the study being affected. *This means that even if you helped design this study you do not have to be a participant and you should not feel under any pressure to participate.*
3. I agree to participate in this study as a research subject. *This means that you agree to participate in a one-week diet and to provide two blood and urine samples.*
4. I understand that my anonymised blood and urine samples and linked anonymous questionnaire data will be sent to University of Exeter Medical School, Royal Devon & Exeter Hospital and my urine sample only will be sent to the Rolvaintain laboratory, a specialist BPA analysis company. *This means that laboratory staff will not know that samples belong to you, but dedicated staff at the University of Exeter, with training and experience in data protection, will be able to link your sample data to your questionnaire data.*
5. I understand that RNA (genetic material) will be extracted from my blood and will be stored anonymously. *This means that Professor Harries' team will use our RNA to provide data that you will help analyse but may also do further research on the samples to identify reasons for any changes seen.*
6. I understand that data relating to my participation in the study will be returned anonymously to my school to be used for educational purposes. *This means that although you will get to analyse data from your samples there is no way you will know which data relates to your samples and which to other participants.*

### Complaints:

If you have any complaints about the way in which this study has been carried out please contact the Chair of the University of Exeter Medical School Research Ethics Committee Peta Foxall PhD, Chair, UEMS Research Ethics Committee: P.J.D.Foxall@exeter.ac.uk.

This project has been reviewed and approved by the University of Exeter Medical School Research Ethics committee UEMS REC REFERENCE NUMBER: 15/07/074)

## BPA: Myth or Reality?

A research study investigating the effect of chemicals in plastic on gene activity and whether dietary interventions can reduce BPA levels in teenagers.



### Involvement & Engagement

The aim of this year-long project is to involve teenagers in a research study that is relevant to them, by allowing them to help design a research project, analyse non-identifiable participant data and help to present and publish the outcomes.

### Participation

Students will be asked to undertake a one week diet to reduce their intake of BPA, a chemical found in plastics. They will be asked to provide urine and blood samples before and after their diet.

## What is BPA?

BPA (Bisphenol A) is a chemical used in the manufacture of plastics. Plastics containing BPA are found in a wide range of products including food and drink containers. BPA in these products can be ingested and there are concerns that high BPA levels in the blood could possibly affect human health. Research is therefore needed to understand its effects on the human body and how we can reduce its consumption by minor changes to our diet.



This project is being run as a student-involvement project to answer two specific questions:

1. Can we see the effects of dietary BPA on our genes?
2. Can we effectively reduce BPA in our diet?

In the past, small-scale experiments have shown that BPA levels in the human body can be reduced by rigid dietary interventions but these interventions would be difficult to implement in the "real world". In this study a one-week dietary intervention designed by teenagers will be used by them to determine whether BPA levels, and the activity of BPA-responsive genes can be effectively reduced in young people by avoiding food packaging that contains this chemical.

## What will I need to do?

### Day 1

- Provide a nurse with a 2.5ml blood sample and a urine sample.

### Day 2 - Day 8

- Follow a diet that you have helped to design.
- The diet will exclude sources of BPA as much as possible but will be nutritionally and calorifically similar to your usual diet.
- You will be asked to complete a food diary and answer a questionnaire about how easy it was to follow this diet.

### Day 8

- Provide a nurse with a 2.5ml blood sample and a urine sample.



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**We recommend that you discuss the project with your family and involve them in planning what you eat and how you will prepare it.**

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## What will happen to my samples and data?

When you participate in the study you will be allocated with a numerical study ID. Your samples and data will be labelled with this number so that we can match your 'before' and 'after' diet samples with your food diary data. Once all data has been collated and coded it will be further anonymised by a person external to the project so that no data can be linked to any of the participants.



Urine samples from before and after the diet will be sent to the Royal Devon & Exeter NHS Foundation Trust for creatinine analysis and to the Royal Devon & Exeter Molecular Genetics Laboratory for BPA analysis. RNA will be extracted from blood samples at the Royal Devon & Exeter Molecular Genetics Laboratory and the expression levels of two BPA-responsive genes will be measured in the samples taken before and after the diet. These anonymised RNA samples will be stored and used only by Professor Harries team for further research on the mechanisms behind our findings.

## What are the benefits of taking part?

This project will help you to understand how you might be able to reduce BPA in your diet and your involvement in the design will give you an excellent insight into clinical research, community outreach and scientific practise. Your role as a participant is unlikely to have any direct health benefits.



## Are there any risks intaking part?

Blood samples will be taken by fully qualified and insured NHS personnel. Any potential discomfort or side-effects will be equivalent to that experienced giving a blood sample to your GP. All data will be fully anonymised before analysis. This means that you will not find out anything about your blood or urine samples. Following the diet may minimally increase the cost of your groceries for the week, but since fresh foods are usually less expensive than pre-packaged foods, we do not expect this to be an issue.



## What will happen to the results of the research study?

You will be given the opportunity to help analyse anonymised data from this project and to help disseminate the outcomes of this research. It is hoped that the findings will be published in peer-reviewed journals and the wider media.

## Who is organising this research?

The research is organised by Professors Lorna Harries & Tamara Galloway of the University of Exeter as part of their research program into BPA and part of the University's outreach program to involve schools in academic research.

Version 4 (2/8/2015)

BPA: Myth & Reality

STUDY ID

CONSENT STATEMENTS		Please circle
1. I confirm that I have read information sheet BPA PIS Version 4 and have discussed participation in this project with my family. I have had opportunity to consider the information, ask questions and have had these questions answered satisfactorily. <i>You should not give consent until you are happy that you understand what the study involves.</i>		YES / NO
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without right to participate in the rest of the study being affected. <i>This means that even if you helped design this study you do not have to be a participant and you should not feel under any pressure to participate.</i>		YES / NO
3. I agree to participate in this study as a research subject. <i>This means that you agree to participate in a one-week diet and to provide two blood and urine samples.</i>		YES / NO
4. I understand that my anonymised blood and urine samples and linked anonymous questionnaire data will be sent to University of Exeter Medical School, Royal Devon & Hospital and my urine sample only will be sent to the Rolvaintain laboratory, a specialist BPA analysis company. <i>This means that laboratory staff will not know that samples belong to you, but dedicated staff at the University of Exeter, with training and experience in data protection, will be able to link your sample data to your questionnaire data.</i>		YES / NO
5. I understand that RNA (genetic material) will be extracted from my blood and will be stored anonymously. <i>This means that Professor Harries' team will use our RNA to provide data that you will help analyse but may also do further research on the samples to identify reasons for any changes seen.</i>		YES / NO
6. I understand that data relating to my participation in the study will be returned anonymously to my school to be used for educational purposes. <i>This means that although you will get to analyse data from your samples there is no way you will know which data relates to your samples and which to other participants.</i>		YES / NO
Name of Participant	Signature	Date
Name of Person Obtaining Consent	Signature	Date
I the above signed testify the participant is providing voluntary and fully informed consent to participate in this study. I am on the delegation log to obtain consent for this study and are trained in obtaining consent.		
This project has been reviewed and approved by the University of Exeter Medical School Research Ethics Committee UEMS REC REFERENCE NUMBER: 15/07/074)		

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**Version 4 (2/8/2015)**

**BPA: Myth & Reality**

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For peer review only



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

	Item No	Recommendation
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found  <b>a) Page 1</b> <b>b) Page 2</b>
<b>Introduction</b>		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported  <b>Page 6, line 82</b>
Objectives	3	State specific objectives, including any prespecified hypotheses  <b>Page 7, line 113</b>
<b>Methods</b>		
Study design	4	Present key elements of study design early in the paper  <b>Page 8, line 140</b>
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection  <b>Page 8, line 152</b>
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up  <b>Page 7, line 123</b>  <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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants <hr/> (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable  Page 7, line 140, Page 8, line 152.

1  
2 Data sources/  
3 measurement 8\* For each variable of interest, give sources of data and details of methods of  
4 assessment (measurement). Describe comparability of assessment methods if there  
5 is more than one group

6  
7 **Page 8, line 140, Page 8, line 152**

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10 Bias 9 Describe any efforts to address potential sources of bias

11  
12 **Page 8, line 154, page 9 line 165**

---

15 Study size 10 Explain how the study size was arrived at

16  
17 **Page 7, line 127**

---

20 Quantitative variables 11 Explain how quantitative variables were handled in the analyses. If applicable,  
21 describe which groupings were chosen and why

22  
23 **Page 9, line 157**

---

25 Statistical methods 12 (a) Describe all statistical methods, including those used to control for confounding

26  
27 **Page 9, line 170**

---

30 (b) Describe any methods used to examine subgroups and interactions

31  
32 **Page 9, line 175**

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35 (c) Explain how missing data were addressed

36  
37 **Page 9, line 164**

---

40 (d) *Cohort study*—If applicable, explain how loss to follow-up was addressed

41  
42 **Page 12, line 206**

43  
44 *Case-control study*—If applicable, explain how matching of cases and controls was  
45 addressed

46  
47 *Cross-sectional study*—If applicable, describe analytical methods taking account of  
48 sampling strategy

---

49 (e) Describe any sensitivity analyses

50  
51 N/A

52  
53 Continued on next page

**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

**Table 1**

(b) Give reasons for non-participation at each stage

**Page 12, line 206**

(c) Consider use of a flow diagram

N/A

Descriptive data 14\* (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders

**Table 1**

(b) Indicate number of participants with missing data for each variable of interest

**Table 1**

(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)

**Page 9, line 172**

Outcome data 15\* *Cohort study*—Report numbers of outcome events or summary measures over time

**Table 1**

*Case-control study*—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 precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included

**Page 12, line 213 to page 13 line 229**

(b) Report category boundaries when continuous variables were categorized

**Page 9, line 176**

(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful



		time period
		N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
		<b>Page 13, line 234</b>
<b>Discussion</b>		
Key results	18	Summarise key results with reference to study objectives
		<b>Page 15, line 276</b>
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
		<b>Page 16, line 298</b>
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
		<b>Page 17, line 334</b>
Generalisability	21	Discuss the generalisability (external validity) of the study results
		<b>Page 18, line 344</b>
<b>Other information</b>		
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
		<b>Page 19, line 374</b>

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

# BMJ Open

## An engaged research study to assess the effect of a 'real-world' dietary intervention on urinary bisphenol A (BPA) levels in teenagers

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<b>Primary Subject Heading</b>:	Public health
Secondary Subject Heading:	Communication
Keywords:	Bisphenol A, Dietary intervention, PUBLIC HEALTH, community, Engaged research

SCHOLARONE™  
Manuscripts

1 **An engaged research study to assess the effect of a ‘real-world’ dietary**  
2 **intervention on urinary bisphenol A (BPA) levels in teenagers**

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18  
19 **Word count 3021**

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28  
29 **Declaration of competing issues**

30 The authors have no competing interests to declare.

31

## 32 **ABSTRACT**

33

### 34 **Objective**

35 Bisphenol A has been associated adverse human health outcomes and exposure to this  
36 compound is near-ubiquitous in the Western world. We aimed to examine whether self-  
37 moderation of BPA exposure is possible by altering diet in a real-world setting.

### 38 **Design**

39 An Engaged Research dietary intervention study designed, implemented and analysed by  
40 healthy teenagers from 6 schools and undertaken in their own homes.

### 41 **Participants**

42 A total of 94 students aged between 17 and 19 years from schools in the South West of the  
43 UK provided diet diaries and urine samples for analysis.

### 44 **Intervention**

45 Researcher participants designed a set of literature-informed guidelines for reduction of  
46 dietary BPA to be followed for 7 days.

### 47 **Main outcome measure**

48 Creatinine-adjusted urinary BPA levels were taken before and after the intervention.  
49 Information on packaging and food/drink ingested was used to calculate a BPA risk score for  
50 anticipated exposure. A qualitative analysis was carried out to identify themes addressing  
51 long term sustainability of the diet.

### 52 **Results**

1  
2  
3 53 BPA was detected in urine of 86% of participants at baseline at a median value of 1.22 ng/ml  
4  
5 54 (IQR 1.99). No effect of the intervention diet on BPA levels was identified overall ( $p = 0.25$ ),  
6  
7 55 but there was a positive association in those participants who showed a drop in urinary BPA  
8  
9 56 concentration post intervention and their initial BPA level ( $p = 0.003$ ). Qualitative analysis  
10  
11 57 identified themes around feelings of lifestyle restriction and the inadequacy of current  
12  
13 58 labelling practices.

## 15 16 17 59 **Conclusions**

18  
19 60 We found no evidence in this self-administered intervention study that it was possible to  
20  
21 61 moderate BPA exposure by diet in a real world setting. Furthermore, our study participants  
22  
23 62 indicated that they would be unlikely to sustain such a diet long term, due to the difficulty in  
24  
25 63 identifying BPA-free foods.

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3 65 **Article Summary**  
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7 67 *Strengths of the study*  
8

9 68

- 10  
11 69 • This study represents the largest assessment to date of the potential for moderating  
12 one's own BPA exposure through diet  
13  
14  
15 71 • The study was carried out in a 'real-world' setting rather than a regulated, controlled  
16 environment.  
17  
18  
19  
20 73 • The study was carried out in teenagers, the demographic with amongst the highest  
21 exposure.  
22  
23  
24 75 • Qualitative analysis reveals challenges with sustaining such a diet.  
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27 76 *Limitations of the study*  
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- 29  
30 77 • Calculation of a risk score is challenging due to the pervasive nature of BPA  
31 contamination  
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## 80 INTRODUCTION

81

82 Bisphenol A is one of the world's highest production volume chemicals. It is used in the  
83 manufacture of polycarbonate and other plastic consumer products, in heat resistant papers,  
84 dental sealants and in the epoxy resin-based lining of food and drink containers [1]. BPA can  
85 be found above the detection limit in the urine of the majority of people worldwide [2].  
86 Concern has been raised for public health, since BPA is classified as an endocrine disrupting  
87 chemical (EDC) which has been linked with several disorders in cell and animal models [3-  
88 5]. Several epidemiological studies have also linked outcomes such as type 2 diabetes,  
89 cardiovascular disease, obesity and abnormalities of sex hormone levels with BPA levels in  
90 human populations [6-10] Epidemiological data in humans has historically been more  
91 contentious however, due to relatively small sample sizes and issues around causality [11].  
92 The Endocrine Society concluded in 2015 that current evidence suggests that BPA and other  
93 endocrine disrupting chemicals may have effects on several reproductive, cardiovascular and  
94 metabolic traits in humans [12]. The current opinion of food regulatory bodies such as the  
95 European Food Standards Agency (EFSA) is that sufficient uncertainty remains to be able to  
96 exclude effects on the reproductive, immune, nervous, metabolic and cardiovascular systems  
97 and on cancer development [3] whilst the European Chemicals Agency (ECHA) has recently  
98 reclassified BPA as a chemical of very high concern due to its endocrine disrupting properties  
99 [13].

100

101 There has been wide interest in the sources of BPA and the potential for individuals to reduce  
102 their own exposure. Human exposure has been reported from inhalation of dust, uptake  
103 across the skin from thermal papers and till receipts and release from dental sealants. The  
104 main source is the ingestion of food and drink contaminated with BPA leached from

1  
2  
3 105 packaging materials [1, 14]. BPA is rapidly metabolised in the gut wall and liver and  
4  
5 106 removed from the blood by the kidneys, with a terminal half-life of 6 hours after oral  
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7 107 ingestion [15]. BPA has been detected in food samples packaged in glass, plastic, paper and  
8  
9 108 paperboard cartons, with an average concentration of 0.46 ng/g, rising to over 700 ng/g for  
10  
11 109 certain canned foods. Conversely, in a dietary intervention study in which 22 volunteers  
12  
13 110 consumed a 3 day fresh food diet which excluded canned or packaged foods, there was a 66%  
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15 111 reduction in urinary BPA excretion compared to concentrations before the intervention [16].  
16  
17 112 This latter study involved full dietary replacement of foodstuffs, an approach which is  
18  
19 113 impractical for the population at large. A follow up study found that households who  
20  
21 114 followed written recommendations produced by health care professionals showed no  
22  
23 115 significant change in their BPA exposure [17].  
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30 117 We present an alternative, citizen-science based approach, where 108 student volunteers  
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32 118 designed and undertook their own intervention diet, following provision of educational  
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34 119 materials. We questioned whether adherence to a self-designed and self-administered 'real  
35  
36 120 world' diet over 7 days would lead to significant reductions in excreted urinary BPA, and if  
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38 121 so, whether such a diet was likely to be sustainable in the long term.  
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## 44 123 **METHODS**

### 45 124

#### 46 125 **Participant group**

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48 127 We chose adolescents because it has been shown that they have higher concentrations of BPA  
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50 128 than adults (aggregated exposure of 1.449 µg/kg body weight per day) [3, 18]. A total of 108  
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52 129 students aged 17-19 from local schools were initially invited to participate in this engaged  
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3 130 research project. Six schools participated in this project (Clyst Vale Community College - 14  
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5 131 students; Exeter School - 12 students; South Dartmoor Community College - 13 students;  
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7 132 Honiton Community College - 11 students; Exeter College – 29 students and Exeter  
8  
9 133 Mathematics School – 29 students). Information and samples were available from 94  
10  
11 134 individuals at both visit one and visit 2 and comprise the complete dataset. This represents the  
12  
13 135 largest intervention study in the population demographic with the one of the highest BPA  
14  
15 136 exposures to date [18]. The number of students invited to participate was based on anticipated  
16  
17 137 effect sizes from previous work of this nature [16], and we allowed for a 10% dropout rate.  
18  
19 138 Students designed all of the materials required for completion of the study (study protocols,  
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21 139 food diaries, lifestyle questionnaires, patient information sheets and consent forms (see  
22  
23 140 Supplementary Information files 1 to 6).  
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### 30 142 **Ethical Permission**

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36 144 Ethical permission was granted by the University of Exeter Medical School Ethics  
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38 145 Committee (reference number 15/07/074) and the study was carried out in accordance with  
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40 146 the Declaration of Helsinki.  
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### 46 148 **The intervention diet**

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50 150 Students designed a “real world” diet designed to reduce consumption of BPA by avoidance  
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52 151 of processed foods and foods packaged in known sources of BPA [1, 14]; supplementary  
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54 152 information file 1). The study was designed at the University of Exeter as a collaboration  
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3 153 between academic staff and participating students and was developed at a series of interactive  
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5 154 workshops attended by all parties.  
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11 156 Students were asked to minimise their intake of known sources of BPA according to a set of  
12  
13 157 guidelines that had been co-designed with them based on the known literature. We requested  
14  
15 158 that calorific intake was maintained as near to their usual diet as possible and recorded details  
16  
17 159 of their daily diet including all food and drink, and its associated packaging, in a self-reported  
18  
19 160 food diary (Supplementary information file 2). Adherence was assessed using a 'BPA risk  
20  
21 161 score'; each individual dietary item potentially containing BPA was given a score of 1.  
22  
23 162 Heavily processed items were also scored 1 per item. These scores were collated at the end of  
24  
25 163 the 7 day trial to give a final risk score. An example of scores for a single participant on a  
26  
27 164 single day is given in supplementary information file 3. Given the short half-life of BPA, we  
28  
29 165 also carried out a secondary analysis considering only the BPA risk score from the 24 hours  
30  
31 166 immediately preceding the second sample. Information on lifestyle factors including sex,  
32  
33 167 BMI and time of urine collection was also collected (Supplementary information file 4). We  
34  
35 168 recognised that there may be a temptation for students to change their diets before the trial  
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37 169 based on their new learning. To avoid this, students were also specifically asked not alter  
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39 170 their diet before the intervention.  
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#### 46 172 **Sample collection and measurement of urinary BPA**

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50 174 Urine samples were collected into BPA-free bottles (Vacutest Kima, Italy) immediately  
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52 175 before and after the intervention, and were frozen at -20°C within 4 hours. Each participant  
53  
54 176 was sampled twice, once at visit 1 before the intervention and once at visit 2 after the  
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177 intervention. Sample collections were staggered to allow for the large number of participants  
178 passing through the facility, but students were sampled during the same time slot at both  
179 visits to account for circadian variation in BPA metabolism. The initial samples were  
180 collected during the early part of the day just prior to the students commencing the trial. The  
181 second samples were taken over the same time period 7 days later, just prior to the students  
182 recommencing their usual diet. Samples were transported on dry ice to a commercial  
183 laboratory (Rovaltain Research Company, Aixain, France) where analysis of total BPA was  
184 assessed by gas chromatography-tandem mass spectrometry. Experimental methods were  
185 validated for linearity, detection limit and accuracy and specificity of quantification based on  
186 the Standard NF T 90-201 for determination of xenobiotics. A quality control check of  
187 known standards injected every 6 samples at two levels of concentration (0.5 ng/ml and 5  
188 ng/ml) was quantified with each batch of unknown samples. Water-only samples were  
189 included as negative controls. Urinary creatinine was measured at the Royal Devon and  
190 Exeter Hospital using the Jaffe method on the Roche P800 platform (Roche, Mannheim,  
191 Germany), to allow correction for urine dilution. Results were expressed as a BPA:creatinine  
192 ratio. Samples where BPA was detected but quantifying at or around the limits of  
193 quantification (LoQ) of 0.1ng/ml were scored as  $LoQ/\sqrt{2}$  according to the method of Hornung  
194 and Reed [19].

195

### 196 **Statistical Analysis**

197

198 The difference between urinary BPA adjusted for creatinine between samples taken at visits 1  
199 and 2 was assessed to generate a  $\Delta$ BPA continuous variable. BPA risk scores were calculated  
200 as a continuous variable. The relationship between urinary BPA levels before and after the 7  
201 day intervention was assessed using a repeated-measure ANOVA, adjusted for sex, time of

202 sampling and BMI, with and without correction for creatinine. The relationship between  
203 urinary BPA at visit 1 and whether or not the participants had lower BPA at visit 2 was also  
204 examined by binary logistic regression, adjusted for sex, time of sampling and BMI. Here,  
205 samples showing small changes  $< 0.5\text{ng/ml}$  in either direction were omitted to avoid natural  
206 stoichiometric variation around zero. The relationship between change in BPA ( $\Delta\text{BPA}$ ) and  
207 BPA risk score was assessed by linear regression, adjusted for sex, time of sampling and BMI  
208 both with and without adjustment for creatinine. Statistical analysis was carried out using  
209 SPSS, v.22 (IBM, USA).

210

### 211 **Impact of following reduced BPA diet on lifestyle**

212

213 We carried out quantitative and qualitative analysis to address long-term sustainability of the  
214 diet. Data on the impact of following the diet on feelings of dietary restriction, time spent  
215 sourcing or preparing meals, calorific intake and long term sustainability were collected via a  
216 questionnaire (See Supplementary information file 4). The questionnaire also included a  
217 freeform section where participants could write about their experiences following the diet in a  
218 non-prescribed fashion for qualitative analysis. Qualitative data was assessed for thematic  
219 content by two experienced qualitative researchers. Key themes were independently  
220 identified and coded until agreement was reached.

221

## 222 **RESULTS**

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### 224 **Participant Characteristics**

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226 There were 108 volunteer participants invited to participate in this engaged research study. A  
 227 small number were absent or unable to produce a urine sample at both visits. A complete  
 228 dataset was thus received from 94 students. Information on the characteristics of the study  
 229 cohort are given in table 1.

230

231 **Table 1: Characteristics of the study population.** A complete dataset was available on 94  
 232 out of 108 participants. IQR = interquartile range, SD = Standard deviation. The units of BPA  
 233 are ng/ml and BMI is defined as Kg/m<sup>2</sup>. LoQ = limit of quantification. Urinary BPA levels  
 234 are given both as unadjusted data and as a BPA (ng/ml) to creatinine (mg/ml) ratio.

Unadjusted urinary BPA at visit 1 (n = 94)	
median (IQR)	1.01 (2.01)
95% confidence intervals	1.19 to 2.57
mean (SD)	1.88 (2.68)
Number of samples below LoQ (0.1ng/ml)	15
Minimum value (ng/ml)	0.07
Maximum value (ng/ml)	13.55
Creatinine-adjusted urinary BPA at visit 1 (n = 94)	
median (IQR)	1.22 (1.99)
95% confidence intervals	1.16 to 1.20
mean (SD)	1.58 (1.64)
Number of samples below LoQ (0.1ng/ml)	15
Minimum value (ng/ml)	0.05
Maximum value (ng/ml)	8.56
Unadjusted urinary BPA at visit 2 (n = 94)	
median (IQR)	1.47 (2.87)
95% confidence intervals	1.59 to 3.97
mean (SD)	2.78 (4.64)
Number of samples below LoQ (0.1ng/ml)	12
Minimum value (ng/ml)	0.07
Maximum value (ng/ml)	31.2
Creatinine-adjusted urinary BPA at visit 2 (n = 94)	
median (IQR)	1.24 (2.51)
95% confidence intervals	1.21 to 5.01
mean (SD)	3.13 (7.36)
Number of samples below LoQ (0.1ng/ml)	12
Minimum value (ng/ml)	0.04
Maximum value (ng/ml)	53.42
Unadjusted ΔBPA (n = 94)	

median (IQR)	0.06 (2.09)
95% confidence intervals	0.05 to 1.75
mean (SD)	0.90 (3.32)
Minimum value	-6.42
Maximum value	17.64
<b>Adjusted <math>\Delta</math>BPA (n = 94)</b>	
median (IQR)	0.05 (2.94)
95% confidence intervals	-0.28 to 3.39
mean (SD)	1.55 (7.16)
Minimum value	-4.47
Maximum value	50.38
<b>BPA risk score (n = 94)</b>	
median (IQR)	17.0 (11.0)
95% confidence intervals	15.4 to 18.8
mean (SD)	17.1 (6.63)
<b>Demographics (n= 94)</b>	
Sex - % male	44
Exposure to estrogens - % of cohort	15
BMI- median (IQR)	20.7 (3.43)
BMI- mean (SD)	21.3 (3.13)

235

236 BPA was detected in the urine of 86% of subjects at visit 1 prior to the intervention. Missing  
 237 samples were due to non-attendance of participants or non-provision of a suitable sample.  
 238 Samples below the limit of quantification were scored as 0.07 ng/ml (LoQ/ $\sqrt{2}$ ).

239

240 **Creatinine-adjusted urinary BPA concentrations do not change significantly after**  
 241 **following an intervention diet designed to reduce BPA exposure for 7 days.**

242

243 The median change in creatinine-adjusted urinary BPA between visits ( $\Delta$ BPA) was 0.05  
 244 ng/ml with an interquartile range of 2.94 ng/ml. We identified no changes in urinary BPA  
 245 between visits ( $p = 0.25$ ; figure 1a). Three outliers with very high urinary BPA readings at  
 246 visit 2 were excluded from the analysis, since these samples lay outside the linear range of  
 247 analysis, so confidence in quantification was poor. No confounding factors included in the  
 248 analysis were associated with change in BPA ( $p = 0.78, 0.43$  and  $0.36$  for sex, time of sample  
 249 collection and BMI respectively). We also identified no change in BPA levels between visits

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3 250 using data uncorrected for creatinine ( $p = 0.20$ ). We also assessed whether participants from  
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5 251 different schools showed variable BPA levels at either visit 1, or change in BPA, but no such  
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7 252 effects were noted.  
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11 254 Similarly, no relationship between change in urinary BPA ( $\Delta$ BPA) and BPA risk score was  
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13 255 identified (beta coefficient 0.08, standard error 0.07,  $p = 0.55$ ; figure 1b). No associations  
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15 256 were noted between change in urinary BPA and BPA risk score in data not adjusted for  
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17 257 creatinine ( $p = 0.27$ ). We found no association between  $\Delta$ BPA and BPA risk score when  
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19 258 considering only the exposure on the day prior to testing, taking into account the short half-  
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21 259 life of BPA ( $p = 0.16$  and  $p = 0.33$  for adjusted and unadjusted data respectively).  
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27 261 **Participants with highest starting urinary BPA levels were more likely to demonstrate**  
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29 262 **lower BPA levels at visit 2.**  
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34 264 We found an inverse relationship between initial BPA levels and whether a participant had  
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36 265 reduced BPA levels at visit 2 ( $p = 0.003$ ). These data indicate that the participants in the  
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38 266 cohort with the highest creatinine-adjusted urinary BPA levels at visit 1 were more likely to  
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40 267 demonstrate a drop in their urinary BPA at visit 2 (figure 2).  
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46 269 **Following the intervention diet has significant effects on participant lifestyle**  
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52 271 Participants indicated that following the diet had no significant cost implications on family  
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54 272 finances, with 50% of participants reporting that it had cost more, and 50% reporting that  
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3 273 costs had decreased or remained the same. Although participants did not spend longer  
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5 274 preparing their food, 78% of participants reported that their shopping took longer. Calorific  
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7 275 intake was not affected for the majority of participants (58%) of participants. A large  
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9 276 percentage of the cohort (91%) reported that they felt at least slightly restricted in their food  
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11 277 choices and 27% of participants reported that they felt very restricted. Finally, 66% of  
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13 278 participants stated that they would find it hard or very hard to follow the diet long term.  
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### 18 280 **Qualitative analysis of the effect of following the diet on lifestyle**

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22 282 We identified 5 overriding themes in our qualitative analysis of the effect of following the  
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24 283 diet on lifestyle. These were 1) the widespread use of plastics possibly containing BPA in  
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26 284 food packaging (“almost everything is packaged in plastic” – participant 70, “Literally  
27  
28 285 everything involved plastic” – participant 28). 2) Lack of clarity in labelling of products and  
29  
30 286 packaging potentially containing BPA (“I found it really hard to know what foods I could eat  
31  
32 287 ... there is never a guarantee it is BPA free” – participant 43, “The biggest problem was that  
33  
34 288 a lot of packaging doesn’t state what type of plastic it is or whether it contains BPA” –  
35  
36 289 participant 74). 3) The perceived restrictions of being on the ‘real world’ BPA avoidance diet  
37  
38 290 (“Difficulty eating out, hard to find foods in college or ‘out’ that hadn’t touched BPA. My  
39  
40 291 family had a takeaway on Saturday night and I couldn’t eat it” – participant 56, “Sometimes I  
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42 292 can’t eat / drink what I want because of the recycling number” – participant 112). 4) The  
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44 293 impact of eating ‘BPA free’ was the only positive theme emerging (“I feel I have eaten much  
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46 294 more healthily this week ... I didn’t eat so much junk food” – participant 74, “I ate more  
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48 295 vegetables and less chocolate” – participant 83). 5) The impact on shopping habits (“You  
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50 296 can’t get it all from supermarkets” – Participant 37; “Had to go to more individual food  
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52 297 shops” – participant 103).  
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**DISCUSSION**

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301 Exposure to the endocrine disrupting chemical Bisphenol A (BPA) is ubiquitous [2], with  
302 growing evidence that it may be associated with adverse health outcomes [4]. Here, 94  
303 researcher participants aged 17-19 years designed and undertook a quantitative and  
304 qualitative engaged research project designed to assess the potential for reduction of personal  
305 exposure to BPA through moderation of diet, which would have utility in a 'real world'  
306 setting. We conclude that the 'real world' diet designed to reduce BPA exposure had no  
307 effect on creatinine-adjusted urinary BPA concentrations in our cohort over a period of 7  
308 days in our dataset.

309

310 Although levels of urinary BPA in our study cohort were slightly lower at the outset of the  
311 study in our cohort than in others [18], measureable levels were present in the vast majority  
312 of our participants. Participants were unable to achieve a reduction in their urinary BPA  
313 levels over the 7 day trial period, despite good compliance to supplied guidelines. Avoidance  
314 of BPA was not easily achieved on an individual level in our study population, with  
315 qualitative analysis indicating that participants experienced feelings of restriction and  
316 difficulties in sourcing BPA-free food due to inadequate labelling of foods and food  
317 packaging. This suggests that the intervention would be difficult to sustain in the longer term.

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319 This work represents the largest group of unrelated participants in a high exposure  
320 demographic to date, since previous work has focused on families and related individuals  
321 [16][17], who may share common sources of BPA. Although other population demographics

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3 322 such as young children may have higher levels of BPA than our chosen study population  
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5 323 [18], it would not have been possible to do the sort of engaged research project that we  
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7 324 envisaged in this group. Our intervention is a 'real world' diet, designed to a set of guidelines  
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9 325 (such as reduction in the usage of tinned foods or foods with high levels of processing), rather  
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11 326 than the strict, prescribed diets that have been used in other studies [16], which suggested that  
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13 327 it was possible for participants to reduce their urinary BPA excretion by approximately 60%  
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15 328 in a period of just 3 days [16]. In our self-designed, self-administered study this was  
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17 329 unachievable. This may reflect the difficulty in identifying and sourcing foods free of BPA in  
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19 330 our commercial environment. Finally, the qualitative thematic analysis we carried out in our  
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21 331 study has given an indication that adherence to even a 'real world' BPA reduction diet with  
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23 332 fewer restrictions and more choice over the longer term was unlikely in our study population  
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25 333 due to difficulties in identifying foodstuffs likely to contain less BPA.  
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32 335 BPA has a terminal half-life of 6 hours [15]. Spot samples may therefore not be as accurate as  
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34 336 continuous sampling strategies (24hr urine collection). However, recent studies suggest that  
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36 337 despite its short half-life, measureable BPA remains present for up to 43 hours post-fasting,  
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38 338 indicating non-food exposures or accumulation in body tissues such as fat [20]. We identified  
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40 339 no impact of time of sample collection on BPA levels in our sample set, in either creatinine-  
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42 340 adjusted or unadjusted data, indicating that our measurements were not influenced by time  
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44 341 since the last meal. Spot sampling as used here may therefore represent an acceptable  
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46 342 compromise and remains a practical option in the community setting of our study. The large  
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48 343 variability in urinary BPA levels within an individual sampled at different times may also  
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50 344 have reduced our ability to observe an effect. This could be facilitated by the use of multiple  
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52 345 sampling, or pools of multiple urines, but was not feasible within the confines of our study.  
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347 Calculating an accurate BPA risk score is challenging. Data were self-reported, and  
348 foodstuffs are not labelled for BPA content. It is difficult to generalise across food types and  
349 large variations in BPA concentrations occur between different products of the same food  
350 type or even different lots of the same product [1]. Foods that were free of BPA-containing  
351 packaging (as far as it was possible to tell) may have been highly processed or contain food  
352 items from a variety of sources. Highly processed and 'fast' food has previously been  
353 demonstrated to be a source of BPA [21]. A study of the temporal trends seen in composite  
354 food samples found no change in the overall BPA content of the food, despite large reduction  
355 in the BPA content of some individual food items, illustrating the difficulties in effectively  
356 excluding BPA from a varied diet [22]. Participants may therefore have changed BPA  
357 containing foods for other, perceived healthier choices, which may still contain BPA by  
358 virtue of processing.

359

360 BPA enters foodstuffs by leaching from polycarbonate or epoxy resin after manufacture, or  
361 by hydrolysis of the polymer itself [23]. The migration rate of BPA increases with higher  
362 temperatures [24], and with time and use, e.g. repeated use of polycarbonate water bottles  
363 [25]. Exposure to BPA can also occur through routes other than food, including dust  
364 ingestion and dermal absorption [26] and this was not taken into account in our study. A  
365 study of volunteers who purposefully handled thermal receipts showed an increase in urinary  
366 BPA excretion of up to 84%, and their BPA levels took longer to return to pre exposure  
367 levels, suggesting a difference in the bio-availability of BPA through skin and oral routes  
368 [27]. It is also possible that some manufacturers may have voluntarily reduced the amount of  
369 BPA-containing food packaging compared to their previous usage, given the attention that

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3 370 endocrine disrupting chemicals have received in the media. However, measurable levels of  
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5 371 BPA were still detected in the majority of participants in our study, which suggests that there  
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7 372 may be other, non-dietary, sources of BPA, and that exposure to BPA remains an issue. We  
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9 373 may also have been underpowered to detect subtle changes in urinary BPA, given the  
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11 374 heterogeneity in food choice; detection of such effects may need thousands of participants.  
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13 375 Finally, our study, like other studies of its type, does not take account of inter-individual  
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15 376 differences in the metabolism and excretion of BPA arising from differences in genetic  
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17 377 background between people. BPA is metabolised primarily by UDP-  
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19 378 glucuronosyltransferases, and altered activity polymorphisms of these enzymes have been  
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21 379 reported [28].  
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28 381 Emerging evidence suggests that that BPA may be linked to several chronic human health  
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30 382 conditions [6-9, 29], suggesting that continued study of the human health effects of BPA  
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32 383 exposure is justified. The opinion of the European Food Safety Authority (EFSA), is that  
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34 384 whilst uncertainty over the human health effects of BPA exists, caution should be exercised  
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36 385 in ingestion of BPA [3]. Our data suggests that in our study population, it is unlikely that  
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38 386 participants could moderate their own BPA exposure in the long term by self-directed  
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40 387 modification of diet in a 'real world' setting, and furthermore, participants would have been  
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42 388 reluctant to adopt such a lifestyle change in the longer term due to the restrictions in dietary  
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44 389 choice and the effects on day to day life. Most of these barriers appear to arise from the  
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46 390 pervasiveness of BPA in our food chain, and inadequate labelling of foods packaged in BPA-  
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48 391 containing substances. We propose that until a definitive assessment of the health risks of  
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50 392 BPA is available, informed choice over whether or not to consume BPA and similar  
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52 393 chemicals in foodstuffs should be facilitated by better labelling.  
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6 395 **CONTRIBUTORSHIP STATEMENT**  
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8  
9 396 TSG - Contributed to study design and co-wrote the paper  
10

11 397 NB - Contributed to study design and participant involvement  
12

13 398 BP - Managed the technical aspects of the project and reviewed the manuscript  
14

15 399 ALK - Contributed to data entry and interpretation and reviewed the manuscript  
16

17  
18 400 BPA Schools Study Consortium members - designed and interpreted the study and  
19  
20 401 contributed to the manuscript.  
21

22 402 MHS - Carried out the qualitative analysis and reviewed the manuscript  
23

24 403 AMS - Managed sample collection, contributed to study design and reviewed the manuscript.  
25

26 404 LWH - PI, managed the study, wrote the manuscript  
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41 409 collection of the urine samples.  
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48 411 **COMPETING INTERESTS**  
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54 413 The authors have no competing interests to declare.  
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6 415 **DATA SHARING STATEMENT**7  
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9 416 Data are available upon reasonable request by emailing Lorna Harries  
10  
11 417 (L.W.Harries@exeter.ac.uk).  
1213  
14 41815  
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3 503 **FIGURE LEGENDS**  
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9 505 **Figure 1. The effect of a ‘real world’ BPA avoidance diet on urinary BPA exposure over**  
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11 506 **a 7 day period.** A. Urinary BPA levels (ng/ml) adjusted for urinary creatinine were plotted at  
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13 507 visit 1 before the intervention and at visit 2 after the intervention. The 3 extreme outliers have  
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15 508 been removed. The trajectories of individual participant measurements are shown. B. Change  
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17 509 in urinary BPA levels in ng/ml following the intervention diet are plotted against the self-  
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19 510 reported BPA risk score.  
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26 512 **Figure 2. The effect of baseline urinary BPA on the probability of achieving a drop in**  
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28 513 **levels following the intervention.** This graph illustrates the median urinary BPA level  
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30 514 adjusted for creatinine at visit 1 prior to the intervention expressed relative to whether or not  
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32 515 a reduction in urinary BPA levels was achieved following the 7 day intervention diet at visit  
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34 516 2. Error bars refer to the interquartile range of measurement.  
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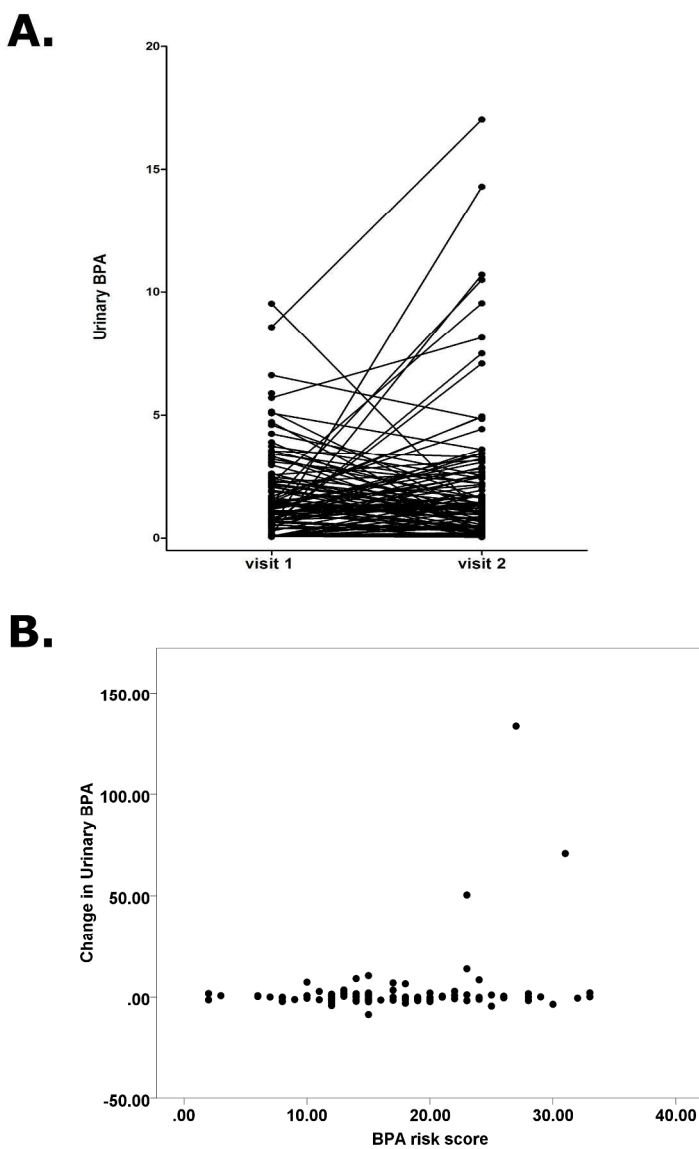


Figure 1

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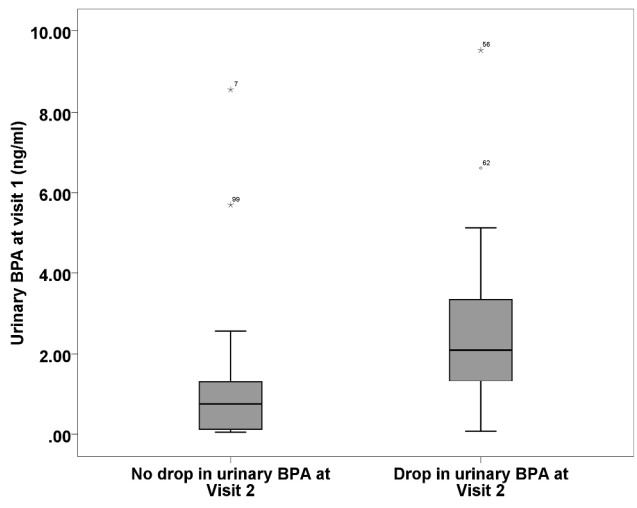


Figure 2

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# BPA Myth and Reality

## Dietary Intervention Guidelines



### General instructions

The purpose of this dietary intervention trial is to follow a diet designed to minimise routes of exposure to the food packaging chemical bisphenol A (BPA). For the dietary intervention period, please follow as closely as possible the instruction given below. Try to maintain your diet during the intervention period to be as closely similar to your normal diet as possible, in terms of the content, amount and calorific value of the food you eat. Please record details of each meal and the drinks and snacks you consume on the forms provided. Below are some general cooking and eating tips and an indication of which foods are best to avoid and those that are considered a low source of BPA.

### Cooking and eating tips for the intervention period.

The general approach is to replace any food items that fall into the 'avoidance' category with an alternative, chosen to minimise exposure to BPA

- **Switch to stainless steel and glass food storage and drink containers.**
- **Move foods to ceramic or glass food containers before microwaving.**
- **Consider a coffee filter or percolator for coffee – home coffee makers (Such as Nespresso™) may have polycarbonate-based water tanks and phthalate-based tubing.**
- **Eat out less, especially at restaurants that do not use fresh ingredients.**
- **Avoid canned food consumption. Where possible, replace with fresh produce or cardboard or tetrapack packaged alternatives.**
- **Choose fresh fruits and vegetables when possible, and frozen if not.**
- **Soak dried beans for cooking rather than tinned.**

## Foods to avoid

**Tinned foods.** Top ten tinned foods that are reported to be sources of BPA include coconut milk, soup, meat, vegetables, meals (e.g. pasta with sauce), juice, fish, beans, meal replacement drinks, fruit.

**Carbonated/fizzy drinks and juices in cans.** Avoid carbonated drinks in cans and drinks stored for prolonged periods in reusable sports bottles, unless they are labelled 'BPA free' (many commercial sports bottles are).

**Fast food from commercial outlets.** Most processed food has passed through numerous processes, and each additional processing step provides an opportunity for BPA to enter through packaging or tubing. Try to replace fast and processed foods with a freshly prepared and cooked alternative.

**Packaged fruit and vegetables.** Replace these where possible with unpackaged, loose fruit and vegetable items as far as possible.

**Convenience/ready meals.** Plastics types considered safest in terms of chemical migration are recycling numbers 2 and 5. Avoid food prepared in packaging with recycling number 7, which includes many different types of polymer and mixed polymers, including polycarbonate, a source of BPA. Try to avoid foods that are designed to be heated in the microwave in their packaging.

**Chocolate and ice cream.** Individuals who report eating chocolate bars and ice cream on a regular basis have been reported to have higher than average BPA exposure. Try to avoid excessive consumption.

## Non-food or food packaging routes of exposure

Although plastics found in consumer goods such as DVDs, CDs, computer goods and sunglasses do contain BPA, this is not an important route of exposure.

Till receipts often contain high levels of BPA, so wash your hands before eating or drinking if you have been handling them.

Dental sealants may contain BPA, so avoid any pre-planned dental work

## Example daily diet

Food Item	Comments
<b>Breakfast</b>	
Cereal, Fruit	
Milk	Polypropylene or glass packaging
Bread	
Yoghurt	Choose polypropylene container
<b>Lunch</b>	
Meat or fish products	Check packaging and avoid those labelled no. 7. Avoid tinned ingredients
Cheese	
Salad items, Fruit	Choose unpackaged where possible, wash before use
Pasta	
<b>Dinner</b>	
Shepherds pie	Cooked in saucepan and oven rather than microwaved in plastic
Green beans	Fresh or frozen
Bread	
<b>Drinks</b>	
Water	Water direct from tap or use stainless steel or BPA free water bottle
Tea/coffee	Prepare in teapot or cafetiere, avoid commercial coffee makers
Carbonated drinks	Avoid canned drinks and those stored in reusable containers for prolonged periods
Milk	Polypropylene or glass packaging
<b>Snacks</b>	
Fruit	
Potato crisps	

Place participant barcode here	FOOD - DAY 1		DRINK - DAY 1	
Contents of meal	Was food packaged in plastic known or suspected to contain BPA?	Was food cooked in plastic known or suspected to contain BPA?	Type of Drink	Packaging (please describe) e.g. canned, plastic (Δ number), tetrapak
<b>Breakfast:</b>				
1.				
2.				
3.				
4.				
5.				
<b>Lunch:</b>				
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<b>Dinner:</b>				
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<b>Snacks:</b>				
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Place participant barcode here	FOOD - DAY 2		DRINK - DAY 2	
Contents of meal	Was food packaged in plastic known or suspected to contain BPA?	Was food cooked in plastic known or suspected to contain BPA?	Type of Drink	Packaging (please describe) e.g. canned, plastic ( $\Delta$ number), tetrapak
<b>Breakfast:</b>				
1.				
2.				
3.				
4.				
5.				
<b>Lunch:</b>				
1.				
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4.				
5.				
<b>Dinner:</b>				
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5.				
<b>Snacks:</b>				
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Place participant barcode here	FOOD - DAY 3		DRINK - DAY 3	
Contents of meal	Was food packaged in plastic known or suspected to contain BPA?	Was food cooked in plastic known or suspected to contain BPA?	Type of Drink	Packaging (please describe) e.g. canned, plastic (Δ number), tetrapak
<b>Breakfast:</b>				
1.				
2.				
3.				
4.				
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<b>Lunch:</b>				
1.				
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5.				
<b>Dinner:</b>				
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<b>Snacks:</b>				
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Place participant barcode here	FOOD - DAY 4		DRINK - DAY 4	
Contents of meal	Was food packaged in plastic known or suspected to contain BPA?	Was food cooked in plastic known or suspected to contain BPA?	Type of Drink	Packaging (please describe) e.g. canned, plastic (Δ number), tetrapak
<b>Breakfast:</b>				
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3.				
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<b>Lunch:</b>				
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<b>Dinner:</b>				
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<b>Snacks:</b>				
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Place participant barcode here	FOOD - DAY 5		DRINK - DAY 5	
Contents of meal	Was food packaged in plastic known or suspected to contain BPA?	Was food cooked in plastic known or suspected to contain BPA?	Type of Drink	Packaging (please describe) e.g. canned, plastic (Δ number), tetrapak
<b>Breakfast:</b>				
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<b>Lunch:</b>				
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<b>Dinner:</b>				
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<b>Snacks:</b>				
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Place participant barcode here	FOOD - DAY 6		DRINK - DAY 6	
Contents of meal	Was food packaged in plastic known or suspected to contain BPA?	Was food cooked in plastic known or suspected to contain BPA?	Type of Drink	Packaging (please describe) e.g. canned, plastic (Δ number), tetrapak
<b>Breakfast:</b>				
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<b>Lunch:</b>				
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<b>Dinner:</b>				
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<b>Snacks:</b>				
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Place participant barcode here	FOOD - DAY 7		DRINK - DAY 7	
Contents of meal	Was food packaged in plastic known or suspected to contain BPA?	Was food cooked in plastic known or suspected to contain BPA?	Type of Drink	Packaging (please describe) e.g. canned, plastic (Δ number), tetrapak
<b>Breakfast:</b>				
1.				
2.				
3.				
4.				
5.				
<b>Lunch:</b>				
1.				
2.				
3.				
4.				
5.				
<b>Dinner:</b>				
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<b>Snacks:</b>				
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**Participant barcode****Additional study information.**

Please do not feel obliged to answer these questions if you are uncomfortable doing so.

**Gender**

- Female  
 Male  
 Prefer not to say

**Tobacco Usage** – Have you used tobacco over the past week

- Yes

If so, what type and how much? \_\_\_\_\_

- No  
 Prefer not to say

**Alcohol Usage** – Have you used alcohol over the past week

- Yes

If so, what type and how much? \_\_\_\_\_

- No  
 Prefer not to say

**Medication**- Have you taken any medication over the last week?

- Yes  
 No  
 Prefer not to say

If so, Please name the medication \_\_\_\_\_  Prefer not to say

**Vegetarian/vegan diet** - Have you eaten or drank any soya products over the past week?

- Yes  
 No  
 Prefer not to say

**Your measurements** - leave blank if you prefer not to say

Your height \_\_\_\_\_

Your weight \_\_\_\_\_

**Supplementary information file 3. Example daily diet diary.** A score of 1 is given to each item containing suspected to contain BPA or be packaged in BPA-containing materials. Highly processed foods are also scored as 1, due to uncertainties in the processing procedures. The daily totals are summed to produce a BPA risk score for the 7 day intervention.

	Item	Packaging	Score
<b>Breakfast</b>			
	Homemade pancakes	None	0
	Sugar	None	0
	lemon	None	0
	milk	HDPE	0
<b>Lunch</b>			
	Homemade Cheese sandwich	none	0
	Homemade sultana cake	none	0
	water	glass	0
<b>Dinner</b>			
	Homemade omelette	none	0
	Sweetcorn	Can	1
	Rice	Cellophane	0
	Tomatoes	none	0
	water	glass	0
<b>Snacks</b>			
	Crisps (processed)	Cellophane	1
	Apple	none	0
	milk	HDPE	0
		<b>Total for day</b>	<b>2</b>



Participant Barcode

## BPA: Myth and Reality diet questionnaire

1. Were there any times during the week that you knowingly/unknowingly did not stick to the diet? Please tick any that apply and give indication of frequency.

School meals  \_\_\_ times

Restaurants/cafés  \_\_\_ times

Friends' houses  \_\_\_ times

Takeaway  \_\_\_ times

Other \_\_\_\_\_  \_\_\_ times

2. If you heated your food in a microwave, what was the food in? Tick any which apply and give indication of frequency.

A food storage container or bowl known or suspected to contain BPA  \_\_\_ times

3. When you or your family drank water, where did your water come from? Tick any which apply and give indication of frequency.

Plastic filter jug known or suspected to contain BPA  \_\_\_ times

Individual water bottle known or suspected to contain BPA  \_\_\_ times

Larger water container known or suspected to contain BPA  \_\_\_ times

4. How many times during the week did you eat food that had been stored or transported in plastic containers known or suspected to contain BPA?

\_\_\_\_\_

5. How many times during the week did you eat tinned food or drink from cans?

\_\_\_\_\_

6. Did the BPA reduced diet affect How much you spent on shopping?

Spent more

Spent less

No difference

Participant questionnaire V3 25Jun15

Participant Barcode

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5 **7. Did it take longer to source your food than usual?**  
6

7 Yes  No

8  
9 If so, why? \_\_\_\_\_  
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16 **8. Did it take longer to prepare food than usual?**  
17

18 Yes  No

19  
20  
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22 If so, why? \_\_\_\_\_  
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29 **9. How restricted did you feel by your food choice?**  
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31  
32  
33  Very  Slightly  No difference  
34  
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36  
37 If you felt you were restricted by the diet, why was this? \_\_\_\_\_  
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44 **10. Did the diet affect your calorific intake?**  
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48 Yes  No

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50 If so, why? \_\_\_\_\_  
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Participant questionnaire V3 25Jun15

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Participant Barcode

**11. How easy would you find it to sustain this diet over a longer period of time?**

- Very easy
- Easy
- Hard
- Very hard
- Not sure

**12. Is there anything else about following the diet that you would like to add?**

Thank you for reading this leaflet. If you wish to participate in this study, you will be asked to agree to the consent statements below in the presence of a member of the research team.

## CONSENT STATEMENTS

1. I confirm that I have read this information sheet and have discussed participation in this project with my family. I have had opportunity to consider the information, ask questions and have had these questions answered satisfactorily. *You should not give consent until you are happy that you understand what the study involves.*
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my right to participate in the rest of the study being affected. *This means that even if you helped design this study you do not have to be a participant and you should not feel under any pressure to participate.*
3. I agree to participate in this study as a research subject. *This means that you agree to participate in a one-week diet and to provide two blood and urine samples.*
4. I understand that my anonymised blood and urine samples and linked anonymous questionnaire data will be sent to University of Exeter Medical School, Royal Devon & Exeter Hospital and my urine sample only will be sent to the Rolvaintain laboratory, a specialist BPA analysis company. *This means that laboratory staff will not know that samples belong to you, but dedicated staff at the University of Exeter, with training and experience in data protection, will be able to link your sample data to your questionnaire data.*
5. I understand that RNA (genetic material) will be extracted from my blood and will be stored anonymously. *This means that Professor Harries' team will use our RNA to provide data that you will help analyse but may also do further research on the samples to identify reasons for any changes seen.*
6. I understand that data relating to my participation in the study will be returned anonymously to my school to be used for educational purposes. *This means that although you will get to analyse data from your samples there is no way you will know which data relates to your samples and which to other participants.*

### Complaints:

If you have any complaints about the way in which this study has been carried out please contact the Chair of the University of Exeter Medical School Research Ethics Committee Peta Foxall PhD, Chair, UEMS Research Ethics Committee: P.J.D.Foxall@exeter.ac.uk.

This project has been reviewed and approved by the University of Exeter Medical School Research Ethics committee UEMS REC REFERENCE NUMBER: 15/07/074)

## BPA: Myth or Reality?

A research study investigating the effect of chemicals in plastic on gene activity and whether dietary interventions can reduce BPA levels in teenagers.



### Involvement & Engagement

The aim of this year-long project is to involve teenagers in a research study that is relevant to them, by allowing them to help design a research project, analyse non-identifiable participant data and help to present and publish the outcomes.

### Participation

Students will be asked to undertake a one week diet to reduce their intake of BPA, a chemical found in plastics. They will be asked to provide urine and blood samples before and after their diet.

## What is BPA?

BPA (Bisphenol A) is a chemical used in the manufacture of plastics. Plastics containing BPA are found in a wide range of products including food and drink containers. BPA in these products can be ingested and there are concerns that high BPA levels in the blood could possibly affect human health. Research is therefore needed to understand its effects on the human body and how we can reduce its consumption by minor changes to our diet.



This project is being run as a student-involvement project to answer two specific questions:

1. Can we see the effects of dietary BPA on our genes?
2. Can we effectively reduce BPA in our diet?

In the past, small-scale experiments have shown that BPA levels in the human body can be reduced by rigid dietary interventions but these interventions would be difficult to implement in the "real world". In this study a one-week dietary intervention designed by teenagers will be used by them to determine whether BPA levels, and the activity of BPA-responsive genes can be effectively reduced in young people by avoiding food packaging that contains this chemical.

## What will I need to do?

### Day 1

- Provide a nurse with a 2.5ml blood sample and a urine sample.

### Day 2 - Day 8

- Follow a diet that you have helped to design.
- The diet will exclude sources of BPA as much as possible but will be nutritionally and calorifically similar to your usual diet.
- You will be asked to complete a food diary and answer a questionnaire about how easy it was to follow this diet.

### Day 8

- Provide a nurse with a 2.5ml blood sample and a urine sample.



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**We recommend that you discuss the project with your family and involve them in planning what you eat and how you will prepare it.**

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

## What will happen to my samples and data?

When you participate in the study you will be allocated with a numerical study ID. Your samples and data will be labelled with this number so that we can match your 'before' and 'after' diet samples with your food diary data. Once all data has been collated and coded it will be further anonymised by a person external to the project so that no data can be linked to any of the participants.



Urine samples from before and after the diet will be sent to the Royal Devon & Exeter NHS Foundation Trust for creatinine analysis and to the Royal Devon & Exeter Molecular Genetics Laboratory for BPA analysis. RNA will be extracted from blood samples at the Royal Devon & Exeter Molecular Genetics Laboratory and the expression levels of two BPA-responsive genes will be measured in the samples taken before and after the diet. These anonymised RNA samples will be stored and used only by Professor Harries team for further research on the mechanisms behind our findings.

## What are the benefits of taking part?

This project will help you to understand how you might be able to reduce BPA in your diet and your involvement in the design will give you an excellent insight into clinical research, community outreach and scientific practise. Your role as a participant is unlikely to have any direct health benefits.



## Are there any risks intaking part?

Blood samples will be taken by fully qualified and insured NHS personnel. Any potential discomfort or side-effects will be equivalent to that experienced giving a blood sample to your GP. All data will be fully anonymised before analysis. This means that you will not find out anything about your blood or urine samples. Following the diet may minimally increase the cost of your groceries for the week, but since fresh foods are usually less expensive than pre-packaged foods, we do not expect this to be an issue.



## What will happen to the results of the research study?

You will be given the opportunity to help analyse anonymised data from this project and to help disseminate the outcomes of this research. It is hoped that the findings will be published in peer-reviewed journals and the wider media.

## Who is organising this research?

The research is organised by Professors Lorna Harries & Tamara Galloway of the University of Exeter as part of their research program into BPA and part of the University's outreach program to involve schools in academic research.

BMJ Open: first published as 10.1136/bmjopen-2019-028183 on February 27, 2020. Protected by copyright.



## Version 4 (2/8/2015)

## BPA: Myth &amp; Reality

STUDY ID

CONSENT STATEMENTS		Please circle
1. I confirm that I have read information sheet BPA PIS Version 4 and have discussed participation in this project with my family. I have had opportunity to consider the information, ask questions and have had these questions answered satisfactorily. <i>You should not give consent until you are happy that you understand what the study involves.</i>		YES / NO
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without right to participate in the rest of the study being affected. <i>This means that even if you helped design this study you do not have to be a participant and you should not feel under any pressure to participate.</i>		YES / NO
3. I agree to participate in this study as a research subject. <i>This means that you agree to participate in a one-week diet and to provide two blood and urine samples.</i>		YES / NO
4. I understand that my anonymised blood and urine samples and linked anonymous questionnaire data will be sent to University of Exeter Medical School, Royal Devon & Hospital and my urine sample only will be sent to the Rolvaintain laboratory, a specialist BPA analysis company. <i>This means that laboratory staff will not know that samples belong to you, but dedicated staff at the University of Exeter, with training and experience in data protection, will be able to link your sample data to your questionnaire data.</i>		YES / NO
5. I understand that RNA (genetic material) will be extracted from my blood and will be stored anonymously. <i>This means that Professor Harries' team will use our RNA to provide data that you will help analyse but may also do further research on the samples to identify reasons for any changes seen.</i>		YES / NO
6. I understand that data relating to my participation in the study will be returned anonymously to my school to be used for educational purposes. <i>This means that although you will get to analyse data from your samples there is no way you will know which data relates to your samples and which to other participants.</i>		YES / NO
Name of Participant	Signature	Date
Name of Person Obtaining Consent	Signature	Date
I the above signed testify the participant is providing voluntary and fully informed consent to participate in this study. I am on the delegation log to obtain consent for this study and are trained in obtaining consent.		
This project has been reviewed and approved by the University of Exeter Medical School Research Ethics Committee UEMS REC REFERENCE NUMBER: 15/07/074)		

**Version 4 (2/8/2015)**

**BPA: Myth & Reality**

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For peer review only

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

	Item No	Recommendation
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found  <b>a) Page 1</b> <b>b) Page 2</b>
<b>Introduction</b>		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported  <b>Page 6, line 82</b>
Objectives	3	State specific objectives, including any prespecified hypotheses  <b>Page 7, line 113</b>
<b>Methods</b>		
Study design	4	Present key elements of study design early in the paper  <b>Page 8, line 140</b>
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection  <b>Page 8, line 152</b>
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up  <b>Page 7, line 123</b>  <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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants <hr/> (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable  Page 7, line 140, Page 8, line 152.



1  
2 Data sources/  
3 measurement 8\* For each variable of interest, give sources of data and details of methods of  
4 assessment (measurement). Describe comparability of assessment methods if there  
5 is more than one group

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7 **Page 8, line 140, Page 8, line 152**

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10 Bias 9 Describe any efforts to address potential sources of bias

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12 **Page 8, line 154, page 9 line 165**

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15 Study size 10 Explain how the study size was arrived at

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17 **Page 7, line 127**

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20 Quantitative variables 11 Explain how quantitative variables were handled in the analyses. If applicable,  
21 describe which groupings were chosen and why

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23 **Page 9, line 157**

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25 Statistical methods 12 (a) Describe all statistical methods, including those used to control for confounding

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27 **Page 9, line 170**

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30 (b) Describe any methods used to examine subgroups and interactions

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32 **Page 9, line 175**

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35 (c) Explain how missing data were addressed

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37 **Page 9, line 164**

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40 (d) *Cohort study*—If applicable, explain how loss to follow-up was addressed

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42 **Page 12, line 206**

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44 *Case-control study*—If applicable, explain how matching of cases and controls was  
45 addressed

46  
47 *Cross-sectional study*—If applicable, describe analytical methods taking account of  
48 sampling strategy

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49 (e) Describe any sensitivity analyses

50  
51 N/A

52  
53 Continued on next page

**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>Table 1</b>
		(b) Give reasons for non-participation at each stage
		<b>Page 12, line 206</b>
		(c) Consider use of a flow diagram
		N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		<b>Table 1</b>
		(b) Indicate number of participants with missing data for each variable of interest
		<b>Table 1</b>
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)
		<b>Page 9, line 172</b>
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time
		<b>Table 1</b>
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures
Main results	16	(a) 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
		<b>Page 12, line 213 to page 13 line 229</b>
		(b) Report category boundaries when continuous variables were categorized
		<b>Page 9, line 176</b>
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful

		time period
		N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
		<b>Page 13, line 234</b>
<b>Discussion</b>		
Key results	18	Summarise key results with reference to study objectives
		<b>Page 15, line 276</b>
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
		<b>Page 16, line 298</b>
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
		<b>Page 17, line 334</b>
Generalisability	21	Discuss the generalisability (external validity) of the study results
		<b>Page 18, line 344</b>
<b>Other information</b>		
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
		<b>Page 19, line 374</b>

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).