



## On influencing population means.

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1 Research letter:

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**On influencing population means**

4

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9

1 Findings on the existence or the lack of temporal trends in sperm concentration at the  
2 population level have been used to discuss the role of environmental factors (including  
3 endocrine disruptors) on male fertility. An assumption sometimes made <sup>1</sup> is that temporal  
4 trends in biological parameters such as sperm concentration will parallel temporal trends in  
5 their risk factors. As we illustrate below, this assumption is a too simple view, outside the  
6 probably rare situation where one prevalent environmental factor has a major impact on the  
7 biological parameter considered.

8 Let us consider the case of an environmental factor A to which no pregnant woman was  
9 exposed before year  $t_0$  and to which 40% of pregnant women were exposed at a later time  $t_1$ ;  
10 we assumed that in utero exposure to this factor causes an average decrease of 20% in  
11 sperm concentration in adulthood among male offspring. We also considered factors B and C,  
12 supposed to have a much stronger impact at the individual level (sperm concentration  
13 decrease by 85%) and whose prevalence in pregnant women rose by 10% (factor B) or 60%  
14 (factor C) between  $t_0$  and  $t_1$ . We estimated the population mean of sperm concentration in  
15 adulthood among men born at period  $t_1$ , assuming that either factor existed alone; we  
16 assumed lack of selection bias, measurement or random error, and of temporal trends in the  
17 prevalence of any other factor. Using a simple simulation approach (detailed in eAppendix),  
18 we also estimated the change in mean concentration assuming that *several* factors  
19 simultaneously impacted on sperm concentration independently.

20 Compared to the unexposed cohort of men born at  $t_0$ , the impact of factor A in men from  $t_1$   
21 birth cohort corresponded to a decrease in sperm concentration by 8% (Table). Sperm  
22 concentration decrease was 9% for factor B, while it reached 51% in the case of the more  
23 prevalent factor C (Table). Finally, when exposure to 5 factors, each having the same  
24 individual impact as factor A (sperm concentration change by -20%) simultaneously increased,  
25 sperm concentration decreased by 34% at the population level; 8 such factors were required  
26 to cause a population decrease by 49% (Table).

27 This study shows that a single factor with a moderate but realistic influence on sperm  
28 concentration at the individual level (-20%, comparable to the reported effect of in utero

1 exposure to tobacco smoke<sup>2</sup>), whose prevalence has increased significantly over time  
2 (+40%) would cause a relatively small decrease in sperm concentration at the population  
3 level (-8%). This is because the population impact of a single factor will remain lower than its  
4 individual impact, except if prevalence increases from 0 to 100%. Several independent  
5 factors with moderate effects in the same direction and with rather high increase in exposure  
6 prevalence might entail substantial changes in sperm concentration.

7 Although some chemicals with a strong impact at the individual level have been identified in  
8 occupational settings,<sup>3</sup> the prevalence of exposure in the general population probably  
9 remained low. Therefore, to our knowledge, a factor with such high impact and prevalence  
10 than those hypothesized here for factor C has to date not been identified. If one looks for  
11 causes of a strong reduction in sperm concentration at the population level, a *combination* of  
12 several factors, each having a limited impact at the individual level and whose prevalences  
13 simultaneously strongly increased appears like a more realistic explanation. We assumed  
14 that factors acted independently, but of course synergy between factors could also exist<sup>4</sup>  
15 (see eAppendix for an illustration). In another setting, a simulation study has quantified the  
16 impact of public health interventions on smoking prevalence.<sup>5</sup>

17 Data on temporal trends in outcome alone (without individual information on exposures),  
18 although very relevant in a public health perspective,<sup>6</sup> correspond to a simple form of  
19 ecological studies and are, outside specific settings,<sup>7</sup> generally very limited to draw strong  
20 conclusions regarding the influence of environmental factors. Indeed, several factors may  
21 have opposed impacts at the individual level or opposed temporal trends. For these reasons,  
22 conclusions on the impact of endocrine disruptors and other families of environmental factors  
23 on male fertility (or the lack thereof) should not be drawn from studies of temporal trends in  
24 male fertility parameters alone.

25 In order to characterize the impact of exposures during the developmental window, mother-  
26 child cohorts with a biomarker-based assessment of exposure during pregnancy and long-  
27 term follow-up constitute a more relevant tool. Such studies are currently very rare.<sup>2, 8</sup>

1 REFERENCES

- 2 1. Bonde JP, Host Ramlau-Hansen C, Olsen J. Trends in Sperm Counts. The Saga  
3 Continues. *Epidemiology*. 2011;**22**:617-9.
- 4 2. Ramlau-Hansen CH, Thulstrup AM, Storgaard L, Toft G, Olsen J, Bonde JP. Is  
5 prenatal exposure to tobacco smoking a cause of poor semen quality? A follow-up study. *Am*  
6 *J Epidemiol*. 2007;**165**:1372-9.
- 7 3. Whorton D, Krauss RM, Marshall S, Milby TH. Infertility in male pesticide workers.  
8 *Lancet*. 1977;**2**:1259-61.
- 9 4. Kortenkamp A, Faust M, Scholze M, Backhaus T. Low-level exposure to multiple  
10 chemicals: reason for human health concerns? *Environ Health Perspect*. 2007;**115 Suppl**  
11 **1**:106-14.
- 12 5. Ahern J, Hubbard A, Galea S. Estimating the effects of potential public health  
13 interventions on population disease burden: a step-by-step illustration of causal inference  
14 methods. *American journal of epidemiology*. 2009;**169**:1140-7.
- 15 6. Buehler JW. Surveillance. In: Rothman KJ, Greenland S, Lash TL, editors. *Modern*  
16 *Epidemiology*. 3rd Edition ed: Lippincott Williams & Wilkins; 2008. p. 459-80.
- 17 7. Clancy L, Goodman P, Sinclair H, Dockery DW. Effect of air-pollution control on death  
18 rates in Dublin, Ireland: an intervention study. *Lancet*. 2002;**360**:1210-4.
- 19 8. Mocarelli P, Gerthoux PM, Needham LL, et al. Perinatal exposure to low doses of  
20 dioxin can permanently impair human semen quality. *Environmental health perspectives*.  
21 2011;**119**:713-8.

22

23

1 TABLE

2

3 **Table: Sperm concentration in adulthood among men born at periods  $t_0$  and  $t_1$ , assuming the**  
 4 **existence of an environmental factor whose prevalence increased between  $t_0$  and  $t_1$ .**

5

Exposure factor and birth cohort	Exposure prevalence <sup>a</sup>	Sperm concentration in male offspring in adulthood (millions/ml)		
		Non-exposed	Exposed	Whole population (Change <sup>b</sup> )
<b>Factor A<sup>c</sup></b>				
Period $t_0$	0%	100	N.A.	$100 \times 1 + 80 \times 0 = 100$
Period $t_1$	40%	100	80 (-20%)	$100 \times 0.6 + 80 \times 0.4 = 92$ <b>(-8%)</b>
<b>Factor B<sup>c</sup></b>				
Period $t_0$	0%	100	N.A.	$100 \times 1 + 15 \times 0 = 100$
Period $t_1$	10%	100	15 (-85%)	$100 \times 0.9 + 15 \times 0.1 = 91.5$ <b>(-8.5%)</b>
<b>Factor C<sup>c</sup></b>				
Period $t_0$	0%	100	N.A.	$100 \times 1 + 15 \times 0 = 100$
Period $t_1$	60%	100	15 (-85%)	$100 \times 0.4 + 15 \times 0.6 = 49$ <b>(-51%)</b>
<b>5 independent factors<sup>d</sup></b>				
Period $t_0$	0%	100		<b>100</b>
Period $t_1$	40%	100	(-20%/factor)	<b>67 (-34%)</b>
<b>8 independent factors<sup>d</sup></b>				
Period $t_0$	0%	100		<b>100</b>
Period $t_1$	40%	100	(-20%/factor)	<b>52 (-49%)</b>

6

7 *N.A.: not applicable.*

8 *In utero* exposure to the hypothetical environmental factor is assumed to decrease sperm concentration in  
 9 adulthood by 20% (factor A) or 85% (factors B or C) on average at the individual level.

10 <sup>a</sup> Frequency of exposure to one single factor among women pregnant the corresponding year.

11 <sup>b</sup>For a prevalence change by  $\Delta p$ , a biological parameter with an initial value of  $C_0$  and an individual impact of  $x$  on  
 12 a multiplicative scale (that is, the parameter is multiplied by  $x$  in exposed subjects), the relative change in the  
 13 mean of the biological parameter in population  $t_1$  is obtained as  $(C_1 - C_0)/C_0 = \Delta p(x - 1)$ . In the case of factor A, this is  
 14  $0.4(0.2 - 1) = -0.08$ , a decrease by 8%.

15 <sup>c</sup>The population is assumed to be exposed *to factor A only* or *to factor B only* or *to factor C only*.

16 <sup>d</sup>Several deleterious factors similar to factor A are assumed to act in men born at  $t_1$ , each having a prevalence of  
 17 40% and entailing a 20% decrease in sperm concentration in adulthood in subjects exposed in utero, with no  
 18 effect measure modification between these factors (that is, the probability of exposure to each factor at  $t_1$  was  
 19 40% and independent from exposure to the other factors, and there was no modification of the effect measure of  
 20 any factor on sperm concentration by any other factor)(see eAppendix for details).

21

22

1 eAppendix:

2

3

4 **Several time-varying risk factors are needed to influence the population mean**  
5 **of a biologic parameter**

6

7 **Content:**

8 I. Overview

9 II. Detail of the steps and of the simulation study

10 III. Simulation results

11 IV. Stata code

12

13

14 **I. Overview**

15 In order to simulate the impact at the population level of an increase in prevalence over time  
16 of several environmental factors on sperm concentration, we used a simulation approach.  
17 The main steps, described below, are:

18

- 19 1) Simulation of a cohort of  $n=10,000$  men born at  $t_0$ , all considered unexposed to the  
20 environmental factors of interest;
- 21 2) Simulation of a cohort of  $n=10,000$ men born at  $t_1$ , assuming that each one has a  
22 probability  $p_{A1}, p_{A2}, \dots, p_{Aq}$  to be exposed to independent factors  $A_1, \dots, A_q$ ,  
23 respectively;
- 24 3) Comparison of the mean sperm concentration between both birth cohorts to provide  
25 an estimate of the impact of factors  $(A_1, \dots, A_q)$  considered altogether.

26

27 These steps have been repeated considering between  $q=2$  and  $q=10$  factors.

28 Finally, we also provide an illustration of a situation in which synergy between exposure  
29 factors is assumed.

30

31

32

33 **II. Detail of the steps of the simulation study**

34

35 **II.1) Step 1**

36 We draw the sperm concentration  $Y_{t_0}$  of a hypothetical population  $P_0$  of  $n=10,000$  men,  
37 assuming a normal distribution with mean  $m_0=100$  (expressed in million spermatozoa/ml) and  
38 standard deviation 50, replacing negative values by 0.

39

$$40 Y_{t_0} = \max[\mathcal{N}(100, 50); 0]$$

41

42 This corresponds to the sperm concentration in adulthood of men born at  $t_0$ .

43

44

1 **II.2) Step 2**

2 We draw the sperm concentration in adulthood  $Y_{t_1}$  of another hypothetical population  $P_1$  of  
3  $n=10,000$  men born at  $t_1 > t_0$ ; we first assume the same distribution as for population  $P_0$ . This  
4 starting value of sperm concentration for a subject  $i$  of  $P_1$  is called  $Y_{t_1}^{i(start)}$ .

5 We then assume that each man of  $t_1$  birth cohort is exposed to the group of factors ( $A_1, \dots$   
6  $A_q$ ) with probability ( $p_{A_1}, \dots p_{A_q}$ ). Factors  $A_1, \dots A_q$  are binary (one is either exposed or non  
7 exposed, or, equivalently, has an exposure above or below a given threshold value). In our  
8 example, for convenience all probabilities are assumed to have the same value  $p = p_{A_1} = \dots$   
9  $= p_{A_q}$ , arbitrarily set to 0.4.

10 Let  $(I_{A_1}^i, \dots, I_{A_q}^i)$  be the indicator variables indicating if subject  $i$  is exposed to factors ( $A_1, \dots$   
11  $A_q$ ), with  $I_{A_p}^i = 1$  if subject  $i$  is exposed to factor  $A_p$  and 0 otherwise. The probability of being  
12 exposed to a given factor is independent of whether or not subject  $i$  is exposed to any other  
13 factor (that is, variables  $(I_{A_1}^i, \dots, I_{A_q}^i)$  are independent one from another). In other words, if we  
14 consider, say, in utero exposure to tobacco smoke and alcohol consumption in adulthood,  
15 then we assume that the probability to drink alcohol is the same in men non-exposed and in  
16 men in utero exposed to tobacco smoke.

17 Each factor  $A_p$  is expected to entail a decrease by 20% on average in sperm concentration.  
18 This is achieved by multiplying sperm concentration by a variable with an expected value of  
19 0.8 for subjects exposed to  $A_p$ . In order to allow for some individual variability in the  
20 sensitivity to  $A_p$ , we assume the effect of  $A_p$  to entail a decrease of 0.2 in average, with  
21 standard deviation 0.1.

22 That is, the effect of factor  $A_p$  is assumed to follow a law:

23  
24 
$$\text{Effect}A_p \sim \mathcal{N}(.8, .1)$$
  
25

26 The sperm concentration of each subject of birth cohort  $t_1$  is estimated by multiplying the  
27 starting value  $Y_{t_1}^{i(start)}$  of each man by the values of the variables  $\text{Effect}A_p$  corresponding to  
28 the effects of each factor the subject is exposed to:

29  
30 
$$Y_{t_1}^i = Y_{t_1}^{i(start)} \cdot (\text{Effect}A_1)^{I_{A_1}^i} \cdot \dots \cdot (\text{Effect}A_q)^{I_{A_q}^i}$$
  
31

32 **II.3) Step 3**

33 Finally, we compare mean sperm concentration between populations  $P_1$  and  $P_0$ . The  
34 simultaneous effect of exposures  $A_1, \dots A_q$  at the population level is estimated as the  
35 difference between the mean values of sperm concentration of populations  $P_1$  and  $P_0$ .

36  
37 Steps 1 to 3 are repeated for  $q=2$  to  $q=10$  exposure factors.  
38  
39



### III. Results

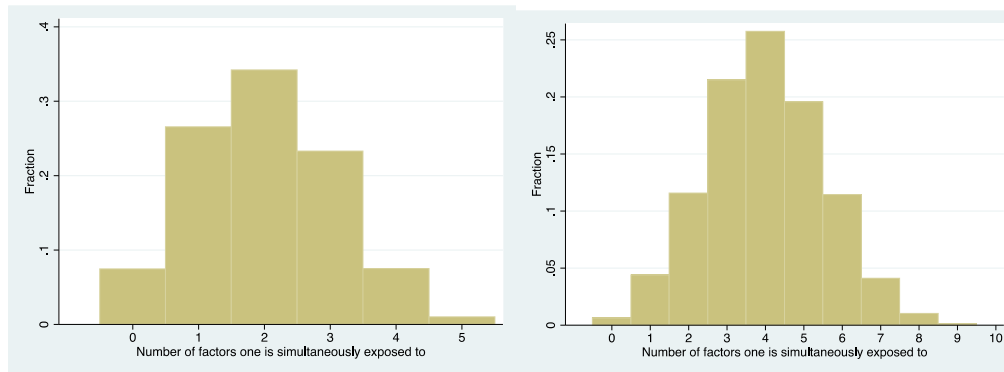
#### III.1) General case with independent environmental factors

The distribution of the number of factors each subject of birth cohort  $t_1$  is simultaneously exposed to is given in Figure S1 for a maximum of 5 factors and a maximum of 10 factors. In the case when 10 factors exist, about 25% of subjects are exposed to 4 factors simultaneously, while 1.3% of subjects are exposed to 8 factors or more simultaneously.

The mean values of sperm concentration in population  $P_1$  for  $q=1$  to  $q=10$  exposure factors is given Table S1. For 8 exposure factors, sperm concentration is on average decreased by 49% (mean, sperm concentration, 52 million/ml) compared to  $t_0$  birth cohort (mean sperm concentration, 100 million/ml). For 10 exposure factors, sperm concentration is on average decreased by 57% (Figure S2).

**Figure S1:** Distribution of the number of factors one is simultaneously exposed to; **A)** Assuming that 5 different exposure factors exist; **B)** Assuming that 10 different exposure factors exist. Results are given for a specific simulation run and may slightly vary from run to run.

**A) Up to 5 environmental factors    B) Up to 10 environmental factors**

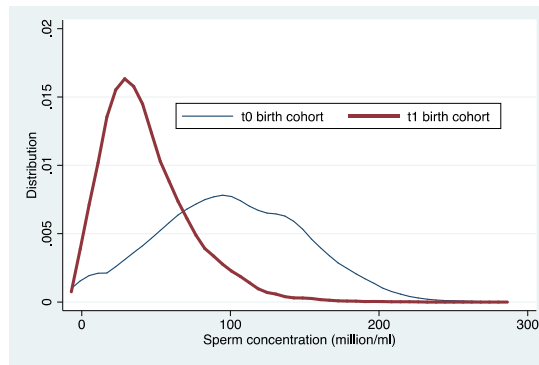


**Table S1:** Mean sperm concentration in adulthood in  $t_0$  and  $t_1$  birth cohorts, assuming that the birth cohort is exposed to 1 to 10 exposure factors with a negative individual impact on sperm concentration.

Number of exposure factors	Mean sperm concentration (sd), $10^6$ /ml		Estimated impact of exposures		
	Birth cohort $t_0$	Birth cohort $t_1$	Change in mean sperm concentration	Sperm concentration $< 10 \times 10^6$ /ml, % (relative risk compared to $t_0$ )	
0	100 (49)	100 (49)	0	3.3	(1)
1	100 (49)	92 (47)	-8%	3.9	(1.2)
2	100 (49)	86 (45)	-15%	4.1	(1.3)
3	100 (49)	79 (43)	-22%	4.3	(1.3)
4	100 (49)	72 (41)	-28%	4.7	(1.4)
5	100 (49)	67 (39)	-34%	5.1	(1.5)
6	100 (49)	61 (37)	-39%	5.4	(1.6)
7	100 (49)	56 (35)	-44%	5.9	(1.8)
8	100 (49)	52 (33)	-49%	6.5	(2.0)
9	100 (49)	48 (31)	-53%	7.3	(2.2)
10	100 (49)	44 (30)	-57%	8.4	(2.6)

1 Table S1 additionally gives the proportion of men with a sperm concentration below 10  
 2 million/ml according to the number of exposure factors considered, and the relative risk of  
 3 having a sperm concentration below 10 million/ml in  $t_1$  birth cohort, compared to the non-  
 4 exposed birth cohort at  $t_0$ . Eight exposure factors induced a doubling in the proportion of men  
 5 with a sperm concentration below 10 million/ml, compared to the unexposed cohort.  
 6  
 7

8 **Figure S2:** Distribution of sperm concentration in  $t_0$  and in  $t_1$  birth cohorts, assuming the existence of 10  
 9 independent environmental factors.



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**III.2) Further results in the presence of effect measure modification**

The previous models assume that the probabilities of exposure to each factor are independent one from another and that the effect measure of a given factor on a multiplicative scale does not depend on the other factors one is exposed to.

Here, we relax the second hypothesis, starting from the situation with 5 exposure factors. Taken altogether and assuming independence, these factors entailed a decrease by 34% at the population level (Table S1). We now assume effect measure modification between factors  $A_4$  and  $A_5$ , in that sperm concentration is further multiplied by 0.2 in men simultaneously exposed to factors  $A_4$  and  $A_5$ . That is, the effect of  $A_4$  (respectively,  $A_5$ ) corresponds to a decrease by 20% in men not exposed to  $A_5$  (respectively,  $A_4$ ), and to a decrease by 87% (multiplication by  $0.8 \times 0.8 \times 0.2 = 0.128$ ) for men simultaneously exposed to these two factors.

In this first case with effect measure modification, the proportion of men of  $t_1$  birth cohort simultaneously exposed to both factors was 16%; the simulation results predict a mean sperm concentration of 60 million/ml in men from  $t_1$  birth cohort, a decrease by 40% compared to  $t_0$  (this decrease was 34% without effect measure modification, Table S1).

If in addition we assume that in men simultaneously exposed to factors  $A_1$ ,  $A_2$  and  $A_3$  sperm concentration is further decreased by 99% (or multiplied by  $0.8^3 \times 0.01 = 0.005$  compared to unexposed men), then the predicted mean sperm concentration of men from  $t_1$  birth cohort is 58 million/ml, a decrease by 42% compared to  $t_0$ . The proportion of men simultaneously exposed to all 3 factors was 5.9%.

## IV. STATA code

```
1
2
3 *****
4 ***** Impact of an increased prevalence in environmental factors
5 *****
6
7 *Last modified 23 Nov 2011.
8
9 version 11.2 /*This code: STATA v.11.2 format*/
10
11 clear
12 set seed 2011 /*Sets the root value of the random number generator*/
13
14 *****
15 *Step I: We generate sperm concentration of men born at period t0
16
17 set obs 10000 /*Generate 10,000 observations (without characteristics so far)*/
18 drawnorm conc, means(100) sds(50) /*Sperm concentration assumed to have normal distribution
19 with mean 100, sd 50.*/
20 replace conc=0 if conc<0 /*Negative values of sperm concentration are meaningless and set to
21 0*/
22
23 sum conc, d
24 hist conc
25 gen period=0 /*0=birth cohort t0 (observations 1 to 10,000 of dataset) */
26 label var period "Year of birth"
27
28 *Step II: We generate sperm concentration of men born at t1.
29 *First, we assume that the overall distribution is identical to that of men born at t0:
30 expand 2 /*We duplicate the dataset*/
31 replace period=1 if _n>10000 /*1=birth cohort t1 (Observations 10,001 to 20,000) */
32
33 drawnorm concb , means(100) sds(50)
34 replace concb=0 if concb<0
35 replace conc=concb if period==1
36
37 *We now successively assume that 1, 2... 10 environmental factors
38 * exist in at t1 and independently impact sperm concentration.
39 * Each factor implies a 20% decrease in sperm concentration (multiplication by .8 on average)
40 * and the prevalence of exposure is 40% at t1 for each factor (0% at t0).
41
42
43 **Option 1: No interaction; we assume that there is some variability in the effect of each
44 factor:
45
46 cap drop A* prob*
47 forvalues i=1(1)10 {
48     gen A`i'=0 if period==1
49     gen probA`i'=uniform() if period==1
50     replace A`i'=1 if probA`i'>0.6 & probA`i'<1
51     /*Ai variable is 1 for subjects exposed to factor Ai (40% of population) */
52     drawnorm effectA`i', means(.8) sds(.1)
53     /*This variable corresponds to the effect of factor Ai */
54     replace conc=conc*effectA`i' if A`i'==1 & period==1
55     /*Concentration if multiplied by effectAi for exposed subjects */
56     *Step III: Comparison between both periods:
57     dis "Number of environmental factors : " `i'
58     ttest conc, by(period)
59 }
60
61 gen nbfact=A1+A2+A3+A4+A5+A6+A7+A8+A9+A10
62 tab nbfact period, col
63
```

```

1  **Option 2: Interaction; we assume that there is some variability in the effect of each
2  factor:
3  replace conc=concb if period==1
4  cap drop A* prob*
5  forvalues i=1(1)5 {
6      gen A`i'=0 if period==1
7      gen probA`i'=uniform() if period==1
8      replace A`i'=1 if probA`i'>0.6 & probA`i'<1
9      /*Ai variable is 1 for subjects exposed to factor Ai (40% of population) */
10     drawnorm effectA`i', means(.8) sds(.1)
11     /*This variable effectAi corresponds to the effect of factor Ai */
12     replace conc=conc*effectA`i' if A`i'==1 & period==1
13     /*Concentration if multiplied by effectAi for exposed subjects */
14
15     }
16
17     sum effectA4 effectA5
18 *Additionally, we assume that sperm concentration is further reduced by 80% for subjects
19 simultaneously exposedto factors 4 and 5:
20     replace conc=conc*.2 if A4==1 & A5==1 & period==1 /*Concentration if multiplied by
21     effectAi for exposed subjects */
22     dis "Number of environmental factors : 5 (with interaction between factors 4 and 5)"
23     ttest conc, by(period)
24
25 *Additionally, we assume that sperm concentration is further reduced by 99% for subjects
26 simultaneously exposedto factors 1, 2 and 3:
27     dis "Number of environmental factors : 5 (with interaction between factors (1, 2, 3)
28     and(4, 5))"
29     replace conc=conc*.01 if A1==1 & A2==1 & A3==1 & period==1
30     ttest conc, by(period)
31
32
33
34
35

```