On influencing population means

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

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

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

This study shows that a single factor with a moderate but realistic influence on sperm concentration at the individual level (−20%, comparable to the reported effect of in utero exposure to tobacco smoke [2]), whose prevalence has increased significantly over time (+40 %) would cause a relatively small decrease in sperm concentration at the population level (−8%). This is because the population impact of a single factor will remain lower than its individual impact, except if prevalence increases from 0 to 100%. Several independent factors with moderate effects in the same direction and with rather high increase in exposure prevalence might entail substantial changes in sperm concentration.

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

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

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

References:

- 1 . Bonde JP , Host Ramlau-Hansen C , Olsen J . Trends in Sperm Counts. The Saga Continues . Epidemiology . 2011 ; 22 : 617 - 9

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

Table

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

	Exposure prevalence [a]	Sperm concentration in male offspring in adulthood (millions/ml)		
Exposure factor and birth cohort		**Non-exposed**	**Exposed**	**Whole population (Change [b])**
Factor A [c]				
Period t_0	0%	100	N.A.	100x1 + 80x0 **=100**
Period t_1	40%	100	80 (−20%)	100x0.6 + 80x0.4**=92 (−8%)**
Factor B [c]				
Period t_0	0%	100	N.A.	100x1 + 15x0 **=100**
Period t_1	10%	100	15 (−85%)	100x0.9 + 15x0.1**=91.5 (−8.5%)**
Factor C [c]				
Period t_0	0%	100	N.A.	100x1 + 15x0 **=100**
Period t_1	60%	100	15 (−85%)	100x0.4 + 15x0.6**=49 (−51%)**
5 independent factors [d]				
Period t_0	0%	100		**100**
Period t_1	40%	100	(−20%/factor)	**67 (−34%)**
8 independent factors [d]				
Period t_0	0%	100		**100**
Period t_1	40%	100	(−20%/factor)	**52 (−49%)**

N.A.: not applicable.

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

a Frequency of exposure to one single factor among women pregnant the corresponding year.

b For a prevalence change by Δp, a biological parameter with an initial value of C_0 and an individual impact of x on a multiplicative scale (that is, the parameter is multiplied by x in exposed subjects), the relative change in the 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 0.4(0.2-1)=−0.08, a decrease by 8%.

c The population is assumed to be exposed *to factor A only* or *to factor B only* or *to factor C only*.

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