Decreasing Sex Difference in Birth Weight

To the Editor:

Among manufactured chemicals, antiandrogenic endocrine disrupters may be especially toxic during fetal life. Indeed, a temporal increase in the prevalence of male genital malformations, including hypospadias and undescended testis, has been observed in recent population-based studies; and geographical differences suggest the role of environmental exposure to antiandrogenic endocrine disrupters.[1]
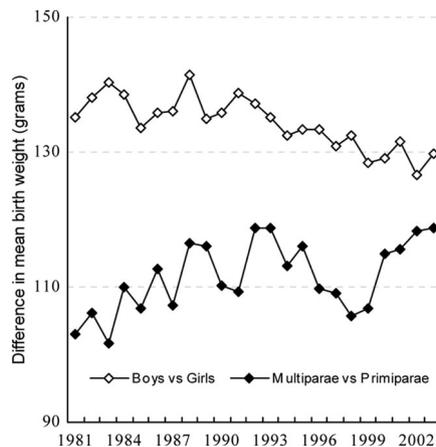
Birth weight has consistently been shown to be higher in boys than in girls.[2] This is apparently due to androgen action: the birth weight of 46 XY individuals with complete androgen insensitivity is similar to that of girls.[3] We hypothesized that if environmental toxicants have disrupted androgen action in male fetuses, the difference between the weight of male and female neonates should have decreased over time.

We used graphical methods to examine temporal trends in mean birth weight of all singleton live births from Statistics Canada's database for the years 1981–2003 (N = 5,086,550).[4] Because of a strong temporal increase in preterm birth and decrease in postterm birth (both of which would tend to reduce overall mean birth weight), the primary analysis was restricted to term births (37–41 completed weeks). To provide a control comparison, we analyzed the corresponding temporal trends in differences in birth weight between infants of multiparous and primiparous women.[2] We also carried out multiple linear regression analyses with birth weight as the dependent variable; gestational age, gestational age squared, maternal age (<20, 20–34, ≥35 years), fetal sex, parity (multiparous vs. primiparous), and year were the independent variables, along with sex-by-year and parity-by-year interaction terms. A negative sex-by-year interaction indicates that the male-female difference has decreased over the study period. All statistical analyses were carried out using SAS version 8.2 (SAS Institute, Cary, NC).

Between 1981 and 2003, mean birth weight for boys increased from 3391 to 3507 g; the corresponding figures for girls were 3248 and 3375 g. Similarly, mean birth weight in infants of multiparous mothers increased from 3368 to 3494 g, whereas the mean for infants of primiparous mothers increased from 3261 to 3375 g. The Figure demonstrates a steady temporal decrease in the male-female difference contrasting with a slight increase in the multiparous-primiparous difference. The multiple linear regression analysis confirmed the graphical results (interaction between sex and year −0.57 g/yr [95% confidence interval = −0.69 to −0.44] and between parity and year +0.17 g/yr [+0.05 to 0.30]).

Recent temporal trends in birth weight seem to differ by infant sex. Control for gestational age and for maternal age and parity in the multiple regression analysis helps ensure that temporal changes in those variables do not confound the declining sex difference in birth weight. Comparisons of temporal trends in the sex difference in birth weight between jurisdictions with variable exposure to endocrine disrupters may help to uncover the biologic mechanisms underlying our findings.

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FIGURE. Temporal trends in the differences in mean birth weight (in grams) between male and female and between infants born to multiparous and primiparous mothers (live singleton term [37–41 weeks of gestation] births from 1981 to 2003 in Canada).

Estimating the Incidence of Autism

To the Editor:

Hertz-Picciotto and Delwiche[1] analyze the databases of the California Department of Developmental Services (DDS) to ascertain the incidence of autism and determine whether increasing incidence can be explained by changing age at diagnosis and by shifting criteria. They conclude there is a true increase in

incidence that cannot be accounted for by these factors. Because an increasing number of investigators are drawing conclusions from these data, it is crucial to identify problems with the datasets and temper overly ambitious conclusions.

First, the databases should not be employed to ascertain incidence,[2] and yet the authors use both individual client records and quarterly reports to measure incidence. As the DDS explains in its quarterly reports:

"Increases in the number of persons reported from one quarter to the next do not necessarily represent persons who are new to the DDS system."[3]

"Differences in the numbers from quarter to quarter reflect the net changes between individuals who are newly reported (ie, included in the later report but not included in the earlier report) and individuals who dropped out."[4]

Furthermore, caseload numbers from DDS Regional Centers suggest a prevalence rate far below the prevalence estimates in widely accepted studies.[5] Thus, the California data seriously underestimate the prevalence of autism, and do not reflect the total population prevalence pool. They should not be used for incidence studies.

Second, the authors included in their analysis children between birth and 36 months of age identified in California's Early Start program. Because the goal of Early Start is to identify an at-risk population, the program's criteria are less restrictive than those used for older children and potentially overestimate the rate of autism. This program may also underestimate the children with autism because many evaluators are reluctant to give (and are not required to give) diagnoses.

Third, the authors place undue confidence on age of first appearance in the DDS dataset as a proxy for date of diagnosis. They also unjustifiably diminish the influence of qualitative factors, such as increased awareness, geographic disparities in caseload, and an emerging industry of therapies for individuals with an autism classification. The authors also dismiss diagnostic sub-

stitution, despite the fact that the total DDS caseload of developmental disabilities has remained stable over the last decade, and despite increasing evidence that substitution significantly increases autism classifications.[6]

Fourth, classifications are made by dozens of field evaluators throughout California's Regional DDS Centers. DDS has no control over the practices of individual Center diagnostic procedures. Some comply with DDS practice standards, whereas others do not. Although diagnosticians use a standard form (Client Development Evaluation Report), it was not designed to be a research tool. Moreover, the evaluators are not engaged in epidemiologic research.

Fifth, the authors note that neither Asperger disorder nor "pervasive developmental disorders not otherwise specified" qualify for "autism" under DDS guidelines, but evaluators routinely include milder cases under the category of autism, to enable these children to receive services. More importantly, neither the Client Development Evaluation Report nor the gold-standard Autism Diagnostic Observation Schedule and Autism Diagnostic Interview-Revised can clearly distinguish among the autism spectrum disorders.

DDS autism classifications need to be subjected to the same scrutiny as other databases used for the evaluation and surveillance of disease. Numerous studies highlight the poor diagnostic accuracy in prevalence studies that rely on administrative data.[7,8] Do diagnosticians in the California regional centers receive reliability training? To what extent are the gold-standard diagnostic procedures employed? Are the caseload data representative of the general population? Do DDS classifications have positive predictive value?

Before researchers make bold interpretations from these data, they must acknowledge the limitations of their scientific value.

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The authors respond:

We appreciate the concerns raised by Grinker and Leventhal[1] regarding limitations of the California Department of Developmental Services (DDS) databases. Indeed, nearly all these issues are discussed in our article[2]—some in considerable detail (underestimation of total autism or autism spectrum disorders incidence, inclusion of milder cases over time).

However, several of their statements are incorrect. They allege that we "conclude there is a true increase that cannot be accounted for . . ." and they call for "temper[ing] overly ambitious conclusions." We stand by our original conclusion: "the possibility of a true increase in incidence deserves serious consideration."

Grinker and Leventhal incorrectly claim that we used quarterly DDS casel-

oad data. We pointed out "caseload statistics do not provide valid information about individuals newly diagnosed." To calculate measures of incidence, DDS provided us with files of individual cases and we obtained state birth records and US census figures for denominators.

They criticize our use of DDS Early Start Reports on children younger than 36 months of age, correctly noting that, in general, diagnoses at younger ages can be unstable. Because of our concern over the same issue, we checked and determined that 87% of these early designations were later confirmed when the child was 36 months or older,[2] possibly reflecting cautious use of this diagnosis on Early Start Reports by Regional Center staff. Exclusion of the 1.5% diagnoses found only on an Early Start Reports, among all 30,832 autism cases, did not alter the study's results.

Another argument is that we placed "undue confidence on age of first appearance in the DDS dataset as a proxy for date of onset." Recognizing this problem, we had initially used the term "pseudo-incidence," but the reviewers pointed out that use of date of first contact with a provider as a proxy is standard practice and asked us to drop such language. Our concern that age at first appearance is not necessarily related to age of onset (which by DSM IV criteria occurs before 3 years of age) was in fact the basis for our analyzing "age at diagnosis" as an artifact.

The use of administrative data for epidemiologic purposes is certainly debatable. Hospital discharge data, vital records, information collected by health maintenance organizations, etc. are routinely used by epidemiologists in health services research. Responsible scientists consider weaknesses in their data sources, particularly how those might have affected the results, which we believe we have done. Grinker and Leventhal raise excellent questions about the California DDS system, and we invite them and others to carry out investigations that could provide answers.

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Interaction of Playing Experience and Age

To the Editor:

We read with great interest the study by Knowles et al,[1] who evaluated risk factors for injury among high school football players. The authors concluded that "prior injury, additional years of playing experience, and older age were predictors of injury incidence."

Closer inspection of the analysis might nevertheless point to the need for further elaboration. As the authors recognize, years of playing experience and age are factors "closely correlated with one another." In addition, prior injury may be associated with those variables, as injuries accumulate through age.

Given the inherent temporal associations among the 3 covariates, the inclusion of statistical interaction terms in the model might be revealing. For instance, after appropriate recategorization, Knowles et al reported an adjusted rate ratio of 1.1 for each additional year of playing experience and 1.2 for each year of age. But can the reader conclude that there is a multiplicative effect between these 2 variables? In other words, is the effect of one year (when it is de facto added simultaneously as year of age and year of playing experience) adequately described by the presented model?

Incorporating at least the interaction of years of playing experience times age interaction, as well as the interaction of prior injury times age, might provide more meaningful results. For example, a negative sign for the interaction of years of playing experience with age might imply a less pessimistic scenario for the risk of injury as the years go by. Indeed, given the large sample size of the cohort, evaluation of such interactions is feasible; it might be worth seeing an analysis incorporating the above.

Assessing statistical interactions is a valuable tool in modern epidemiology; nevertheless, interactions and their basis are frequently omitted, as reported in a recent critical analysis.[2] When dealing with variables inherently determining one another, such as the ones studied here, their innate interdetermination and directly consequent effect modifications might be worth expressing as statistical interactions.

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The authors respond:

We thank Sergentanis and Mariolis for their thoughtful comments[1] and their suggestion to investigate age and years of playing experience as mutual effect modifiers. We have conducted an analysis evaluating the joint role of age and years of playing experience. The increase in the overall injury rate due to increasing age was slightly smaller for players with more playing experience (rate ratio = 1.14 [95% confidence interval = 0.89–1.47]) than for those with less playing experience (1.35 [0.86–2.13]) (Table 1). Any modification in the overall injury rate ratio is small, relative to the imprecision of the estimates. We assessed modification based on departure from pure additivity of effects.

We also stratified this analysis by a third factor, evaluating these effects separately for games and practices. An interesting picture emerges. For athletes with less experience, the effect of increasing age on injury occurred during practices (1.87 [0.82–4.26]) and not during games

TABLE 1. Adjusted[a] Incidence Rate Ratios (RRs) Evaluating Increasing Age and Years of Playing Experience as Effect Modifiers, Stratified by Game Situation, n = 3948 Athlete-Seasons, NCHSAIS, 1996–1999

Risk Factor	Adjusted[a] RR, per 1000 Total Athlete-Exposures (95% CI)	Adjusted[a] RR for Games, per 1000 Game Athlete-Exposures (95% CI)	Adjusted[a] RR for Practices, per 1000 Practice Athlete-Exposures (95% CI)
	Adjusted[a] RRs Associated With Each Year of Increasing Age		
Year of playing experience			
0–1 year	1.35 (0.86–2.13)	0.97 (0.46–2.04)	1.87 (0.82–4.26)
2–4 years	1.18 (0.98–1.42)	1.28 (1.00–1.63)	1.15 (0.74–1.79)
5–8 years	1.14 (0.89–1.47)	1.40 (1.03–1.89)	0.79 (0.48–1.29)
	Adjusted RRs Associated With Each Year of Increasing Playing Experience		
Age			
≤16 years	1.08 (0.95–1.23)	1.10 (0.93–1.31)	1.07 (0.90–1.26)
≥17 years	1.07 (1.00–1.14)	1.17 (1.08–1.25)	0.92 (0.83–1.02)

[a]Adjusted for injury history, study year, grade, multiple sports participation, coaching qualities, body mass index, age, and competition division.

(0.97 [0.46–2.04]). For athletes with more experience, the converse is true: the effect of increasing age on injury was during games (1.40 [1.03–1.89]), rather than during practices (0.79 [0.48–1.29]).

As one would expect, the same result was observed when we examined age as a modifier of the effect of playing experience on injury risk, with older players showing an effect of increased experience in games (1.17 [1.08–1.25]) but not in practices (0.92 [0.83–1.02]). These results, though not strong, suggest that age is an effect modifier. One explanation for these results is that older athletes who are less experienced feel under greater pressure to secure a place on the starting roster for the team, and consequently play with greater intensity during practices (thereby exposing themselves to greater injury hazards). Inexperienced athletes who are younger may not feel the same pressure during practices. Furthermore, older athletes who have more years of experience with the sport are more likely to be "playmakers," and probably receive more playing time during a game and are involved in a higher proportion of plays in each game.

Although there is close correlation between age and playing experience, these analyses suggest that these factors might combine synergistically or antagonistically, depending on whether it is a game or a practice session. Thus, there is potentially a 3-way interaction among game/practice, age, and playing experience.

Given the imprecise estimates and overlapping 95% confidence intervals, these conclusions should be seen as tentative. As sports injury research continues to evolve, the investigation of effect modification may provide additional insights for injury prevention.

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On the Chromium Reanalysis

To the Editor:

The commentary by Smith[1] praising the Beaumont et al reanalysis[2] of original work by Zhang et al[3–5] implied inappropriate behavior regarding the Zhang and Li 1997 article.[5,6] A separate

manuscript[7] discussing the shortcomings of the reanalysis has been published by researchers who studied the JinZhou pollution incident under Dr. Zhang's guidance. The main points of Smith's commentary that may have misled readers are as follows.

First, Smith[1] suggests there was a reversal of scientific conclusions between the 1987 and 1997 publications of Dr. Zhang.[4,5] However, both papers identified excess cancer risks in the agricultural villages with groundwater chromium(VI) contamination. The 1997 analysis[5] added dose-response considerations identified by Zhang in 1980[3] that were not included with the brief 1987 synopsis.[4] The 1997 paper was simply a more complete account of Zhang's earlier research, and it is not fairly described as a "reversal."

Second, Smith[1] implies that some conflict of interest was behind the 1997 paper[5] by suggesting it was "the work of a US consulting firm, ChemRisk, which had been hired by industry clients with liability for chromium pollution." To the contrary, the translations summarizing Zhang's original research from 1980[3] did not make it into our work, and industry clients took no part in creating or editing the 1997 manuscript.[5] Dr. Zhang had sole authority on authorship and content, signed a permission letter for journal submission including his contact information, and wrote to sincerely thank my colleagues for their assistance.[8] Unfortu-

nately, it is unclear that this information was reviewed and given serious consideration prior to the editorial retraction of the 1997 paper[5] in 2006.[6] Coauthor ShuKun Li separately published her objections[9] to that overzealous action on behalf of her deceased colleague.

Third, Smith cites a commentary[10] that speculates on the motivations of Zhang and colleagues and describes misconduct allegations by Beaumont and trial attorneys as "evidence." Contrary to the claims of the trial lawyers,[11] Dr. Zhang never claimed that his research proved chromium(VI) ingestion caused cancer.[3–5]

Smith[1] suggests that an epidemiologist's "ultimate nightmare" is being unable to adjust rate data properly even for age and sex. In my view, "ultimate nightmare" more aptly describes the continued dissemination[1,10,11] of false misconduct allegations. Conflicts of interest at some level can be assigned to almost any scientific researcher,[12] so it is important that opinions about differing scientific interpretations of data should be limited to the basis for those opinions, and not to innuendo about impropriety.

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The authors respond:

In response to the letter from Dennis Paustenbach, I note that my Commentary[1] was confined to facts and does not contain innuendos as he claims. This response will also focus on published facts.

The real issue is whether those living near the ferrochromium factory in the Liaoning Province, China, had increased rates of cancer due to chromium contamination of their drinking water. The first publication by Zhang and Xilin Li,[2] referring to the chromium polluted areas, stated that "stomach cancer mortality rates were . . . higher than the average for the district as a whole" for the period 1970–1978. The second publication by Zhang and ShuKun Li and written in English, stated that the "results do not indicate an association of cancer mortality with exposure."[3]

Paustenbach states that I suggested "there was a reversal of scientific conclusions between the 1987 and 1997 publications of Dr. Zhang." I did not state that, although readers can judge for themselves. He later states "it is not fairly described as a 'reversal'," quoting himself. The facts remain that the initial publication reported increased cancer rates in chromium-polluted areas, and the second reported that the "results do not indicate an association of cancer mortality with exposure."

Another fact is that this second article by Zhang and ShuKun Li was retracted by the journal JOEM because "financial and intellectual input to the paper by outside parties was not disclosed."[4] In a recent publication coauthored by Paustenbach, we are informed that the payment made to Dr. Zhang was US $1960 over an 8-month period.[5] We are also told that Dr. ShuKun Li, who coauthored the second paper with Dr. Zhang, stated that Dr. Zhang did not consider this "small consulting stipend" to be "worthy of mention." A payment of $1960 over an 8-month period needs to be considered in light of urban per capita income in China at that time, which was 4288 Yuan, or about US $518 at 1995 exchange rates.[6] Surely nobody would consider a payment several times the per capita annual urban income "not worthy of mention"?

This study area in China had perhaps the highest exposure to hexavalent chromium in water that will ever be experienced by a population large enough to estimate cancer rates.[1] If such exposure results in elevated cancer rates, as Zhang and Xilin Li had originally suggested and as was supported by Beaumont's more detailed analysis,[7] then this important information should not be obscured.

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Chromium(VI) Ingestion and Cancer

We address 2 errors in the paper by Beaumont et al[1] that reanalyzes the data of the late Dr. Zhang,[2,3,4] which in 1995 we coauthored (S.L.) and helped him submit for publication (B.K., W.B., T.Y.).

First, among the 5 exposed villages, there is no consistent pattern of association of cancer rates with the gradient of exposure to Cr6+ as noted earlier by Dr. Zhang.[2,5] The villages more distant from the alloy plant had higher, not lower, cancer rates while being exposed later and at lower concentrations than the nearer villages. Beaumont et al[1] are incorrect in stating there was no gradient in exposure when data for the beginning (1965), middle (1972), and end (1979) of the episode support such a gradient. (The data[6,7] for the 2 later time periods are not presented by Beaumont et al.) The geologic and recharge characteristics of the local aquifer caused the main contamination zone to be localized between the alloy plant and the near villages[6,7] and the most contaminated groundwater to travel away from the more distant villages.

Second, Beaumont et al (Table 5)[1] use incorrect cancer comparison groups for the exposed agricultural villages. The majority of the difference in the local stomach cancer rates is due to TangHeZi (14.5 per 100,000) having a substantially lower rate than the average both for the unexposed villages (27.6 per 100,000) and for the exposed villages (35.4 per 100,000) (Table 4).[1] TangHeZi cannot represent the expected stomach cancer rate in the exposed villages "but for" the Cr6+ contaminated water when its stomach cancer rate is significantly lower by about the same magnitude compared with the unexposed villages. A comparison of the average stomach cancer rate in the exposed and the unexposed villages indicates little difference (RR = 1.29; 95% CI 0.75–2.21).[8,9] Neither are the average Province cancer rates (Table 5, bottom)[1]

appropriate as they refer to a vast, heterogeneous geographic area and differ by about the same magnitude from the averages for the unexposed and exposed villages.

Gwiazda,[10] an external reviewer selected by Cal-EPA for these analyses by Beaumont and colleagues, described as "misguided" the use of any comparison group that does not represent the expected cancer rates for the 5 exposed villages but for the exposure to Cr6+ contaminated water. This criticism applies equally to the inclusion of TangHeZi in the local comparison group and to the use of the cancer rates for the Province.

It is not necessary to know what specific risk factors are the source of the lower stomach cancer rates for TangHeZi and for the Province to recognize they are inappropriate comparison groups. TangHeZi is among those industrial towns created in the 1950s by the communist Chinese government and populated by skilled workers from the overcrowded major cities. This town has been shown to or is expected to differ from agricultural villages on demographics, urbanization, industrialization and occupation, socioeconomic status, diet, and access to medical care.[9,11–12]

Finally, Zhang's first manuscript[2] reported the absence of a dose-response relationship, and his second[3] cautioned that the higher cancer rates in the villages with groundwater contamination relative to the Province average "can only be considered to be possibly connected to Cr6+ contamination of the groundwater, soil and crops." Zhang's fourth manuscript[5] similarly cautioned that "Cr6+ contamination cannot be ruled out completely as the reason for the high cancer death rates in these villages," and acknowledged that the lacking dose-response trends "do not support such a relationship." The secondary analyses of Beaumont et al[1] are questionable because, as explained above, they misuse the data and reverse the interpretations of the original researcher.[9]

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The authors respond:

We appreciate the opportunity to discuss epidemiologic issues in our analysis of data from the study by Drs. Jiandong Zhang and Xilin Li.[1,2] It is helpful that Kerger et al acknowledge that in 1995 they coauthored and helped Dr. Zhang submit a paper for publication.[3] It should be clarified that this paper was eventually retracted by the journal in which it was published, and that coauthor Dr. Li is not the same Dr. Li (Xilin Li) who coauthored the original report published in a Chinese medical journal in 1987.[2,4]

Kerger et al say that we stated there was no gradient of exposure with distance from the alloy plant. We did not say that. We said that distance was not a reliable surrogate of dose due to rapid groundwater movement, direction of ground water flow, pollution prevention, reduction of Cr^{+6} in ground water with ferrous sulfate, and self-limitation of exposure due to water color and taste. Because of this, we did not attempt to correlate cancer rates for the 5 villages with contaminated water with distance from the alloy plant. Kerger et al did just such an analysis, however, reporting a regression coefficient of 0.01 ($P = 0.93$) for stomach cancer.[5] While the coefficient was positive and technically indicative of higher stomach cancer rates in more distant villages, we think that the coefficient and its hypothesis-test probability more strongly suggest lack of association.

While Kerger et al say that the main contamination zone was localized between the alloy plant and the near villages, water monitoring data indicate otherwise. Hydrogeologic investigation and water analysis found that the plume had formed a long and narrow contamination zone.[6] Chromium was detected in the drinking water of the most distant down-gradient study village (Wenjiatun, 5 km from the alloy plant) in 1965, 5 years before the start of mortality observation in 1970.[7] We did not report chromium concentration data from 1972 because, after 4 independent translations of the Chinese text, it was not clear which data were applicable to the cancer study.[6] We did not report concentrations measured after 1978 because cancer mortality observation ended that year.

Kerger et al assert we used "incorrect cancer comparison groups" in our analysis. We note precedents for the use of the same unexposed study regions and Liaoning Province as cancer comparison groups. Specifically, the unexposed study regions were defined by Jiandong Zhang and Xilin Li in their original analysis, and Kerger et al used Liaoning Province as a comparison group in their 1997 article.[3,8] Kerger et al raise an important question about potential bias from differences in urbanization. In recent decades, rural stomach cancer mortality rates in China have indeed been higher than urban rates. In the 1970s, however, rural and urban rates were similar.[9] During 1973–1975, the midpoint of the 1970–1978 study period, the national rural and urban stomach cancer mortality rates were 19.4 and 20.1 per 100,000 per year, respectively.[10]

Kerger et al say that our paper reversed the interpretation of the original researchers, when in fact our results are consistent with the findings of Jiandong Zhang and Xilin Li. These researchers reported in 1987 that mortality rates for all cancer, lung cancer, and stomach cancer in the contaminated area were increased above the rates in the general population.[2] We reached very similar conclusions.

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