because of some aspect of maleness. Even today almost exactly 12 years after the Women’s Health Initiative trial showed definitively that estrogen does not protect women against ischaemic heart disease or mortality, research interest is still focused on hormones in women, whereas the obvious alternative candidate, hormones in men, remains backgrounded, little researched and largely unmentionable.

In the past 10 years, the three leading epidemiology journals (International Journal of Epidemiology, American Journal of Epidemiology and Epidemiology) have published 177 papers about estrogen and 47 papers about testosterone, based on a PubMed search of these journals keyworded on ‘estrogen or estradiol’ and ‘androsterone or testosterone’, respectively. Most of these papers concerned only women (90% of the 177 estrogen papers and 32% of the 47 testosterone papers). Such lack of interest has allowed vested interests to promote testosterone to men successfully as an antidote to ageing with minimal evidence of benefit and mounting (but under-researched and hence sparsely documented) evidence of harm. Moreover, action to control these potential harms from testosterone, both in terms of allocation of health resources to expensive and ineffective treatments and in terms of potential harms of this treatment, appears to be largely outside the scope of public health; instead the lead is currently being taken by regulators and the legal profession, despite the potential for public health dividends for both men and women. For example, if testosterone was seen in epidemiology as the increasing risk of cardiovascular disease, as Health Canada is warning—’possible cardiovascular risks including heart attack, stroke, blood clots in the lungs or legs, and irregular heart rate’—then environmental drivers or and consequences of testosterone would represent a new class of potential intervention targets for the leading cause of mortality. Such new possibilities might even act via backgrounded but modifiable mechanisms. For example, haematocrit is raised by testosterone and was suggested as an easily modifiable target for heart disease over 50 years ago, consistent with evidence from randomized controlled trials. Let’s hope that Kronfeldner’s drawing attention to how norms shape causes and frame the questions we study will enable us, as a discipline, to take a more agnostic and comprehensive view of the drivers of population health, hopefully without having to wait, to paraphrase Max Planck, for the demise of the holders of the current norms, most likely from cardiovascular disease.

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References
11. Coyne DW. The health-related quality of life was not improved one.

Cohort effects explain the increase in autism diagnosis: an identifiability problem of the age-period-cohort model

From Stefan N Hansen* and Erik T Parner

Section for Biostatistics, Department of Public Health, Aarhus University

*Corresponding author. stefanh@biostat.au.dk

Keyes et al. used an age-period-cohort model in an effort to disentangle time trends in autism to distinguish effects attributable to age, period and cohort, respectively. It is well known, in particular in the statistical literature, that the age-period-cohort model suffers from
an identifiability issue\(^2\) since the date of diagnosis is the sum of the date of birth and the age at diagnosis. This issue is often resolved by using a constraint-based approach. However, any such constraint cannot be validated from data itself\(^2\) and thus has to come from prior knowledge.

In their original paper, the authors of Keyes et al. used the constraint that the age-effect should be constant between ages 8 and 12 years, based on the observed rates in their data being approximately constant after age 8. However, the observed rate as a function of age does not depict the age-effect. In a letter to the editor, Spiers\(^3\) questioned their choice of constraint and pointed out that in the statistical literature it is known that even a slight inconsistency between the constraint and reality can have a large impact on estimated effects. In a response to Spiers,\(^4\) the authors of Keyes et al. however argued that ‘there is substantial evidence that diagnoses are more common among 3- and 4-year-old children than older children, thus a simple constraint that diagnosis is constant after the age of 8 years allowed us to parsimoniously model the data without assuming that period- and cohort-effects are nonlinear variation from overall drift’. Whereas it is true that the authors of Keyes et al. assume nothing about the period- and cohort-effects, what is missing is still an exploration of how sensitive their estimated age-, period- and cohort-effects are to the constraint imposed on the age-effect. The purpose of this letter is to illustrate, on the same data as Keyes et al.,\(^1\) that even a small change in their constraint can yield very different conclusions.

Below we repeat, in the left-hand graph of Figure 1, the estimated age-, period- and cohort-effects that appeared in the original paper: that is, under the constraint of a constant age-effect between ages 8 and 12 years. The authors of Keyes et al. concluded that the prevalence increase is driven mainly by a cohort-effect. The right-hand graph shows the estimated age-, period- and cohort-effects still consistent with the observed autism rates but under a minor change in that constraint. Instead of assuming a constant age-effect between ages 8 and 12, we have used the constraint that the age-effect is linear with a slightly negative slope, i.e. this constraint is very close to the constraint of a constant age-effect between ages 8 and 12. From these results it appears that the prevalence increase was driven mainly by a period-effect.

Since the two constraints used in Figure 1 are almost identical, it is our impression that the estimated age-, period- and cohort-effects are very sensitive to the assumptions made. We acknowledge that the authors of Keyes et al. did perform some sensitivity analyses of their results, as the authors write that ‘for these data we carefully examined the graphical trends in the data, estimated models with varying assumptions…’. However, there are still reasonable constraints that the authors failed to explore, as seen in Figure 1. The same sensitivity to specific constraints was also observed when we applied an age-period-cohort analysis for autism diagnoses in Denmark among children born in the same period with similar follow-up. The huge difference in conclusion with very similar constraints illustrates the limitations of the age-period-cohort model.

References