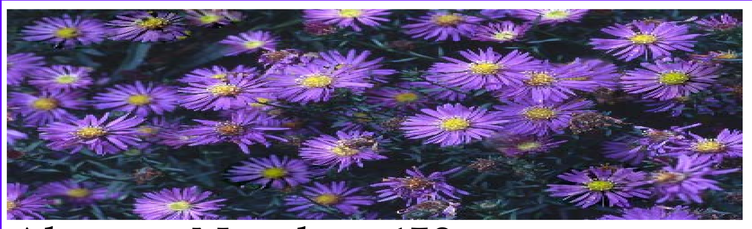

Abstract Number: 459

Methodologic and Ethical Failures in Epidemiologic Research, as Illustrated by Research Relating to Tobacco Harm Reduction

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Background

- Tobacco harm reduction (THR) is the substitution of less risky nicotine products for cigarettes.
  - Epidemiologic evidence clearly shows that non-smoked sources of nicotine (smokeless tobacco and pharmaceutical nicotine) have approximately 1% of the health risk of cigarettes.
  - Despite the dramatic potential risk reduction of THR, many clinicians and public health practitioners oppose THR efforts.
  - Opponents overstate the risks from smokeless tobacco, which is currently the most promising reduced harm substitute, sometimes by perverting epidemiologic research.
- We have previously identified the epidemiologic "methods" used by politically-driven THR opponents:
  - Not acknowledging potential residual confounding;
  - Inconsistent exposure, outcome, and covariate definitions;
  - Nonsensical meta-analyses;
  - Misinterpreting descriptive epidemiology that clearly shows the success of THR in Sweden; and
  - Engaging in **publication bias *in situ* (PBIS)** (intentionally biasing results from a study; e.g., running many different models and reporting only the one that produces the preferred results).

- Ethical obligations of researchers and journals.
  - Researchers should report their findings honestly, signifying respect for scientific truth and the right of their readers to interpret results rather than feed authors' preferred conclusions.
  - This may require reporting results that contradict favored hypotheses or might call into question some conclusions from other results.
  - Journals are currently incapable of ensuring adequate methodology, but can endeavor to reduce PBIS, particularly when it is called to their attention.

- We reviewed a series of articles based on a large cohort of Swedish construction workers and exposure to snus (the type of smokeless tobacco common in Sweden) to illustrate the apparent failure to conduct and publish epidemiologic research according to the above observations about ethics.
  - Following the publication of Zendehdel (2008), we identified signs of PBIS in this series of articles which shared population/data and exposure of interest, and looked at a variety of endpoints..
  - In particular, it appears that each study used its own data-driven model, presumably to increase the magnitude of reported associations.

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Results and discussion

- Table 1 compares the sample size and variables used in 8 analyses of the Swedish construction workers cohort that included snus use as an emphasized independent variable.
- The authors were undoubtedly aware of the methods used in prior studies due to overlapping authorship, etc. (And yet, strangely, the later articles did not usually cite the former ones.)

Table 1: Sample size and variables definitions used in different analysis of the Swedish construction workers cohort

Reference	n and person-time (pt)	Snus use	Age in stratified and multivariable analysis	BMI	Smoking
Zendehdel 2008	n=336,381 pt=7,475,628	Ever versus never	Attained age Stratified analysis: <70, >=70 RR adjusted for age as time scale	Quartiles	Ever or never Current, previous, or never Amount (g/day): <10, 10-19, >=20 Product: cigarette only, pipe only, cigar only
Luo 2007	n=279,897 pt=5,611,075	Never, previous, or current Amount used (g/day): <10, 10	Attained age RR adjusted for attained age (continuous) as time scale.	<25, 25–29, and ≥30	Never, previous, or current Smoking tobacco (g/day) (continuous)
Odenbro 2007	n=339,802 pt=7,663,400	Pure snuff users vs tobacco nonusers (TNU) Duration (years): 1-29, >=30	Incidence rate ratios adjusted for age (possibly in 5-year age groups)	<18.5, 18.5-25, 25-30, >30	Cigarette tobacco (g/day): TNU, 1-9, 10-19, >=20 Pure cigarette smokers vs TNU Pure pipe smokers vs TNU Pure cigar smokers vs TNU Mixed tobacco use vs TNU
Fernberg 2007	n=336,381 pt=7,475,628	Pure snuff users vs TNU	Incidence rate ratios adjusted for age in years as time scale.	<18.5, 18.5-25, 25-30, >30	Current smokers, ex-smokers and TNU Amount currently smoked (g/day): <10, 10-20, >20 Pure cigarette smokers vs TNU Pure pipe smokers vs TNU
Hergens 2007	n=118,395 pt=2,222,262	Never, current, former Amount used (g/week) Amount used by current users (g/day): <12.5, 12.5–24.9, 25–49.9, >=50 Duration Time since snuff use cessation Regular snuff use	Stratified analysis: 35-54 and 55-65 years old RR adjusted for age as time scale.	<20, 20-24, 25-30, 30+ (adjusted for age distribution at entry)	Not included
Fang 2006	n=280,558 pt=5,505,849	Pure snuff use vs TNU	RR adjusted for age in 5-year categories	Not included	Former, current, non-tobacco use Amount (g/day): <=15, >15 Cigarette smokers, cigar, pipe or mixed smokers vs TNU Only smokers, both smokers and snuff users vs TNU Only smokers, snuff users only, both smokers and snuff users vs TNU
Odenbro 2005	n=337,311 pt=6,536,910	Snuff users vs TNU Duration (years): TNU, <30, >=30	Incidence rate ratios adjusted for age (possibly in 5-year age groups)	<18.5, 18.5-25, 25-30, >30	Previous, current vs TNU Smoking tobacco (g/day): TNU, <=10, 11-15, >15 Years of smoking: TNU, <=15, 16-25, >25 Years since smoking cessation: TNU, <10, >=10 Cigarette smoker vs TNU Cigar smoker vs TNU Pipe smoker vs TNU Mixed user vs TNU Cigarettes/day: TNU, <10, 11-20, >=201 Pipe tobacco (g/week): TNU, <80, >=80
Adami 1996	n=135,006 pt=2,369,006	Ever versus never (includes cigarette, pipe and cigar smokers)	Rate ratios adjusted for age as a categorical variable (<45, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79 80+)	Not included	Never, previous and current Cigarettes/day: 0, 1-4, 5-14, 15-24, >25 Duration among ex-smokers (years): never smokers , 1-10, 11-20, >21 Duration among current smokers (years): never smokers, 1-10, 11-20, 21-30, 31-40, >41 Pipe tobacco (g/week): never smokers, <30, 30-100, >100

Results and discussion - continued

Conflicting eligibility criteria

- Different eligibility criteria were used, without justification, leading to vastly different sample sizes.
- The main difference was whether males enrolled from 1971-75 were included.
- Some articles excluded these participants due to "ambiguities in the coding of smoking status in the questionnaires used during 1971–75," (quote from Luo 2007, which cited as a basis for this a paper by Zendehdel and yet Zendehdel included 1971-75 enrollees).
  - This is particularly important for the Zendehdel (2008) results because that paper emphasized the larger associations for the age 70+ person-time, which comes disproportionately from the 1971-75 cohort.

Results and discussion – continued

- Snus exposure, age, smoking and BMI variables were not consistent across studies. While it is theoretically possible that different functional forms, choices of covariates, etc. are appropriate for different diseases, these papers did not adequately justify the differences or suggest they were anything other than data-driven.
- Age
  - Zendehdel justified their age cutpoint by stating that the RRs diverged at age 70 and indicated that older men were more likely to have been exposed to products with different chemistry than contemporary products.
  - But if the difference is real and not just a data-driven statistical artifact, then the authors should have emphasized the <70 results since they claim to be providing information relevant to health policy decisions about current products. But they chose to emphasize the bigger RR from the 70+ population, suggesting a goal of biasing the reader's perception of their results.

- In the most typical manifestation of PBIS, the abstract of the article focuses on outliers.
- The authors focus on statistical significance testing which is, of course, generally frowned upon. But it is particular bad when 60 RRs are calculated for different cuts at the data, and no attempt is made to adjust for the multiple comparisons.

Our attempt to point out inconsistencies and possible errors

- In April 2008, KH, CVP and BR submitted a letter to the International Journal of Cancer pointing out most of what appears above.
- We suggested that the authors of this series should either make the data available for the scientific community to assess the apparent PBIS, or they should at least run the different models for different endpoints to demonstrate that their results were not entirely driven by model selection.
- The letter was rejected because it did not pass the editors' "prima facie suitability" standards and was not a "priority for publication."
- It is difficult for us to understand what could be a more relevant letter to publish about these articles.
- Even after appeal, the editors refused to publish the letter. This is quite embarrassing for epidemiology as a science. It reinforces the perception that epidemiology is junk science and that journals just churn out results without any attention to their flaws.

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Dear Dr. Heavner,

Thank you for submitting your manuscript "A biased and deficient study of snus use and esophageal/gastric cancer" to the International Journal of Cancer. The Editors have now considered the paper with regards to its prima facie suitability for publication in the International Journal of Cancer. Unfortunately, the manuscript does not appear to be well suited for the journal.

This conclusion is not a reflection on the quality of the work. Instead, it reflects the sense that the work is not of sufficient scope and priority for publication in International Journal of Cancer as evaluated by the Board of Editors.

I reiterate that the decision is not a reflection of the quality of the work. It is simply that the journal receives far more manuscripts than it can publish and thus many difficult decisions must be made. Thank you again for considering our journal and I hope that our decision in this instance does not dissuade you from submitting your work to the International Journal of Cancer in the future.

Sincerely yours,

Prof. Harald zur Hausen
Editor-in-Chief

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Conclusions

- Taking advantage of the weaknesses of epidemiology to advance a worldly agenda not only hurts scientific integrity, but makes epidemiology a junk science.
- PBIS skews perceptions of study results, and so misleads anyone who is genuinely interested in determining true health risks.
- PBIS is not taken seriously by most epidemiology/public health journals.
- A simple way to reduce PBIS is reporting, as a sensitivity analysis, results calculated based on related statistical models that were previously published. This can show whether a result is largely driven by the choice of model. Doing this is particularly easy when the same authors created the previous models using the same data.
- However, the most robust solution to PBIS is to end the practice of publishing based on secret data using half-described methods.
- Novel forums are needed to discuss variations in study methodology when the journal that published the original article is not receptive to such concerns.

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