Review of: "Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports"

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Potential competing interests: I am an anti-smoking/tobacco harm-reduction advocate.

Hackshaw and colleagues in their study titled **"Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports",**[1] plot a nonlinear dose-response curve for cigarette smoke and cardiovascular disease, associating one cigarette per day with half the risk of 20 cigarettes per day (CPD).

However, this nonlinear curve is attributable to three basic oversights rather than a true effect:

1. The curve represents **brackets of cigarette consumption** plotted by their **midpoints**.
   However, in normal distributions, prevalence is higher at values closer to the mean. Thus, within consumption brackets spanning below the mean, the distribution of smokers will be skewed upwards (towards the mean). Consequently, midpoints will understate exposure in below-mean brackets.
   The inverse is true for above-mean brackets: the distribution of smokers will be skewed downwards and concentrated below the bracket midpoint. Consequently, midpoints will exaggerate exposure within above-mean brackets.
   This will manifest in a trendline exaggerating outcomes at lower exposures and understating outcomes at higher exposures.
2. **Regression towards the mean:** Light smoking tends to increase over the course of follow-up: Among 1-4 CPD smokers at baseline, continuing smokers mostly moved to higher consumption brackets within a decade.[2] Regression to the mean also entails that outlier smokers tend to have a history of smoking at levels that are closer to the mean than measured.
   While Hackshaw et al cite one study reporting a large cardiovascular disease risk for continuous <1 CPD smokers, that same study also shows an anomalous tenfold increase in lung cancer at the same dose,[3] contradicting the broad evidence for a linear relationship between smoking and lung cancer (or a quadratic curve climbing at a steeper rate with greater exposures).[4][5] Regression to the mean is less evident in relation to lung cancer because of the decades lag between smoking and resultant lung cancer.[6]
3. **Compensatory inhalation**: Light smokers inhale much more smoke per cigarette than do heavier smokers. The 2010 Surgeon General's Report on smoking states:[7]
   "As use exceeds 10 to 15 cigarettes per day, a progressively smaller increment in serum cotinine for each increment in the number of cigarettes smoked per day is observed (Caraballo et al. 1998; O'Connor et al. 2006). This flattening of the relationship between exposure and cigarettes smoked per day was similar to flattening of

> ***the relationship between the RR of CHD and the number of cigarettes smoked."***
> Hackshaw and colleagues adjust for compensatory inhalation, but rely on a single biomarker study anomalously showing 1-10 CPD representing only a quarter of 20 CPD's exposure. The data cited above (from the Surgeon General's Report) indicates otherwise, in addition to subsequent studies.[8][9]

It is important to note that a high risk for light smokers still holds true: The points above indicate that light smokers (1) tend to be at the high of the "light" range (2) tend to increase consumption over time and (3) inhale much more smoke per cigarette than do heavier smokers.

However, the shape of the dose-response curve remains relevant for tobacco harm-reduction in assessing the effects of the widespread "dual-use" of smoked cigarettes and alternative nicotine products, where smoking is partially substituted but not eliminated.[10][11] In addition, some have extended the ostensible nonlinear dose-response curve to conclude that vaping likely poses a large fraction of the cardiovascular risk posed by smoking.[12][13]

External Evidence

The authors also cite Law & colleagues[14] who infer a nonlinear curve from secondhand smoke epidemiology using the following premises:

1. Toxicant exposure in passive smokers is about 1% that of active smokers.
2. Passive smoking is associated with a 30% increased cardiovascular disease risk.
3. Active smoking is associated with a 100-200% increased cardiovascular disease risk.

However, points 1-2 are flawed:

Relative exposure: Law et al cite studies measuring cotinine for relative exposure. However, subsequent studies evaluating cotinine's relationship with the alternate tobacco biomarker, NNAL, indicate that cotinine can underestimate toxicant exposure in passive smokers by an order of magnitude (largely attributed to nicotine's rapid dissipation from indoor air).[15][16]

Publication bias and heterogeneity: In large meta-analyses, Egger's tests indicate publication bias,[17][18] backed by a strong inverse relationship between statistical power and effect size.[18] Significant inter-study heterogeneity is also present.[17][18] Statistical adjustments for publication bias (like the trim-and-fill method) are known to be unreliable in presence of heterogeneity.[19]

Law et al argue that it would require an implausible 240 studies for eight studies to produce a significant positive outcome by chance. However, this calculation could only negate publication bias as the sole explanation of the entire effect size. It does not negate publication bias from exaggerating a true outcome (or one created by other systematic biases). Furthermore, their calculation assumes a homogeneous distribution of outcomes, but heterogeneity is present. In addition, publication bias *in situ* has been documented in this field,[20] which entails selecting from multiple outcomes or study

models within a single dataset.[21]

Confounding: The 2006 Surgeon General's Report on passive smoking[5] rules out confounding, citing broad multivariate adjustments in the Nurses' Health[22] and CPS-II[23] studies. Yet, these same two cohorts show similar sized reductions in cardiovascular disease for antioxidant vitamin supplements[24][25][26] that are refuted by randomized controlled trials.[27][28][29] This shows that multivariate adjustments in cohort studies cannot reliably exclude confounding effects for cardiovascular correlations of these sizes, as others demonstrate more broadly.[30][31]

Prospective versus retrospective studies: Limiting meta-analyses to prospective studies substantially reduces the RR to 1.09 or 1.17.[18][17] Case-control studies allow for recall/reporting bias and show a significant relationship between cardiovascular disease and coffee,[32] contrary to prospective studies.[33]

If case controls are deemed reliable, then they also show a linear relationship between CPD and cardiovascular disease.[34][35][36]

Cigar epidemiology: An FDA authored systematic review on cigars found no relationship between daily light/non-inhaling cigar smoking and cardiovascular disease.[37] This is evidence against a nonlinear effect because cigar smokers are exposed to secondhand smoke. Law et al argue that cigar smokers are exposed to smoke over a shorter duration per day than passive smokers and that most cigars are not inhaled. However, the lung cancer risk in cigar non-inhalers is far higher than for passive smokers[37]

Smoking bans: Hackshaw & colleagues also cite reduced cardiovascular hospital admissions following indoor smoking bans. However, these studies have been controversial.[38] They generally do not control for the long-term decline in cardiovascular disease. In addition, the large number local bans & diverse methodology makes publication bias inevitable. Indeed, an analysis excluding (a) studies where adjustments for a trend of decline was not possible and (b) studies reporting local estimates where national estimates are available found an effect of only 2.9% (0.01-5.6%), which is attributable to the effects of indoor smoking bans on CPD in smokers or the limitations of ecological studies.[39]

Particulate matter: Pope & colleagues in their analysis of the CPS-II study plot a continuous nonlinear dose-response curve from low-dose outdoor PM2.5 through secondhand smoke and high-dose cigarette smoking PM2.5.[40] However, If this continuous nonlinear dose-response curve is valid, then among cigarette smokers already at the high end of the dose-response curve, outdoor pollution would have little correlation with cardiovascular mortality, but the relationship is greater among cigarette smokers.[41]

Pope & colleagues also indicate that 0-3 CPD smokers have 40% of the excess cardiovascular mortality posed by 20 CPD. However, this is consistent with relative NNAL and cotinine levels in large US biomarker studies.[8][9] Furthermore, as mentioned above, regression towards the mean would entail that these low CPD smokers will tend to have both a history & future of smoking levels closer to the mean.

References

1. ^(2018). Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports. BMJ. doi:10.1136/bmj.k1611.
2. ^Bjartveit & Tverdal.. (2005). "Health consequences of smoking 1–4 cigarettes per day." (Table 5). Tobacco Control.
3. ^Maki Inoue-Choi, Linda M. Liao, Carolyn Reyes-Guzman, Patricia Hartge, et al. (2017). Association of Long-term, Low-Intensity Smoking With All-Cause and Cause-Specific Mortality in the National Institutes of Health–AARP Diet and Health Study. JAMA Intern Med, vol. 177 (1), 87. doi:10.1001/jamainternmed.2016.7511.
4. ^MR Law, JK Morris, HC Watt, NJ Wald. (1997). The dose-response relationship between cigarette consumption, biochemical markers and risk of lung cancer. Br J Cancer, vol. 75 (11), 1690-1693. doi:10.1038/bjc.1997.287.
5. a, b(2006). The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General. doi:10.1037/e601432007-001.
6. ^American Association for Cancer Research. (2012). AACR cancer progress report 2012. (Figure 10). Clinical Cancer Research.
7. ^(2010). How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General. doi:10.1037/e590462011-001.
8. a, bB. Rostron. (2012). NNAL Exposure by Race and Menthol Cigarette Use among U.S. Smokers. Nicotine & Tobacco Research, vol. 15 (5), 950-956. doi:10.1093/ntr/nts223.
9. a, bSaul Shiffman, Michael S. Dunbar, Neal L. Benowitz. (2014). A Comparison of Nicotine Biomarkers and Smoking Patterns in Daily and Nondaily Smokers. Cancer Epidemiol Biomarkers Prev, vol. 23 (7), 1264-1272. doi:10.1158/1055-9965.epi-13-1014.
10. ^Hayden McRobbie, Anna Phillips, Maciej L. Goniewicz, Katie Myers Smith, et al. (2015). Effects of Switching to Electronic Cigarettes with and without Concurrent Smoking on Exposure to Nicotine, Carbon Monoxide, and Acrolein. Cancer Prev Res, vol. 8 (9), 873-878. doi:10.1158/1940-6207.capr-15-0058.
11. ^Caroline O Cobb, Jonathan Foulds, Miao-Shan Yen, Susan Veldheer, et al. (2021). Effect of an electronic nicotine delivery system with 0, 8, or 36 mg/mL liquid nicotine versus a cigarette substitute on tobacco-related toxicant exposure: a four-arm, parallel-group, randomised, controlled trial. The Lancet Respiratory Medicine. doi:10.1016/s2213-2600(21)00022-9.
12. ^Kenneth C Johnson. (2018). Just one cigarette a day seriously elevates cardiovascular risk. BMJ. doi:10.1136/bmj.k167.
13. ^Stanton Glantz. (2016). Accumulating evidence suggests e-cigs 1/3 to 1/2 as bad as cigs (maybe higher). tobacco.ucsf.edu.
14. ^M R Law, J K Morris, N J Wald. (1997). Environmental tobacco smoke exposure and ischaemic heart disease: an evaluation of the evidence. BMJ, vol. 315 (7114), 973-980. doi:10.1136/bmj.315.7114.973.
15. ^Neal Benowitz, Maciej Lukasz Goniewicz, Mark D. Eisner, Eduardo Lazcano-Ponce, et al. (2010). Urine Cotinine Underestimates Exposure to the Tobacco-Derived Lung Carcinogen 4-(Methylnitrosamino)-1-(3-Pyridyl)-1-Butanone in Passive Compared with Active Smokers. Cancer Epidemiol Biomarkers Prev, vol. 19 (11), 2795-2800. doi:10.1158/1055-9965.epi-10-0497.
16. ^Rachel I. Vogel, Steven G. Carmella, Irina Stepanov, Dorothy K. Hatsukami, et al. (2011). The ratio of a urinary

tobacco-specific lung carcinogen metabolite to cotinine is significantly higher in passive than in active smokers. *Biomarkers, vol. 16 (6), 491-497. doi:10.3109/1354750x.2011.598565.*

17. [a, b, c] *Xiaofei Lv, Jichao Sun, Yufang Bi, Min Xu, et al. (2015). Risk of all-cause mortality and cardiovascular disease associated with secondhand smoke exposure: A systematic review and meta-analysis. International Journal of Cardiology, vol. 199 , 106-115. doi:10.1016/j.ijcard.2015.07.011.*
18. [a, b, c, d] *Peter N Lee, Barbara A Forey, Jan S Hamling, Alison J Thornton. (2017). Environmental tobacco smoke exposure and heart disease: A systematic review. WJMA, vol. 5 (2), 14. doi:10.13105/wjma.v5i2.14.*
19. ^ *Julian PT Higgins and Sally Green. (2011). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1. (10.4.4.2 Trim and fill).*
20. ^ *James E Enstrom. (2007). Defending legitimate epidemiologic research: combating Lysenko pseudoscience. Epidemiol Perspect Innov, vol. 4 (1), 11. doi:10.1186/1742-5573-4-11.*
21. ^ *Carl V Phillips. (2004). Publication bias in situ. BMC Med Res Methodol, vol. 4 (1). doi:10.1186/1471-2288-4-20.*
22. ^ *Ichiro Kawachi, Graham A. Colditz, Frank E. Speizer, JoAnn E. Manson, et al. (1997). A Prospective Study of Passive Smoking and Coronary Heart Disease. Circulation, vol. 95 (10), 2374-2379. doi:10.1161/01.cir.95.10.2374.*
23. ^ *Kyle Steenland, Michael Thun, Cathy Lally, Clark Heath. (1996). Environmental Tobacco Smoke and Coronary Heart Disease in the American Cancer Society CPS-II Cohort. Circulation, vol. 94 (4), 622-628. doi:10.1161/01.cir.94.4.622.*
24. ^ *Stavroula K Osganian, Meir J Stampfer, Eric Rimm, Donna Spiegelman, et al. (2003). Vitamin C and risk of coronary heart disease in women. Journal of the American College of Cardiology, vol. 42 (2), 246-252. doi:10.1016/s0735-1097(03)00575-8.*
25. ^ *M. L. Watkins, J. D. Erickson, M. J. Thun, J. Mulinare, et al. (2000). Multivitamin Use and Mortality in a Large Prospective Study. American Journal of Epidemiology, vol. 152 (2), 149-162. doi:10.1093/aje/152.2.149.*
26. ^ *Meir J. Stampfer, Charles H. Hennekens, JoAnn E. Manson, Graham A. Colditz, et al. (1993). Vitamin E Consumption and the Risk of Coronary Disease in Women. N Engl J Med, vol. 328 (20), 1444-1449. doi:10.1056/nejm199305203282003.*
27. ^ *S.-K. Myung, W. Ju, B. Cho, S.-W. Oh, et al. (2013). Efficacy of vitamin and antioxidant supplements in prevention of cardiovascular disease: systematic review and meta-analysis of randomised controlled trials. BMJ, vol. 346 (jan18 1), f10-f10. doi:10.1136/bmj.f10.*
28. ^ *Yizhou Ye, Jing Li, Zhongxiang Yuan. (2013). Effect of Antioxidant Vitamin Supplementation on Cardiovascular Outcomes: A Meta-Analysis of Randomized Controlled Trials. PLoS ONE, vol. 8 (2), e56803. doi:10.1371/journal.pone.0056803.*
29. ^ *David J.A. Jenkins, J. David Spence, Edward L. Giovannucci, Young-in Kim, et al. (2021). Supplemental Vitamins and Minerals for Cardiovascular Disease Prevention and Treatment. Journal of the American College of Cardiology, vol. 77 (4), 423-436. doi:10.1016/j.jacc.2020.09.619.*
30. ^ *Kevin C. Maki, Joanne L. Slavin, Tia M. Rains, Penny M. Kris-Etherton. (2014). Limitations of Observational Evidence: Implications for Evidence-Based Dietary Recommendations. doi:10.3945/an.113.004929.*
31. ^ *Vicky Tai, Andrew Grey, Mark J. Bolland. (2014). Results of Observational Studies: Analysis of Findings from the Nurses' Health Study. PLoS ONE, vol. 9 (10), e110403. doi:10.1371/journal.pone.0110403.*

32. ^Sander Greenland. (1993). A Meta-analysis of Coffee, Myocardial Infarction, and Coronary Death. Epidemiology, vol. 4 (4), 366-374. doi:10.1097/00001648-199307000-00013.
33. ^Ming Ding, Shilpa N. Bhupathiraju, Ambika Satija, Rob M. van Dam, et al. (2014). Long-Term Coffee Consumption and Risk of Cardiovascular Disease. Circulation, vol. 129 (6), 643-659. doi:10.1161/circulationaha.113.005925.
34. ^Koon K Teo, Stephanie Ounpuu, Steven Hawken, MR Pandey, et al. (2006). Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case-control study. The Lancet, vol. 368 (9536), 647-658. doi:10.1016/s0140-6736(06)69249-0.
35. ^Cristina Bosetti, Eva Negri, Alessandra Tavani, Luigi Santoro, et al. (1999). Smoking and Acute Myocardial Infarction among Women and Men: A Case–Control Study in Italy. Preventive Medicine, vol. 29 (5), 343-348. doi:10.1006/pmed.1999.0557.
36. ^N R Dunn, B Faragher, M Thorogood, L de Caestecker, et al. (1999). Risk of myocardial infarction in young female smokers. Heart, vol. 82 (5), 581-583. doi:10.1136/hrt.82.5.581.
37. a, bCindy M Chang, Catherine G Corey, Brian L Rostron, Benjamin J Apelberg. (2015). Systematic review of cigar smoking and all cause and smoking related mortality. BMC Public Health, vol. 15 (1). doi:10.1186/s12889-015-1617-5.
38. ^Kris Novak. (2007). Out from the haze. Nature, vol. 447 (7148), 1049-1051. doi:10.1038/4471049a.
39. ^Peter N. Lee, John S. Fry, Alison J. Thornton. (2019). Updating the evidence relating smoking bans to incidence of heart disease. Regulatory Toxicology and Pharmacology, vol. 101 , 172-186. doi:10.1016/j.yrtph.2018.11.014.
40. ^C. Arden Pope, Richard T. Burnett, Michelle C. Turner, Aaron Cohen, et al. (2011). Lung Cancer and Cardiovascular Disease Mortality Associated with Ambient Air Pollution and Cigarette Smoke: Shape of the Exposure–Response Relationships. Environmental Health Perspectives, vol. 119 (11), 1616-1621. doi:10.1289/ehp.1103639.
41. ^Michelle Catherine Turner, Aaron Cohen, Richard T Burnett, Michael Jerrett, et al. (2015). Interactions Between Cigarette Smoking And Ambient PM2.5 For Cardiovascular Mortality In The Cancer Prevention Study-II. ISEE Conference Abstracts, vol. 2015 (1), 535. doi:10.1289/isee.2015.2015-535.