**Burden of proof to attribute risk factor contributions to the global burden of disease**

*Professor Tony Blakely ,1, 2*

*Ms Samantha Howe 1*

1. Population Interventions Unit, Melbourne School of Population and Global Health, University of Melbourne
2. Corresponding author: ablakely@unimelb.edu.au

The latest round of the global burden of disease (GBD) has landed, delayed due to COVID-19 but now including COVID-19 in its estimations. One can think of burden of disease studies, and the GBD in particular, as having three overarching goals: 1) estimate the burden, i.e. the disability adjusted life years (DALYs) by sex and age in every country, for the current year (2021 in this round of the GBD) and in the recent past 1; 2) attribute that DALY burden by 88 risk factors that contributed to it, e.g. smoking, indoor air pollution 2; and 3) forecast what the DALY burden might be into the future under business-as-usual and various scenarios.3 A fourth goal, not yet a core focus of the GBD but one being advanced by other researchers, including ourselves, is using forecasts to then simulate population cohorts into the future and assess the health and economic benefit of interventions in specific contexts (e.g. the impact of tobacco endgame policies in New Zealand 4).

The paper in *The Lancet* by Brauer et al includes important methodological advances in relation to the second risk attribution goal. Three innovations stand out from the ‘burden of proof’ approach first developed by Zheng and colleagues 5 that improve upon the quantitative assessment of the strength and quality of casual associations between risk factors and disease. First, the Institute of Health Metrics and Evaluation (IHME) in-house meta-analyses now include meta-regression of the included studies, where each study is adjusted for at least six binary measures coded by IHME staff of how well it adjusted for biases – attempting to convert each study to its counterfactual unbiased self. This meta-regression is a positive step forward, but the method needs more transparency and further development: the validation of the bias coding is not available; and the binary coded biases are assumed to have the same direction and magnitude of bias across all studies (i.e. if confounding is deemed likely, there is no allowance for negative confounding in some studies and positive confounding in others).

The second innovation moves beyond just presenting an I2 statistic measure of heterogeneity alongside rate ratio estimates and instead folds-in between-study heterogeneity, generating (often) wider uncertainty intervals. For example, there may be genuine variation in the relative association of fasting plasma glucose with heart disease across countries. The ‘standard’ confidence interval produced for this association comes from assuming that every country has the same underlying true rate ratio, and the only error is random error, and hence underestimates the true uncertainty due to between-country variation.

The third notable advance is a star rating system, whereby each risk factor-outcome pairing is rated as one (weak and uncertain association) to five (strong association). This is important because the weak and uncertain associations may not be truly causal. So, the GBD now presents a sensitivity analysis that limits risk factor-outcome pairings used to those with 3+ stars, resulting in a moderate decline of risk factor attributable DALYs from 41.4% to 37.5% of total DALYs. From a research angle, the lower star evidence should be prioritized in future research to shore up the evidence base.

Methodological advances noted, the key substantive findings in this 2021 iteration of the GBD are comparable to previous iterations.  Namely, and putting pandemics aside, ‘old world’ risk factors such as child growth failure, unsafe water and sanitation continue to diminish, meaning the relative contribution of risk factors such as ambient particulate matter pollution, high systolic blood pressure, high body-mass index, and high fasting plasma glucose continue to increase.  It must be noted, though, that much of the rise in absolute burden from these latter risk factors is due to increases in population size and population aging. Only two of the top 25 risk factors in 2021, high fasting plasma glucose and high body mass index, had increases in age-standardized DALY rates from 2000 to 2021 (final column of Figure 3 in Brauer et al).  While that is good news, there is still much more health gain to be made from much greater absolute reductions in levels of hazardous exposure to these risk factors.

The GBD’s attribution of burden to risk factors, and how that has changed over time, provide a high-level roadmap for policy makers and researchers.  Looking to future evolution of the GBD and global health metrics, a more detailed roadmap requires taking these cross-sectional estimates through to forecasts of cohort disease and burden rates to use in simulation studies of the (cost) effectiveness of actual interventions.

1. GBD. Causes of Death Collaborators. Global burden of 288 causes of death and life expectancy decomposition in 204 countries and territories and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet* 2024.

2. GBD 2021 Risk Factors Collaborators. Global burden and strength of evidence for 88 risk factors in 204 countries and 811 subnational locations, 1990–2021: a systematic analysis for the Global Burden of

Disease Study 2021. *Lancet* 2024; **in press**.

3. GBD 2021 Forecasting Collaborators. Burden of disease scenarios for 204 countries and territories, 2022–2050: a forecasting analysis for the Global Burden of Disease Study. *Lancet* 2024; **in press**.

4. Ait Ouakrim D, Wilson T, Waa A, et al. Tobacco endgame intervention impacts on health gains and Maori:non-Maori health inequity: a simulation study of the Aotearoa/New Zealand Tobacco Action Plan. *Tob Control* 2023: tc-2022-057655.

5. Zheng P, Afshin A, Biryukov S, et al. The Burden of Proof studies: assessing the evidence of risk. *Nat Med* 2022.