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Decisions of the GBD Scientific Council

Global Burden of Diseases, Injuries, and Risk Factors Study 2013

The Council voted to approve the updated methodology for calculating relative risks for physical inactivity.

> Cohort studies examining the risk of physical activity and disease outcomes have used a variety of approaches to measure exposure; particularly the older studies used imprecisely defined exposure categories and tended to concentrate on leisure activity rather than all forms of activity; also, for newer studies there are considerable differences in how physical activity has been measured. The current method tries to take a more rigorous approach to making exposure levels between studies more comparable by converting all measures into MET units, adjusting sources for the number of domains of activity included (leisure, work, transport, home). We apply a Bayesian meta-regression approach to pooling estimates across studies. Similarly, we are imposing the same rigorous structure onto the exposure measurement from surveys and published studies from which we derive our prevalence estimates.

The Council voted to approve the approach to estimating the burden attributable to reduced estimated glomerular filtration rate.

> Prospective observational studies have demonstrated an association between reduced glomerular filtration rate and increased risk of key cardiovascular outcomes. Collaboration with experts in the field has enabled us to determine the degree of increased risk of cardiovascular outcomes per stage of chronic kidney disease (CKD) through analysis of combined microdata of international cohorts. We apply these relative risks to prevalent stages of chronic kidney disease from the Global Burden of Disease database to determine the population-attributable fraction of stroke, ischemic heart disease, and peripheral arterial disease to chronic kidney disease for CKD stages 3-5.

The Council voted to approve the updated estimation approach to injuries.

> The approach to estimating non-fatal health outcomes from injuries has changed in several ways from GBD 2010 to GBD 2013. First, we use a disaggregated list of nature-of-injury categories (47 in GBD 2013 vs. 23 in GBD 2010). Second, we assume a 1:1 relationship between injury case and N-code. This addresses an inconsistency in the GBD 2010 approach by which an injury was allowed to have multiple N-codes in some aspects of the model pipeline and not in others. To achieve this 1:1 relationship, we develop a ranking of injury severity by N-code and keep only the most severe N-code in datasets where patients are coded with multiple N-codes. Third, we now separately estimate the duration of short-term health loss and the probability of developing long-term health loss for treated and untreated injuries. Previously, the difference in treated and untreated injuries was captured only in assigned disability weight. Fourth, we now empirically derive a duration for short-term outcomes of treated injuries, rather than relying purely on

expert opinion. Fifth, we incorporate the latest disability weight survey, which estimates a lower weight for fractures and a higher weight for spinal cord lesion, as well as adding a couple of previously missing disability weight estimates for specific health states.

The Council voted against using bias-adjusted relative risks for water and sanitation estimation.

While there is an advantage to using bias-adjusted relative risks for water and sanitation, doing so would result in important ramifications for the comparative risk assessment framework of GBD. Despite known sources of bias, at present we are unable to make similar adjustments to relative risks for other risk factors. Using bias-adjusted relative risks for some and not others would create an inconsistency and reduce comparability between risk factors. Moreover, the bias adjustment factor is relatively uncertain, so these adjustments would have a significant impact on the uncertainty of our results. The extent, limitations, feasibility, and data availability for this procedure will be considered and implemented systematically for all risk factors in future iterations of GBD.

The Council voted to update the age standard we use to generate age-standardized rates.

For GBD 2013, we updated the standard population structure used by GBD since 2003 to reflect the recent development in demographic transition around the world, using the same methodology that generated the current GBD standard population structure. We use the estimated population by age for 2010 to 2035 from the World Population Prospects 2012 revision to get age structure for each country. Then we use the simple arithmetic mean of all country-level age structures to generate the new GBD standard population structure.

The Council approved the updated methodology for all-cause mortality estimation.

In GBD 2013, we have made the following changes to the all-cause mortality estimation process compared to GBD 2010: 1. Data bias adjustment for raw child mortality data based on source-type specific fixed effects and source-specific random effects within country. By making such an adjustment, we are able to make more consistent child mortality estimates for countries with multiple overlapping estimates of child mortality that differ in levels. 2. Improved functional form for both child mortality rate and adult mortality rate estimation that reflect the correct functional relationship between mortality rates in the child and adult age groups and death rates due to HIV/AIDS in the corresponding age groups. 3. Improved relational model life table system. For GBD 2013, we developed a unified standard life table selection process that utilizes empirical weights for the selected life tables. In addition, we redistribute excess mortality rate due to HIV/AIDS based on the observed excess mortality pattern from ICD-10-coded vital registration data from around the world.

The Council approved the updated methodology for modeling diarrhea and lower respiratory infection etiologies using a counterfactual approach.

The new approach to estimating the burden attributable to lower respiratory infection (LRI) and diarrhea is based on the fact that observational studies do not have enough sensitivity and specificity to determine the true causes of LRI and diarrhea. Diagnostic methods to detect LRI pathogens including respiratory syncytial virus (RSV), influenza, *Streptococcus pneumoniae*, and *Haemophilus influenzae* type b (Hib) are not sensitive. Moreover, vaccine clinical trials showed a significant decrease in invasive pneumonia by other pathogens, indicating a significant interaction between pathogens. So, in this counterfactual approach, the relative risks from vaccine efficacy trials and before-after studies are adjusted for efficacy using invasive disease as a marker as well as serotype coverage for pneumococcal conjugate vaccine (PCV) as previously described (Klugman KP. Contribution of vaccines to our understanding of pneumococcal disease. *Philosophical Transactions of the Royal Society B: Biological Sciences*. 2011; 366: 2790–8. Watt JP, Wolfson LJ, O'Brien KL, et al. Burden of disease caused by Haemophilus influenzae type b in children younger than 5 years: global estimates. *The Lancet*. 2009; 374: 903–11. O'Brien KL, Wolfson LJ, Watt JP, et al. Burden of disease caused by Streptococcus pneumoniae in children younger than 5 years: global estimates. *The Lancet*. 2009; 374: 893–902.). We estimated the PAF for RSV and influenza similar to the diarrhea pathogens explained below.

To estimate the burden of diarrhea by pathogens (and RSV and influenza) we used an alternative PAF formula using the distribution of pathogens from published literature and the relative risks of diarrhea in patients versus non-patients (control group).

Miettinen's formula: paf = P(pathogen in cases)* (1-1/RR)

The distribution of pathogens in patients is estimated using a meta-regression of published studies for all countries, sexes, ages, and years. Diarrhea pathogens' relative risks were estimated by the reanalysis of GEMS (Global Enteric Multicenter Study) in a mixed effect conditional logistic regression model.

The Council approved the addition of intimate partner violence-HIV as a risk-outcome pair.

In GBD 2010, the expert group on intimate partner violence (IPV) and child sexual abuse proposed to include HIV as an outcome of intimate partner violence. After evaluating the evidence for a causal relationship between IPV and HIV/AIDS, the GBD core team decided that evidence from a single cohort study in South Africa with supportive evidence from cross-sectional studies was insufficient to warrant inclusion of the risk-outcome pair. Subsequently, the IPV experts have included a second cohort study from Uganda which shows similar magnitude of the relative risk as in the South African study and showed evidence for a dose-response relationship with a higher RR for more severe categories of violence.

As the RR is for incident HIV disease and we need to apply attributable fractions to prevalence and death, we will estimate for each age cohort (by country, sex, and year of estimation) the past cumulative risk of HIV infection that can be attributed to IPV (using the RR on incidence, the prevalence of IPV at the appropriate age for years prior to the index year, and the estimated incidence of HIV in each year for the appropriate age group) as a fraction of total cumulative risk of HIV infection.

The Council approved the proposal to remove cannabis-psychosis as a risk-outcome pair.

In GBD 2010, regular cannabis use (defined as use more than once weekly) was included as a risk factor for an earlier onset of schizophrenia and a greater severity. As the estimates were very small (6,500 DALYs in 2010) it was decided to drop this risk factor from GBD 2013.

The Council rejected a proposal to add "harmful alcohol use" as a category.

The estimates for alcohol use disorders in GBD 2010 included alcohol dependence and fetal alcohol syndrome. Alcohol experts asked for inclusion of an additional category for harmful alcohol use, a recognized category in ICD-10 and DSM-IV classification systems. Prevalence data are available from most of the mental health and alcohol and drug surveys used for the alcohol dependence estimates. The experts suggested a lay description to derive a disability weight: "this person regularly gets drunk, putting the person at risk of injuries and other harm to health." It was decided that this health state is not consistent with the construct of health loss we apply to all other health states for two reasons. First, the risk of harm does not constitute actual health loss. The health loss from alcohol-related injuries or other harm is captured as part of those outcomes. Second, getting drunk is a health behavior akin to tobacco smoking or physical inactivity, neither of which we consider a cause of health loss per se. The decision was, therefore, not to include harmful alcohol use as a sequela in GBD.

The Council voted to approve the addition of new disability weights data.

Additional disability weight surveys have been conducted in the Netherlands, Sweden, Italy, and Hungary, funded by the ECDC and IHME. The surveys included 172 of the 220 lay descriptions that were used in the GBD 2010 disability surveys, 33 reformulated lay descriptions addressing issues with the original wording, 32 new health states (11 for inclusion in GBD 2013 and 21 in anticipation of inclusion of new conditions in GBD 2014). The results from the GBD 2010 surveys and the new surveys have been analyzed together to create an updated set of weights. GBD 2013 will use the results of the combined analysis. Of the 33 health states with reformulated lay descriptions, we will adopt 32. The only exception is the rewritten lay description for blindness, which resulted in a lower weight in the European surveys than the disability weight for severe vision loss in the combined analysis. We decided not to use the new blindness disability weight as it would be inconsistent to have a lower weight for blindness than for severe vision loss.

The Council voted to approve updates to the risk factor list.

The GBD 2013 will report 72 risk factors, an increase from the 67 risk factors that were reported in the GBD Study 2010. The additions for the GBD 2013 include:

- Aggregate burden of all risk factors
- Aggregate burden of air pollution
- Aggregate burden of physiological risk factors
- Low glomerular filtration rate
- Unsafe sex

Risk factors are categorized at different levels of detail, so there is a need to aggregate their effects at the main categories for a better understanding of the contribution of different risk factors to disease burden. Being able to show the fraction of each disease that can be attributed to a risk factor helps us understand where we have very little knowledge of causes of diseases and morbidities. We have accordingly added three categories of aggregates as part of this update.

Global Burden of Diseases, Injuries, and Risk Factors Study 2015

The Council voted to approve updates to the GBD 2015 cause list:

- Ebola
- Podoconiosis
- Non-melanoma skin cancer Squamous-cell carcinoma
- Non-melanoma skin cancer Basal cell carcinoma
- Lymphoid leukemia
    - Acute lymphoid leukemia ALL
    - Chronic lymphoid leukemia CLL
- Myeloid leukemia
    - Acute myeloid leukemia AML
    - Chronic myeloid leukemia CML
- Motor neuron disease
- Exposure to environmental forces, non-disaster
- Exposure to forces of nature, disaster

The Council voted to change the updated lower and upper bound for the TMREL uncertainty interval for sodium to 1-5 grams per day.

We recognize that adverse effects of extreme, rapid sodium reduction cannot be excluded; and that true optimal lower limits remain uncertain. Yet, considering all evidence together, we conclude – similar to multiple national and international organizations – that the optimal level of sodium intake is ~ 2.0 g/d, and could be even lower.

The current GBD TMREL is not justified by all of the available evidence. 2.3 g/d is certainly within the range of uncertainty. It could also be considered a reasonable central target, based on the US Dietary Guidelines; as could 2.0 g/d, based on the WHO guidelines. However, 2.3 g/d is clearly NOT the lower bound of uncertainty, based on any IOM report and, more specifically, based on the conclusions of multiple objective organizations including the WHO, AHA, and UK NICE.

The science makes clear that the proposed GBD TMREL range is not evidence-based, excluding as it does even the central targets (let alone the lower range of uncertainty) from most major national and international guidelines. It will take much less effort to correct this now, rather than later and after bringing more confusion upon the already confused public, media, and the larger scientific community.

An evidence-based TMREL would center around the consensus of all major national and international organizations (around 2.0 g/d), with valid uncertainty from as low as 1.0 g/d to as high as 3.0 g/d.

The Council voted to reduce the TMREL for total cholesterol from 3.80-4.00 mmol/lit to 2.78-3.38 mmol/lit.

Different randomized controlled trials showed a health benefit and decrease in cardiovascular disease (CVD) outcomes of lowering low-density lipoprotein (LDL) cholesterol to very low levels. For example, a meta-analysis of statin trials showed the decrease in LDL decreases CVD risk significantly even at 1mmol/lit (see Table 1 on page 6 of the attached briefing document). A TMREL of 0.70-1.30 mmol/lit for LDL can be assumed, which corresponds to 2.78-3.38 mmol/lit of total cholesterol in NHANES data.

Therefore, for the GBD 2015 iteration, it is proposed to reduce the TMREL for total cholesterol from 3.80-4.00 mmol/lit to 2.78-3.38 mmol/lit.

The Council voted to approve the following additions and modifications to the cause list.

- Zika virus
- Guinea worm disease
- Congenital musculoskeletal and limb anomalies
- Urogenital congenital anomalies
- Digestive congenital anomalies
- Addition of two sub-causes to “Self-harm”
- Self-harm by firearm
- Self-harm by other specified means
- Addition of two sub-causes to “Interpersonal violence”: sexual violence and other interpersonal violence
- Replacement of “Forces of nature, war, and legal intervention” with legal intervention, terrorism, and military operations

The Council voted to approve the following additions and modifications to the risk factor list.

- Small for gestational age – see definition in attached notes
- Smokeless tobacco – see definition in attached notes
- Temperature
- Absence of measles vaccine
- Absence of diphtheria vaccine
- Absence of pertussis vaccine
- Absence of tetanus vaccine
- Absence of haemophilus influenzae B vaccine

- Absence of pneumococcal conjugate vaccine
- Absence of rotavirus vaccine
- Absence of insecticide treated bed nets
- Absence of effective antimalarial drug treatment
- Absence of antiretroviral therapy

The Council voted to add bullying as a risk factor.

> It was proposed to include bullying victimization in school-aged children and adolescents by peers as a risk factor for depressive disorders and anxiety disorders. The proposed definition is bullying victimization in school-aged children and adolescents by peers.

The Council voted to add diabetes as an outcome of ambient particulate matter pollution and household air pollution.

The Council voted to change the cause name of "iron deficiency" to "dietary iron deficiency".

> Since the measurement of iron deficiency is based on a narrow case definition, it was proposed that the cause be renamed to "Dietary iron deficiency."

The Council approved the measurement of iron deficiency by YLD only. Iron deficiency will not be estimated as an underlying cause of death.

> We have searched the medical literature (PubMed, UptoDate) and discussed with experts in iron deficiency and anemia, including Dr. Camaschella, but have not identified a single case report of a death due to iron deficiency that was not associated with another underlying cause. Transgenic mouse and rat models of severe iron deficiency have demonstrated deficiencies in problem solving and exercise capacity, but not heart failure or other acute physiologic insults. This is still not to say that iron deficiency-induced anemia and heart failure cannot lead to death, but rather that according to the GBD definition of iron deficiency as being the absence of any other underlying causes, it cannot.

The Council approved the measurement of iodine deficiency by YLD only. Iron deficiency will not be estimated as an underlying cause of death.

> Inadequate iodine intake can lead to goiter, hypothyroidism, and in severe cases can lead to irreversible mental retardation, a syndrome referred to as "cretinism." It is therefore an important public health problem in many countries, especially those that do not have salt iodization policies in place. There is lack of evidence that iodine deficiency manifestations alone lead to death, however (Kapil 2007 Sultan Qaboos Univ Med J "Health Consequences of Iodine Deficiency" and UpToDate.com "Iodine deficiency disorders"). Consistent with the literature, a majority of locations with vital registration systems have not coded a single death to iodine deficiency since 1980, even many of those with large proportions of their populations living at high elevations. Our proposal is therefore to no longer include iodine deficiency as a cause of death. We will plan to complete a systematic review of evidence for iodine deficiency as a risk factor for other causes (e.g. infections) and continue to estimate its prevalence, nonfatal burden, and contribution to intellectual disability globally.

The Council voted to approve the following new locations:

- Cook Islands
- Principality of Monaco
- Republic of Nauru
- Republic of Niue
- Republic of Palau
- Saint Kitts and Nevis
- Republic of San Marino
- Tokelau
- Tuvalu

The Council voted to approve subnational analysis for the following countries:

- Italy
- Nigeria
- Pakistan
- Philippines
- Poland

The Council voted to approve the following additions and modifications to the cause list:

- Primary pulmonary arterial hypertension
- Hepatoblastoma
- Burkitt lymphoma
- Other non-Hodgkin lymphoma
- Eye cancer (level 3), retinoblastoma (level 4) and other eye cancers (level 4)
- Soft tissue and other extraosseous sarcomas
- Malignant bone tumors
- Neuroblastoma and other peripheral nervous cell tumors
- Osteoarthritis of the hand or foot
- Other osteoarthritis
- Rubella