**GBD’s approach:**

* Remove double-counted effects (mediation factors)
* Then, assume all risks are uncorrelated
* Calculate a PAF

**Our approach:**

* Remove double-counted effects (mediation factors)
* Back-calculate risk-risk effects and apply them (leads to risks being correlated)
* Calculate our own PAF with our introduced correlation

**Problem 1:** GBD’s approach to removing double-counted effects creates effects which do not aggregate to the overall effect. This never bites them because they never actually model risk-risk effects.

**Example:** Say GBD reports a BMI to IHD RR of 2. They have a mediation factor of 0.4 with SBP in this pathway. They also report that SBP has an RR of 3 on IHD.

We back-calculate a delta from the GBD formula: an increase of one unit in BMI must increase SBP by about 0.3 units. This implies that BMI has an RR on IHD *through SBP* of 1.4. That is actually the interpretation of a GBD mediation factor: the RR *through the mediator* has that portion of the *excess* risk (“excess risk” means the part of the RR above 1).

GBD’s formula for the direct (unmediated) RR gives us 1.6. So, the GBD mediation factor (with only one mediator) is just splitting the excess risk. MF of 0.4 and RR of 2 (i.e. excess risk of 1) means 1.4 RR mediated, 1.6 RR direct.

That isn’t how relative risks aggregate, however. Applying an RR of 1.4 *and* an RR of 1.6 does not give you an RR of 2, because they *multiply* to 2.24. Now BMI has a larger effect on IHD in our model if we model SBP than if we don’t!

**Problem 2:** GBD’s approach to removing double-counted effects in the presence of multiple mediators is ???

GBD’s multiplicative approach to combining mediation factors is not documented in the methods appendix, the only way we know it is from some R code Ali found.

I cannot wrap my head around how to interpret this approach. It seems to say that, assuming that the excess risk is combined additively as noted above, when there are multiple mediators, they are mediating some of the *same* excess risk. In other words, there is overlap between the excess risk that goes through mediator 1, and the excess risk that goes through mediator 2.

This contradicts the concept of a causal effect, absent effect modification. When we say an increase of one unit in SBP has a RR of 3 on IHD, and this effect isn’t modified by anything, we mean that if everything else is held constant, *no matter what it is held constant at*, the ratio between IHD incidence with SBP=X and IHD incidence if SBP=X+1 is 1 : 3. The same goes for FPG (another mediator of BMI->IHD we haven’t mentioned yet): it has some RR with this same interpretation. Clearly, if we hold everything constant at the status quo, and then increase SBP by one, the IHD incidence rate will triple. If we then hold everything constant *including the increased SBP* except that we increase FPG, the FPG RR will apply in full as well. There is no way for these RRs to “overlap,” as long as they are true regardless of the value of any other variable (no effect modification).

In fact, due to the issue discussed in Problem 1, multiple mediated RRs combine the *opposite* way. Assuming all RRs > 1, *each* time you partition a RR into two parts, the parts should add up to *less* than the total RR (they should multiply to the total RR). Having two mediators means having the RR partitioned into three (mediated by m1, mediated by m2, direct), which is equivalent to doing a single partition as in Problem 1, and then partitioning one of the parts again (it does not matter which order you do this). Each partition only increases the amount by which the excess risk of the individual RRs should sum to *less* than the excess risk of the total RR, not *more* as in GBD’s approach.

I could go out on a limb and speculate that *maybe* GBD did this because they don’t really believe that RRs can stack multiplicatively, that there must be some effect modification, otherwise there would be individuals with absurdly high rates of incidence. But surely this would break everything? And surely there is some alternative to RRs they could have used then? E.g. additive risk differences would be better than RRs if you thought this was how the real world worked.

**If I’m right**: If the GBD mediation factors are fundamentally incompatible with actually applying RRs, and we want to stick with RRs, I think we could use a “take it apart and put it back together again” approach.

If GBD tells us when they used the delta calculation and when they used the crude-adjusted calculation, we could take each individual mediation factor and work backwards to the underlying mediation data point: delta if they used the delta approach, RR\_adjusted if they used the crude-adjusted approach (assuming RR\_crude in that formula equals the total RR reported by GBD – we think this is the case, but can’t immediately find a source).

The “back calculation” if they used the delta approach:

The “back calculation” if they used the crude-adjusted approach:

Then, we could work forwards again, and find the deltas (if necessary) and the direct RR with formulas based on the *multiplicative* application of RRs.

How RRs are applied:

Therefore, our “forward calculation” from adjusted RRs to deltas (skip if GBD used the delta method):

Then from deltas (across all mediators) to direct RR: