Suissa K, et al,. A mediation analysis on the relationship between dietary glycemic load, obesity and cardiovascular risk factors in preschool children.

SUPPLEMENTAL METHODS

First, we estimated the total effect of GI and GL on TG and HDL on the additive scale (note that X hereby denotes both GI and GL and Y hereby denotes different outcomes including TG and HDL). To this end, we regressed Y_i on X_i and confounders (C_i) as such:

$$E[Y|X,C] = \beta_0 + \beta_1 X_i + \beta_2 C_i \qquad \text{(Model 1)}$$

β_1 from model 1 will be the estimate of the total effect provided that the measured confounders are sufficient to control for the confounders of the X-Y relation. Second, we estimated the direct effect of X on Y using the conventional approach described by Baron and Kenny.[1] For this, we regressed each outcome Y on X, C and adiposity (the mediator M) by fitting a linear regression model as such:

$$E[Y|X,C,M] = \beta_0 + \beta_1 X_i + \beta_2 C_i + \beta_3 M_i \qquad \text{(Model 2)}$$

β_1 from model 2 will be the estimate of the direct effect of X that is not mediated through M, provided that the measured confounders that are adjusted for are sufficient to control for the confounders of the relation between X and Y. Third, we tested for interaction by including interaction terms between X and M in model 2, and because these terms were not statistically significant they were dropped from the model.

Next, we assessed mediation following the causal approach: For this, we computed the controlled direct effect using a weighted generalized estimating equation (GEE) to estimate the weighted marginal structural model (MSM), an approach proposed by VanderWeele[2] and Valeri[3] for continuous exposure, mediators and outcomes.[4] The following model was fitted:

$$g(\mu) = \beta_0 + \beta_1 X_i + \beta_2 M_i + \beta_3 X_i M_i \qquad \text{(Model 3)}$$

where g was a monotone link function. In this case, the continuous outcome followed a linear link function. Inverse probability weights were used to balance covariates and hence control for confounding between X and Y and M and Y. Weights were constructed for both exposure variables (glycemic index and glycemic load) and the mediators (continuous BMI z-score and percent fat mass). We used stabilized weights, which are preferred to standard weights because they are considered more stable; and because of the continuous nature of X and M, unstabilized weights would have infinite variance.[5] For the continuous exposure and mediator variables, we used the density function of X in the numerator and the density function of X adjusted for confounders C as the denominator for the X-Y weights and repeated the same method for the M-Y weights.[5] The final weight used in the MSM was obtained by calculating the product of the two stabilized weights for each participant.

The controlled direct effect (CDE) for a change in exposure from level x^* to level x was obtained as follows with estimates from the final weighted model (model 3):

$$CDE = (\beta_1 + \beta_3 m)(x - x^*)$$

The CDE is an estimate of how much the mean of the outcome changes when the mediator is kept constant at a level m uniformly in the population while the exposure changes from level x^* to level x. Although sometimes unrealistic, a requirement for the CDE is that an intervention be effective at setting every subject to having the same value of the mediator. In general, m would be set as the mean BMI z-score or percent fat mass in the study sample. For the purpose of this study, CDE was equal to β_1 because the interaction term β_3 was not significant.

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