Is collider stratification bias one plausible explanation for the obesity paradox?

Hailey R. Banack & Jay S. Kaufman

Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Canada

Introduction

•Obesity is associated with an increased risk of mortality in the general population

•Several authors have reported that obesity confers a survival advantage among individuals with cardiovascular disease (CVD), a phenomenon known as the "obesity paradox"

•Objectives:

1. To explore whether collider stratification bias is a plausible explanation for the paradoxical protective effect of obesity on mortality among individuals with CVD

1. To use sensitivity analyses to determine the range of parameters required to produce this paradoxical effect

Methods

- Data from NHANES III (1988-1994) linked to mortality information in the National Death Index up to December 31, 2006
- CVD defined as any acute cardiac event (MI or stroke)
- To estimate the total effect of obesity on mortality (Model 1):

logit [mortality=1| Obese=obese, C=c] = α + $\beta_1$obese+β'_2C

Where c=age, gender, race, education, and smoking status

- To estimate the controlled direct effect (CDE) of obesity on mortality (Model 2):

logit [mortality=1| Obesity=obese, CVD=cvd, C=c]
= θ_0 + θ_1 obese + θ_2 cvd + θ_3 obese´cvd + θ'_4C

- The coefficients estimated in Model 2 were used to calculate average marginal effects (AME; Model 3):

expit (θ_0 + θ_1 obese + θ_2 cvd + θ_3 obese*cvd + θ'_4C) (θ_1 + θ_3 cvd)

- Confidence intervals and standard errors calculated by linearization method
- AMEs can be interpreted as risk differences, thus we can define the total and controlled direct effects on the linear scale using the coefficients from Model 3:

Total effect:
E[mortality(obese)- mortality(obese*)| C=c)= θ_1

Controlled direct effect:
E[mortality(obese, CVD=cvd)-mortality(obese*, CVD=cvd)| C=c] = (θ_1 + θ_3 cvd) (obese-obese*)

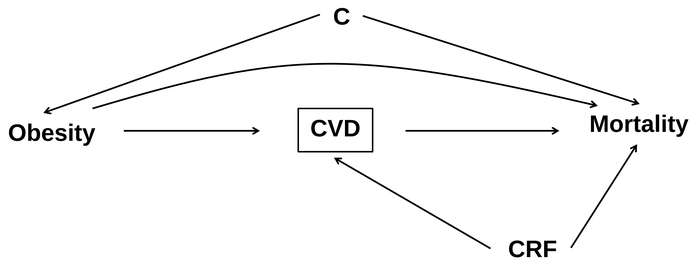

Figure 1. Directed acyclic graph depicting causal relations between obesity, cardiovascular disease, mortality, and confounding variables
[Note: Obesity defined as BMI ≥ 30 kg/m^2 , CRF= cardiorespiratory fitness]

Results

- The crude total effect of obesity on mortality was 0.05 (95% CI 0.03, 0.07)
- The adjusted total effect was 0.03 (95% CI 0.02, 0.05)
- Adjusted, CVD stratum specific estimates of obesity on mortality:

Among individuals without CVD:	CDE_0 = 0.03 (95% CI 0.01, 0.05)
Among individuals with CVD:	CDE_1 = -0.12 (95% CI -0.20, -0.04)

- Is the apparently protective effect of obesity on mortality due to unmeasured confounding of the CVD-mortality relationship by CRF?
- Magnitude of bias in the CDE is given by (VanderWeele, 2010):

Bias ($CDE_{obese,\ obese^*}$(CVD))= δγ

  - γ = E[mortality|obese, CVD, c, CRF=1] - E[mortality|obese, CVD, c, CRF=0]
  - δ = P(CRF|obese, CVD, c) – P(CRF|obese*, CVD, c)

- The product of δγ was subtracted from the value of the controlled direct effect among individuals with CVD (Table 1)

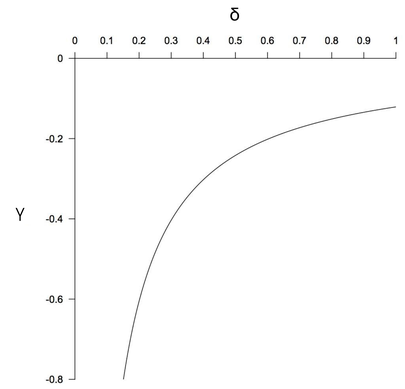

Figure 2. Values of γ and δ that would be required to reverse the sign of the point estimate for the controlled direct effect among individuals with CVD. Values of γ and δ that lie below the curve would completely eliminate the obesity paradox.

Discussion

- Total effect of obesity on mortality was harmful, however, the estimated controlled direct effect indicated that obese individuals with CVD have a lower mortality risk than normal weight counterparts.
- Protective effect of obesity on mortality upon stratification by CVD status is sensitive to realistic levels of confounding from a binary unmeasured common cause (CRF)
- If just one hypothesized binary U variable is able to bring the effect estimate to the null, it is possible that the combined effect of several U variables may bring the CDE among individuals with CVD closer to the harmful total effect of obesity seen in the entire population (even if the effect of each individual unmeasured confounder is relatively small, all of the U variables together could induce a substantial amount of bias)

Limitations

- Only evaluates the possibility of unmeasured confounding by a single, binary unmeasured confounder
- Analysis does not consider possibility of other explanations such as true heterogeneity across strata (Glymour & Vittinghoff, 2014), reverse causality (Preston & Stokes, 2014), or survival effects, such as death prior to disease onset (Flanders, Eldrigde, & McClellan, 2014)

	δ = 0.1	δ =0.2	δ =0.3	δ =0.4	δ =0.5	δ =0.6	δ =0.7	δ =0.8	δ =0.9
γ = -0.2	-0.10 (-0.18, -0.02)	-0.08 (-0.16, 0.003)	-0.06 (-0.14, 0.02)	-0.04 (-0.12, 0.04)	-0.02 (-0.10, 0.06)	-0.001 (-0.08, 0.08)	0.02 (-0.06, 0.10)	0.04 (-0.04, 0.12)	0.06 (-0.02, 0.14)
γ = -0.3	-0.09 (-0.17, -0.01)	-0.06 (-0.14, 0.02)	-0.03 (-0.11, 0.05)	-0.001 (-0.08, 0.08)	0.03 (-0.05, 0.11)	0.06 (-0.02, 0.14)	0.09 (0.006, 0.17)	0.12 (0.04, 0.20)	0.15 (0.07, 0.23)
γ = -0.4	-0.08 (-0.16, 0.003)	-0.04 (-0.12, 0.04)	-0.08 (-0.08, 0.08)	0.04 (-0.04, 0.12)	0.08(-0.004, 0.08)	0.12 (0.04, 0.20)	0.16 (0.07, 0.24)	0.20 (0.12, 0.28)	0.24 (0.16, 0.32)
γ = -0.5	-0.07 (-0.15, 0.01)	-0.02 (-0.10, 0.06)	0.03 (-0.05, 0.11)	0.08 (-0.004, 0.16)	0.13 (0.05, 0.21)	0.18 (0.10, 0.26)	0.23 (0.15, 0.31)	0.28 (0.20, 0.36)	0.33 (0.25, 0.41)
γ = -0.6	-0.06 (-0.14, 0.02)	-0.001 (-0.08, 0.08)	0.06 (-0.02, 0.14)	0.12 (0.04, 0.20)	0.18 (0.10, 0.26)	0.24 (0.16, 0.32)	0.30 (0.22, 0.38)	0.36 (0.28, 0.44)	0.42 (0.34, 0.50)
γ = -0.7	-0.05 (-0.13, 0.03)	0.02 (-0.06, 0.10)	0.09 (0.01, 0.17)	0.16 (0.08, 0.24)	0.23 (0.15, 0.31)	0.30 (0.22, 0.38)	0.37 (0.29, 0.45)	0.44 (0.36, 0.52)	0.51 (0.43, 0.59)
γ = -0.8	-0.04 (-0.12, 0.04)	0.04 (-0.04, 0.12)	0.12 (0.04, 0.20)	0.20 (0.12, 0.28)	0.28 (0.20, 0.36)	0.36 (0.28, 0.44)	0.44 (0.36, 0.52)	0.52 (0.44, 0.60)	0.60 (0.52, 0.68)

Table 1. Results of sensitivity analysis for CDE. **Note:** White background indicates a protective effect of obesity on mortality, light grey indicates an inconclusive effect where the CI crosses the null, and dark grey indicates a harmful effect of obesity on mortality.

References available upon request from hailey.banack@mail.mcgill.ca