Practical on Total, Direct and indirect effects

Let be Y the outcome, X the exposure, and M the mediator. Let Y_{xm} indicate the potential value that the outcome Y would hypothetically take were the exposure X and mediator M set to fixed values x and m, respectively. Y, X and M are all binary variables.

1) Based on: Pearl J., Direct and indirect effects in *Proceedings of the Seventeenth Conference on Uncertainty in Artificial Intelligence*, San Francisco, CA: Morgan Kaufmann, 411-20, 2001

   Consider a drug treatment that has a side effect, for example headache. Patients who suffer from headache tend to take aspirin which, in turn, may have its own effect on the disease or may strengthen/weaken the impact of the drug on the disease. Furthermore the aspirin intake may vary from individual to individual, depending on other factors besides drug-induced headache.

   Y = absence(0)/presence (1) of disease, X=1 if treated and X=0 if untreated, M=1 if aspirin intake and M=0 if no intake.

   a. *What effect would you estimate to determine how beneficial the treatment is to the population as a whole under existing patterns of aspirin use?*

   b. *Even if individual effect cannot be estimated, consider an hypothetical patient who takes aspirin if and only if treated, and for whom the treatment is effective only when aspirin is present. What can you deduce on the controlled direct effect and on natural direct effect for such a person?*

   c. *What effect would you estimate to decide whether the aspirin should be encouraged or discouraged during the treatment at a population level? Or, equivalentl,y to predict the difference in the recovery rates between treated and untreated patients when a prescribed dose of aspirin is administered to all patients in the population?*

   d. *What effect would you estimate to evaluate whether an observed improvement in recovery rates between treated and untreated patients is attributable to the treatment itself or to preferential use of aspirin among treated patients?*

   e. *Assume that the drug manufacturer is considering ways to eliminate the adverse side-effect of the drug, i.e. headache. What effect would you estimate to evaluate whether the drug would still retain its effectiveness in the population of interest?*

   f. *What effect would you estimate to evaluate whether an observed improvement in recovery rates between treated and untreated patients is attributable to the treatment-induced aspirin intake and not to the treatment itself?*

2) Based on: Richiardi L, Bellocco R, Zugna D. Mediation analysis in epidemiology: methods, interpretation and bias. *Int J Epidemiol.* 2013 Oct; 42(5):1511-9.

We report four scenarios of hypothetical data in the following Table:

Exposure (X)	Mediator (M)	Risk	Cases (Y=1)	Non cases (Y=1	Total
			I scenario		
0	0	1%	100	9900	10000
1	0	3%	150	4850	5000
0	1	1%	5	495	500
1	1	3%	30	970	1000
			II scenario		
0	0	1%	100	9900	10000
1	0	3%	150	4850	5000
0	1	5%	25	475	500
1	1	7%	70	930	1000
			III scenario		
0	0	1%	100	9900	10000
1	0	3%	150	4850	5000
0	1	2%	10	490	500
1	1	20%	200	800	1000
			IV scenario		
0	0	1%	100	9900	10000
1	0	3%	150	4850	5000
0	1	2%	20	980	1000
1	1	20%	1100	4400	5500

a. *For each scenarios, calculate the total effect, the controlled direct effect and the natural direct and indirect effects of the exposure on the outcome*

b. *Comment the results*

3) Based on: Ananth CV, Vanderweele TJ. (2011) Placental abruption and perinatal mortality with preterm delivery as a mediator: disentangling direct and indirect effects. *Am J Epidemiol*. 1;174(1):99-108.

In normal pregnancies, placental separation occurs immediately following the birth of baby, while in pregnancies complicated by abruption, the placental detachment occurs prematurely. Placental abruption is associated with increased risks of maternal and perinatal morbidity and mortality. Women diagnosed with abruption are at 4-6 fold increased risk of delivering at preterm gestations. Abruption is also associated with disproportionately high risk of perinatal death.
Authors used data on livebirths-infant death between 1995 and 2002 in the United States to evaluate the mediating role of preterm delivery (mediator M) between abruption (exposure X) and perinatal mortality (outcome Y). They defined preterm delivery as gestational age between 22 and 36 completed weeks and examined risks of stillbirth and early (0-6 days) and late (7-27 days) neonatal mortality in relation to abruption. Furthermore they examined perinatal mortality defined as stillbirths plus early neonatal births.

a. *Assuming that C is a confounder and defining the risks ratio for controlled direct effect for some fixed level of M=m as*

$RR_{CDE}=\Pr(Y_{1m}=1\mid C=c)/\Pr(Y_{0m}=1\mid C=c)$

the risks ratio for natural direct effect as

$RR_{NDE}=\Pr(Y_{1M(0)}=1\mid C=c)/\Pr(Y_{0M(0)}=1\mid C=c)$

and the risk ratio for natural indirect effect as

$RR_{NIE}=\Pr(Y_{1M(1)}=1\mid C=c)/\Pr(Y_{1M(0)}=1\mid C=c)$

what do RR_{CDE}, RR_{NDE} and RR_{NIE} represent?

b. *The unadjusted and gestational-age adjusted risks ratios for perinatal mortality in relation to abruption were 18.89 (95% CI: 18.55-19.22) and 4.79 (95% CI: 4.70-4.89). The estimates of direct and indirect effects (mediated through preterm delivery at <37 weeks) of the association between placental abruption and mortality risk and the proportion of mortality due to abruption that is mediated through preterm delivery is reported in the Table. Furthermore data show that the mortality proportion that is mediated through preterm gestations overcomes a gradual increase with deliveries occurring at earlier gestational age, from 7.5% at 34-36 weeks of gestations to 76.5% at <28 weeks of gestations for early neonatal mortality, and from 10.9 to 79.57% for late neonatal deaths.*

Which conclusions would you draw? Do you think that there is evidence of interaction between abruption and gestational duration?

Perinatal mortality	Adjusted risk ratio					Mortality proportion mediated through preterm delivery
	Controlled direct effect Preterm=No	Controlled direct effect Preterm=yes	Natural direct effect	Natural indirect effect	Total effect	
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	%
Stillbirth	29.31 (27.98,30.70)	3.81 (3.51,4.14)	13.07 (12.49,13.68)	1.29 (1.27,1.32)	16.91 (16.45,17.36)	24.1
Early neonatal mortality	10.94 (9.93,12.06)	2.65 (2.40,2.92)	5.59 (5.19,6.02)	1.61 (1.55,1.67)	8.89 (8.58,9.37)	42.5
Late neonatal mortality	3.95 (3.29,4.75)	2.56 (2.13,3.08)	3.28 (2.90,3.71)	1.79 (1.67,1.91)	5.86 (5.44,6.28)	53.1
Perinatal mortality	22.31 (21.41,23.26)	3.32 (3.18,3.46)	10.18 (9.80,10.58)	1.35 (1.33,1.38)	13.76 (13.45,14.08)	28.1

Risk ratios were adjusted for maternal age, liveborn parity, marital status, maternal race, smoking during pregnancy, and chronic hypertension trough log-binomial regression models

Mortality proportions mediated through preterm delivery were estimated as follows: (RRNDE*(RRNIE -1)/(RRNDE*RRNIE -1)), where RRNDE and RRNIE refer to the corresponding risk ratios for natural direct effect and natural indirect effect, respectively.