

**Appendices to the article:**  
**The Mediation Proportion:**  
*A Structural Equation Approach for Estimating the  
Proportion of Exposure Effect on Outcome Explained  
by an Intermediate Variable*

**Appendix A    The mediation proportion:  
details of the basic statistical regression model**

Assume exposure  $A$ , intermediate variable  $B$ , and response  $C$  with mean vector which may without loss of generality be taken as  $(0, 0, 0)$  and covariance matrix  $\Sigma = (\sigma_{ij}; i, j = A, B, C)$ , where  $\sigma_{ii}$  are usually denoted  $\sigma_i^2, i = A, B, C$ . Here  $\sigma_i^2$  is the variance of the variable  $i$ , and  $\sigma_{ij}$  is the covariance between the variables  $i$  and  $j$ . The conditional joint distribution of the intermediate variable  $B$  and the response  $C$  is assumed bivariate normal. No normality assumption is necessary for the exposure  $A$  as it is only entering as an independent variable in the analysis.

The effect of exposure  $A$  on response  $C$  would usually be reported by calculating the regression of  $C$  on  $A$ :

$$C = \beta A + \epsilon$$

where  $\beta = \sigma_{AC}/\sigma_A^2$ . We want to decompose  $\beta$  into a sum of a “direct” effect of  $A$  on  $C$  and an “indirect” effect of  $A$  on  $C$  via  $B$ .

Now the effect of  $A$  on  $B$  is expressed by the regression

$$B = \gamma_2 A + \epsilon_1, \quad \gamma_2 = \sigma_{AB}/\sigma_A^2$$

and the effects of  $A$  and  $B$  on  $C$  by the regression

$$\begin{aligned} C &= \gamma_1 A + \gamma_3 B + \epsilon_2, \\ \gamma_1 &= \frac{\sigma_{AC}\sigma_B^2 - \sigma_{AB}\sigma_{BC}}{\sigma_A^2\sigma_B^2 - \sigma_{AB}^2}, \\ \gamma_3 &= \frac{\sigma_{BC}\sigma_A^2 - \sigma_{AB}\sigma_{AC}}{\sigma_A^2\sigma_B^2 - \sigma_{AB}^2}. \end{aligned}$$

These regressions are illustrated in the diagram



and by insertion we obtain

$$\begin{aligned}
 C &= \gamma_1 A + \gamma_3 B + \epsilon_2 \\
 &= \gamma_1 A + \gamma_3(\gamma_2 A + \epsilon_1) + \epsilon_2 \\
 &= (\gamma_1 + \gamma_3 \gamma_2) A + \epsilon
 \end{aligned}$$

where simple algebra shows that

$$\begin{aligned}
 \gamma_1 + \gamma_3 \gamma_2 &= \left( \frac{\sigma_{AC} \sigma_B^2 - \sigma_{AB} \sigma_{BC}}{\sigma_A^2 \sigma_B^2 - \sigma_{AB}^2} \right) + \left( \frac{\sigma_{BC} \sigma_A^2 - \sigma_{AB} \sigma_{AC}}{\sigma_A^2 \sigma_B^2 - \sigma_{AB}^2} \right) \left( \frac{\sigma_{AB}}{\sigma_A^2} \right) \\
 &= \frac{\sigma_{AC}}{\sigma_A^2} \\
 &= \beta
 \end{aligned}$$

so that we have obtained the desired decomposition of the *total effect*  $\beta$  of  $A$  on  $C$  into the *direct effect*  $\gamma_1$  and the *indirect effect*  $\gamma_2 \gamma_3$ . The *mediation proportion* is defined as the dimensionless proportion of the effect of  $A$  on  $C$  mediated through  $B$ :

$$\frac{\text{Indirect effect}}{\text{Total effect}} = \frac{\gamma_2 \gamma_3}{\gamma_1 + \gamma_2 \gamma_3}.$$

Obviously the interpretation is easiest when all entering regression coefficients  $\gamma_1, \gamma_2, \gamma_3$ , and hence  $\beta$ , are positive.

The mediation proportion is just the percentage change of the regression coefficients when we include an intermediate variable in the model: how much changes the regression coefficient of  $C$  on  $A$  when going from the small model to the larger model including the intermediate variable  $B$ , that is, how large is  $\beta$  relatively to  $\gamma_1$ :

$$\frac{\beta - \gamma_1}{\beta} = \frac{\gamma_2 \gamma_3}{\gamma_1 + \gamma_2 \gamma_3} = \text{The Mediation Proportion.}$$

**Invariance to linear transformations.** The mediation proportion is invariant to linear transformations:

Assume in model (1) that we measure A, B and C on different scales, such that  $A^* = \mu_1 A$ ,  $B^* = \mu_2 B$  and  $C^* = \mu_3 C$ . Then  $\gamma_1^* = \frac{\mu_3}{\mu_1} \gamma_1$ ,  $\gamma_2^* = \frac{\mu_3}{\mu_2} \gamma_2$  and  $\gamma_3^* = \frac{\mu_2}{\mu_1} \gamma_3$ , where  $\gamma_i^*$ ,  $i = 1, 2, 3$  are the regression coefficients in the model with  $A^*$ ,  $B^*$  and  $C^*$ , and  $\gamma_i$ ,  $i = 1, 2, 3$  are the regression coefficients in the model with A, B and C. We have that the part of the effect of  $A^*$  on  $C^*$  mediated through  $B^*$  is:

$$\frac{\text{Indirect effect}}{\text{Total effect}} = \frac{\gamma_2^* \gamma_3^*}{\gamma_1^* + \gamma_2^* \gamma_3^*} = \frac{\frac{\mu_3}{\mu_2} \gamma_2 \frac{\mu_2}{\mu_1} \gamma_3}{\frac{\mu_3}{\mu_1} \gamma_1 + \frac{\mu_3}{\mu_2} \gamma_2 \frac{\mu_2}{\mu_1} \gamma_3} = \frac{\gamma_2 \gamma_3}{\gamma_1 + \gamma_2 \gamma_3}.$$

**Confidence intervals.** The standard error of the fraction can be found using the covariance matrix of the estimates of  $\gamma_i$ ,  $i = 1, 2, 3$  by the delta method or by the Fieller-method,<sup>1,2</sup> and thus confidence intervals on the mediation proportion can routinely be calculated. Freedman<sup>2</sup> has found that Fieller's method is superior in coverage properties. When the quantity  $g = z_\alpha^2 \text{Var}(\hat{\beta}) / \hat{\beta}^2$ , where  $z_\alpha$  is the  $100(1-\alpha/2)$  percentile of the normal distribution and  $\hat{\beta}$  is the estimate of  $\beta$ , the unadjusted effect of social class on symptom load, is very small, the two methods give approximately the same confidence limits.<sup>1</sup> The confidence limits (0.218–0.315) given in Equation (3) of the main article are calculated with Fieller's method. The corresponding confidence limits with the delta method were calculated to (0.203–0.325), so there were no substantial difference between the two, in agreement with  $g$  being very small (0.02).

The standard error of the mediation proportion can be calculated by the  $\delta$ -method in the following way:

Let the covariance of  $(\gamma_i, \gamma_j)$  be denoted by  $\sigma_{ij}$ ;  $i, j = 1, 2, 3$ , where  $\sigma_{ii}$  are denoted  $\sigma_i^2$ ,  $i = 1, 2, 3$ . The variance of the mediation proportion will approximately be

$$\frac{\gamma_2^2 \gamma_3^2 \sigma_1^2 + \gamma_1^2 \gamma_3^2 \sigma_2^2 + \gamma_1^2 \gamma_2^2 \sigma_3^2 - 2\gamma_1 \gamma_2 \gamma_3^2 \sigma_{12} - 2\gamma_1 \gamma_2^2 \gamma_3 \sigma_{13} + 2\gamma_1^2 \gamma_2 \gamma_3 \sigma_{23}}{(\gamma_1 + \gamma_2 \gamma_3)^4}$$

## Appendix B Miscellaneous

**Threshold models.** In the following the threshold models to handle ordered categorical variables will be described.

Assume an indicator variable  $x$  ordered categorical with  $k$  levels, to which we attach a latent counterpart: a continuous, normally distributed variable  $x^*$ . The threshold model relates the ordinal observed variable  $x$  to its latent continuous counterpart  $x^*$  as illustrated in Figure 1 for the case of a three category variable with two thresholds (besides the outer thresholds  $-\infty$  and  $\infty$ ). The relation between  $x$  and  $x^*$  is defined through  $k + 1$  threshold values  $t_j, j = 0, \dots, k$  such that  $x = k$  if  $t_{k-1} \leq x^* \leq t_k$ . Let  $N$  be the number of observations, and  $n_i, i = 1, \dots, k$  the number of observations in level  $i$ . We estimate the  $k + 1$  threshold values by setting  $t_0 = -\infty, t_k = \infty$  and  $t_j$  such that  $P(Z < t_j) = (\sum_{i \leq j} n_i)/N, j = 1, \dots, k - 1$  where  $Z$  is normally distributed with mean 0 and variance 1, and  $P(Z < t_j)$  is the probability that  $Z$  is less or equal to  $t_j$ . Now the regression models assuming normally distributed variables are made using the  $x^*$  variables with the indicated relation to the ordered categorical, observed variables.

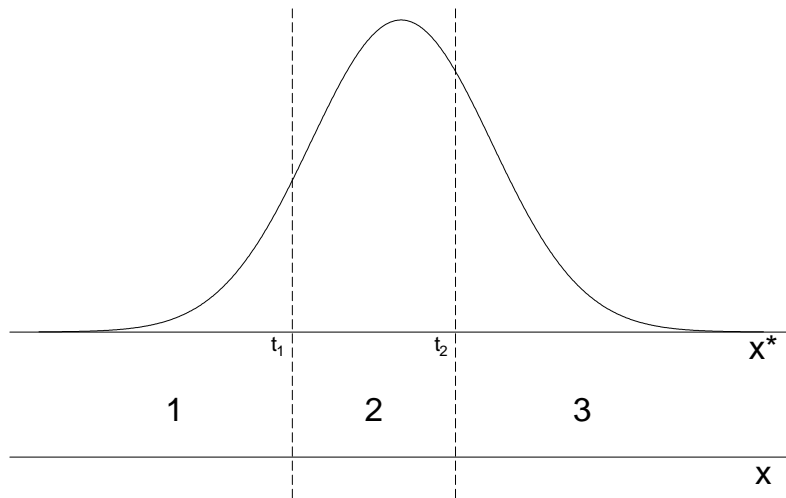


Figure 1: Illustration of a three category, two threshold variable  $x$ , and the corresponding underlying continuous variable  $x^*$ .

**Dependence between indicator variables.** In the following the arrows connecting the error terms in Figures 3 and 4 of the main article will be described.

As a starting point the indicator variables are assumed to be conditionally independent given the latent variable, that is  $\text{Corr}(\delta_i, \delta_j) = 0$ . However, it is possible to allow for correlation beyond the connection through the latent variable.

An arrow connecting the error terms of two indicator variables indicates that the correlation between the two variables exceeds what can be explained by the connection through the latent variable. For example, in the case of  $\delta_9$  and  $\delta_{10}$ , the questions were about pain in back, joints and muscles ( $y_1$ ), and pain in arms, shoulders, hands, legs, knees and feet ( $y_2$ ), which must be expected to be more correlated than what can be explained by the latent variable of symptom load. Such would not be the case if we observe either of the two variables of physical pain and compare it to e.g. anxiety ( $y_5$ ). In this case we would expect those variables to be independent given the latent variable of symptom load. Allowing for dependence between some of the indicator variables improved the overall fit of the model, but it had no significant influence on the regression coefficients of interest.

## Appendix C Mplus codes

Mplus code for the analysis of application to ophthalmology data in the main article.

```
TITLE:                Ophthalmology Analysis.

DATA:                 FILE IS OphthalmologyData;
                     FORMAT IS FREE;
                     TYPE IS INDIVIDUAL;

VARIABLE:
NAMES ARE            Z S T;

USEVARIABLES ARE Z S T;
```

CATEGORICAL ARE S T;

MISSING ARE .;

MODEL:            Slatent BY S;  
                  Tlatent BY T;  
  
                  Tlatent ON Slatent Z;  
                  Slatent ON Z;  
  
                  Slatent@1;  
                  Tlatent@1;

ANALYSIS:        TYPE IS GENERAL MEANSTRUCTURE;

OUTPUT:           STANDARDIZED RESIDUAL TECH1 TECH3 TECH4;

Mplus code for the analysis of social class, symptom load, and cynical hostility (example of one intermediate variable) of the main article.

TITLE:            Social class - cynical hostility - symptom load  
                  analysis for men.

DATA:            FILE IS c:\mplus\data;  
                  FORMAT IS FREE;  
                  TYPE IS INDIVIDUAL;

VARIABLE:  
NAMES ARE        x1 x2 x3 x4 x5 x6 x7 x8 y1 y2 y3 y4  
                  y5 y6 y7 y8 y9 y10 y11 y12 y13  
                  SOC AGE;

USEVARIABLES ARE x1 x2 x3 x4 x5 x6 x7 x8 y1 y2 y3 y4  
                  y5 y6 y7 y8 y9 y10 y11 y12 y13  
                  SOC AGE;

CATEGORICAL ARE x1 x2 x3 x4 x5 x6 x7 x8 y1 y2 y3 y4

```

y5 y6 y7 y8 y9 y10 y11 y12 y13
SOC;

MISSING ARE .;

MODEL:      HOST    BY x1 x2 x3 x4 x5 x6 x7 x8;
            HEALTH BY y1 y2 y3 y4 y5 y6 y7 y8
                y9 y10 y11 y12 y13;

            HOST    ON SOC AGE;
            HEALTH ON SOC HOST AGE;
            SOC     ON AGE;

            x1 WITH x2;
            y1 WITH y2;
            y4 WITH y5;
            y5 WITH y6;
            y8 WITH y9;
            y11 WITH y12;
            y4 WITH y12;

ANALYSIS:   TYPE IS GENERAL MEANSTRUCTURE;

OUTPUT:     STANDARDIZED RESIDUAL TECH1 TECH3 TECH4;

```

The output will include the estimated regression coefficients and their covariance matrix. Then the mediation proportion can be calculated from Equation (1) of the main article.

## References

1. Armitage, P, Berry, G, Matthews, JNS (2002): *Statistical Methods in Medical Research*. Blackwell Science.
2. Freedman, L (2001): *Confidence intervals and statistical power of the "validation" ratio for surrogate or intermediate endpoints*. J Statistical Planning and Inference 96, 143-153