Interventional effects for mediation analysis with multiple mediators

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1 Introduction

The introduction of counterfactual-based distribution-free definitions of direct and indirect effect in epidemiology[2,3] – so-called natural (in)direct effects – has spurred a major revival of mediation analysis[4–6]. It has led to a renewed and improved understanding of the ignorability assumptions required to identify (in)direct effects. It has moreover enabled the development of a formal framework for mediation analysis that is applicable to nonlinear models. These developments have facilitated applications of mediation analysis that better respect the nature of the data and reflect greater consideration of the need for confounding control. Notwithstanding this, mediation analysis based on natural (in)direct effects has been the subject of recent critiques. The usefulness of natural (in)direct effects

has been called into question because they are not directly informative about real-life interventions[7,8]. Concerns have moreover been raised about the impossibility to conduct experiments in which the identification assumptions for natural (in)direct effects are guaranteed to be satisfied[7,9,10]. Remaining concerns arise from the difficulty or impossibility to identify these effects in realistic settings that involve multiple and/or repeatedly measured mediators[11–13], and settings that involve exposure-induced confounding of the mediator-outcome association[1,14,15]. These concerns all originate from the fact that natural (in)direct effects are defined in terms of so-called cross-world counterfactuals[7] that are unobservable, even from experimental data; they call for alternative effect measures that are less remote from the observed data.

In this article, we revisit and refine so-called interventional (in)direct effects, previously introduced by VanderWeele, Vansteelandt and Robins[1]. These are not defined in terms of cross-world counterfactuals. They can therefore be identified under weaker conditions, but have the drawback of not always adding up to the total effect. We will adapt this proposal to overcome this, and next extend it to the case of multiple mediators. Interestingly, our proposal decomposes the total effect into different path-specific effects via the different mediators, even when – as often – the structural dependence between the multiple mediators (for instance, the direction of the causal effect, or the possible presence of unmeasured common causes) is unknown. It thus opens avenues towards a flexible and realistic mediation analysis with multiple mediators.

2 Single mediator models

2.1 Effect measures

Let A, M and Y denote the exposure, mediator and outcome. Let C represent baseline covariates not affected by the exposure. We let Y_a and M_a denote respectively the values of the outcome and mediator that would have been observed had the exposure A been set to level a; let Y_{am} denote the value of the outcome that would have been observed had A been set to level a, and M to m. Throughout, we make the consistency assumption[16] that $Y_a = Y$ and $M_a = Y$ when $A = a$, and that $Y_{am} = Y$ when $A = a$ and $M = m$.

Suppose a and a^* are two values of the exposure we wish to compare, e.g. $a = 1$ and $a^* = 0$. The corresponding average controlled direct effect, fixing the mediator to level m, is then defined by $E(Y_{am} - Y_{a^*m})$. It captures the effect of exposure A on outcome Y, intervening to fix M to m[2,4]; it may be different for different levels of m. The natural direct effect, $E(Y_{aM_{a^*}} - Y_{a^*M_{a^*}})$, differs from the controlled direct effect in that the intermediate M is set to the level M_{a^*}, the level that it would have naturally been under some reference condition a^* for the exposure[2,4]. By subtracting it from the total effect, $E(Y_a - Y_{a^*})$, one obtains the average natural indirect effect, $E(Y_{aM_a} - Y_{aM_{a^*}})$; this compares the effect of the mediator at levels M_a and M_{a^*} on the outcome when exposure is set to $A = a$. Finally,

we define the interventional direct effect as

$$E\left(Y_{aG_{a^*|C}} - Y_{a^*G_{a^*|C}}\right) = E\left[\sum_m \left\{E\left(Y_{am}|C\right) - E\left(Y_{a^*m}|C\right)\right\} P(M_{a^*} = m|C)\right].$$

It differs from the controlled direct effect in that the intermediate is set for each subject to a random draw from the conditional distribution of M_{a^*}, given the observed covariates C for that subject (a related definition[1] uses $P(M = m|a^*, C)$ in lieu of $P(M_{a^*} = m|C)$). It may thus be viewed as the controlled direct effect of comparing exposure levels a versus a^* under a stochastic intervention, $G_{a^*|C}$, which controls the mediator for each subject at some value randomly drawn from the distribution of M_{a^*}, given the observed covariates C. We will moreover call

$$E\left(Y_{aG_{a|C}} - Y_{aG_{a^*|C}}\right) = E\left[\sum_m E\left(Y_{am}|C\right)\left\{P(M_a = m|C) - P(M_{a^*} = m|C)\right\}\right]$$

the interventional indirect effect. For this effect to be non-zero, the exposure would have to change the mediator, which in turn would have to change the outcome, thus confirming that it captures a notion of mediation. For instance, VanderWeele et al.[17] investigate pack-years of smoking as a mediator of the effect of genetic variants on lung cancer. The interventional indirect effect expresses the change in lung cancer risk that would be seen if the distribution of pack-years of smoking were shifted from what it would be if all subjects carried two risk alleles to what it would otherwise be. Arguably, this effect is more relevant than the corresponding natural indirect effect, as it is informative about the effect of particular interventions on smoking. One could alternatively define interventional (in)direct effects with respect to a mediator distribution other than $P(M_a = m|c)$. This can be of interest when interventions on the exposure are not conceivable. For instance, changing $P(M_a = m|c)$ to $P(M = m|a, c)$ would change the interpretation to the average change in lung cancer risk that would be seen if the distribution of pack-years of smoking were shifted from what it is in subjects with two risk alleles to what it is in the remaining subjects[1]. In the remainder of the article, we choose not to do this because unmeasured confounding may render $P(M = m|a, c)$ dependent on a, even when the exposure has no effect on the mediator.

2.2 Assumptions

Controlled direct effects can be identified when:

(i) the effect of exposure A on outcome Y is unconfounded conditional on C (i.e., $Y_{am} \perp\!\!\!\perp A|C$, where $X \perp\!\!\!\perp Y|Z$ denotes that X is independent of Y conditional on Z);

(ii) the effect of mediator M on outcome Y is unconfounded conditional on A, C and possibly some additional covariate vector L that may be affected by A (i.e., $Y_{am} \perp\!\!\!\perp M|\{A = a, C, L\}$).

Average interventional (in)direct effects are identified if, in addition to these assumptions,

(iii) the effect of exposure A on mediator M is unconfounded conditional on C (i.e., $M_a \perp\!\!\!\perp A|C$).

Randomisation of the exposure (possibly conditional on C) ensures the validity of this additional assumption as well as assumption (i). Under (i)-(iii), the interventional direct and indirect effect can be identified as[1]

$$\sum_c \sum_l \sum_m \{E(Y|a,l,m,c)\,P(l|a,c) - E(Y|a^*,l,m,c)\,P(l|a^*,c)\}\,P(m|a^*,c)P(c) \quad (1)$$

$$\sum_c \sum_l \sum_m E(Y|a,l,m,c)\,P(l|a,c)\,\{P(m|a,c) - P(m|a^*,c)\}\,P(c). \quad (2)$$

These expressions reveal a major weakness that we will attempt to overcome: the sum of the effects (1) and (2), which is sometimes called the 'overall effect'[1], may differ from the total effect. One exception is when assumptions (i) and (iii) hold, and in addition, assumption (ii) holds with L empty. In that case, the direct and indirect interventional effects sum to the total effect $E(Y_a - Y_{a^*})$, even when there are interactions and non-linearities.

Natural direct and indirect effects always sum to the total effect. However, their identification requires much stronger assumptions. It requires that assumptions (i) and (iii) hold, that assumption (ii) holds with L empty (thus excluding the possible presence of exposure-induced confounders), and in addition that a technical cross-world independence assumption[3] holds, which places an independence restriction on the joint distribution of the variables Y_{am} and M_{a^*}:

(iv) $Y_{am} \perp\!\!\!\perp M_{a^*}|C$.

Under these assumptions, these effects reduce to expressions (1) and (2) obtained for average direct and indirect interventional effects, but with L empty. It thus follows that in single mediator models without post-treatment confounding, natural (in)direct effects obtained under assumption (iv) can also be interpreted as interventional (in)direct effects (even when that assumption is violated).

2.3 Natural versus interventional (in)direct effects

Average interventional direct effects encode the exposure effect that would be realised while controlling the mediator distribution to be fixed. This is realised by setting the mediator for each subject to a random draw from the distribution of the mediator at exposure level a^*, given covariate values c. Natural direct effects adopt a similar notion, but fixing the mediator at the counterfactual mediator value (corresponding to exposure level a^*) itself. This may yield a direct effect of a different magnitude, in part because

the counterfactual level of the mediator may depend on much more than the considered covariates c. Both measures would thus be relatively close if the covariate set c were so rich as to leave little variation in M_{a^*} for a given c (beyond the variation due to causes unrelated to Y_{am}), but not necessarily otherwise. While the natural direct effect may thus more closely capture the notion of mechanism, this need not lead us to prioritise them. First, natural direct effects employ cross-world counterfactuals like $Y_{aM_{a^*}}$ about which information cannot be obtained even from experimental data. The data analyst who reports natural direct effects is thus obligated to make strong untestable assumptions like (iv) (and/or to conduct a sensitivity analysis[18]), under which these effects reduce to the interventional direct effect (1) (with L empty). Second, the relevance of natural (in)direct effects has been questioned on the basis that they do not connect to the effect of particular policies[8].

In contrast to natural (in)direct effects, interventional (in)direct effects are policy-relevant[19]: they are relevant about a policy that involves fixing the mediator distribution, or shifting it to the extent that it is affected by the exposure. They continue to be meaningful, even when assumptions (i) and (iii) fail or when the exposure is not manipulable (e.g. when the exposure is race[20]), so long as assumption (ii) is satisfied. For instance, when L is empty, then the interventional direct effect (1) reduces to

$$\sum_c \sum_m \{E(Y_m|a,c) - E(Y_m|a^*,c)\} P(m|a^*,c)P(c),$$

since $E(Y|a,m,c) = E(Y_m|a,c)$ under assumption (ii). This can be interpreted as the average outcome difference that would remain between exposure groups $A = a$ and $A = a^*$ if the mediator distribution in the former group were shifted to equal that in the latter group[20]. Similar comments are relevant for indirect effects.

3 Multiple mediator models

3.1 Review

For pedagogic purposes, we consider a setting with two mediators M_1 and M_2, and defer more general results to the eAppendix. VanderWeele and Vansteelandt (2013) define the natural direct effect of A on Y, not mediated by either or both mediators, as $E(Y_{aM_{1a^*}M_{2a^*}} - Y_{a^*M_{1a^*}M_{2a^*}})$. The remaining indirect effect via both mediators is then $E(Y_{aM_{1a}M_{2a}} - Y_{aM_{1a^*}M_{2a^*}})$. These effects can be identified as

$$\sum_c \sum_{m_1} \sum_{m_2} \{E(Y|a,m_1,m_2,c) - E(Y|a^*,m_1,m_2,c)\} P(m_1,m_2|a^*,c)P(c) \qquad (3)$$

and

$$\sum_c \sum_{m_1} \sum_{m_2} E(Y|a,m_1,m_2,c) \{P(m_1,m_2|a,c) - P(m_1,m_2|a^*,c)\} P(c), \qquad (4)$$

when

(i') the effect of exposure A on outcome Y is unconfounded conditional on C (i.e., $Y_{am_1m_2} \perp\!\!\!\perp A|C$);

(ii') the effect of both mediators M_1 and M_2 on outcome Y is unconfounded conditional on A and C (i.e., $Y_{am_1m_2} \perp\!\!\!\perp (M_1, M_2)|\{A = a, C\}$);

(iii') the effect of exposure A on both mediators is unconfounded conditional on C (i.e., $(M_{1a}, M_{2a}) \perp\!\!\!\perp A|C$);

(iv') the cross-world assumption holds that $Y_{am_1m_2} \perp\!\!\!\perp (M_{1a^*}, M_{2a^*})|C$.

Unfortunately, these effects provide no insight into the distinct pathways that may exist between exposure and outcome.

When the mediators are sequential (i.e., M_1 may affect M_2 but not vice versa), further progress[1,12] can sometimes be made by supplementing the previous analysis with a single mediator analysis with respect to M_1. In particular, if assumptions (i)-(iv) hold with M_1 in lieu of M, one can additionally identify the natural direct effect $E(Y_{aM_{1a^*}} - Y_{a^*M_{1a^*}})$. This can be decomposed as

$$E(Y_{aM_{1a^*}} - Y_{aM_{1a^*}M_{2a^*}}) + E(Y_{aM_{1a^*}M_{2a^*}} - Y_{a^*M_{1a^*}M_{2a^*}}),$$

where the first component represents the effect mediated by M_2 but not M_1, and the second component can be identified as detailed in the previous paragraph. Such sequential analysis thus enables one to infer the direct effect that is not mediated by either M_1 or M_2 or both, i.e. $E(Y_{aM_{1a^*}M_{2a^*}} - Y_{a^*M_{1a^*}M_{2a^*}})$, the effect that is mediated by M_1, i.e. $E(Y_{aM_{1a}} - Y_{aM_{1a^*}})$ (including any effect mediated by both M_1 and M_2), and the effect that is mediated by M_2 but not M_1, i.e. $E(Y_{aM_{1a^*}} - Y_{aM_{1a^*}M_{2a^*}})$. However, one important limitation is that the causal structure between M_1 and M_2 (i.e. whether M_1 affects M_2, or vice versa) is often not known when different mediators are assessed at the same time. Moreover, even when assumptions (i')-(iv') hold, assumptions (i)-(iv) (with M_1 in lieu of M) will often not be satisfied[12]. For instance, when both mediators share an unmeasured common cause, as in the causal diagram of Figure 1, then M_2 confounds the association between M_1 and Y, thereby inducing a violation of assumption (ii). In that case, the effect mediated via M_1 is not identified because the data carry no information about the effect of M_1 on M_2. Regression adjustment for M_2 provides no remedy because M_2 is an exposure-induced confounder so that adjusting for it would violate assumption (iv). This problem is important because the mediators are strongly related in many applications; for instance M_1 and M_2 may represent realisations of a repeatedly measured mediator, or be manifestations of an underlying latent process.

In view of these limitations, we will next propose novel definitions of interventional (in)direct effects for the multiple mediator setting, which do not have the disadvantage

that they do not sum to the total effect. The proposed formalism will decompose the total effect of exposure on outcome into various path-specific effects. It can be used even when the causal structure between the mediators is unknown or when various mediators share unmeasured common causes.

3.2 Proposal

We define the interventional direct effect of exposure on outcome other than via the given mediators as

$$E\left[\sum_{m_1}\sum_{m_2}\left\{E\left(Y_{am_1m_2}|c\right)-E\left(Y_{a^*m_1m_2}|c\right)\right\}P(M_{1a^*}=m_1,M_{2a^*}=m_2|c)\right]. \quad (5)$$

This expresses the exposure effect when fixing the joint distribution of both mediators (by controlling the mediators for each subject at a random draw from their counterfactual joint distribution with the exposure set at a^*, given covariates C). This corresponds to the effect $A \to Y$ in the causal diagrams of Figures 1, 2 and 3.

We define the interventional indirect effect of exposure on outcome via M_1 as

$$E\left[\sum_{m_1}\sum_{m_2}E\left(Y_{am_1m_2}|c\right)\left\{P(M_{1a}=m_1|c)-P(M_{1a^*}=m_1|c)\right\}P(M_{2a^*}=m_2|c)\right]. \quad (6)$$

This expresses the effect of shifting the distribution of mediator M_1 from the counterfactual distribution (given covariates) at exposure level a^* to that at level a, while fixing the exposure at a and the mediator M_2 to a random subject-specific draw from the counterfactual distribution (given covariates) at level a^* for all subjects. The latter is chosen independently of M_1, so as to avoid assumptions on the joint distribution of the counterfactuals M_{1a} and M_{2a^*} corresponding to different exposure levels.

The effect (6) corresponds to the effect $A \to M_1 \to Y$ in the causal diagrams of Figures 1 and 2, and to the combination of the effects $A \to M_1 \to Y$ and $A \to M_2 \to M_1 \to Y$ in Figure 3. The latter can be seen upon noting that the difference $P(M_{1a} = m_1|c) - P(M_{1a^*} = m_1|c)$ encodes the combination of the effects $A \to M_1$ and $A \to M_2 \to M_1$. The interventional indirect effect of exposure on outcome via M_1 thus captures all of the exposure effect that is mediated by M_1, but not by causal descendants of M_1 in the graph. Interestingly, this interpretation holds regardless of the underlying causal structure.

We define the interventional indirect effect of exposure on outcome via M_2 similarly as

$$E\left[\sum_{m_1}\sum_{m_2}E\left(Y_{am_1m_2}|c\right)\left\{P(M_{2a}=m_2|c)-P(M_{2a^*}=m_2|c)\right\}P(M_{1a}=m_1|c)\right]. \quad (7)$$

This corresponds to the effect $A \to M_2 \to Y$ in the causal diagrams of Figures 1 and 3, and to the combination of the effects $A \to M_2 \to Y$ and $A \to M_1 \to M_2 \to Y$ in

Figure 2. It thus captures all of the exposure effect that is mediated by M_2, but not by causal descendants of M_2 in the graph; again, this interpretation holds regardless of the underlying causal structure.

The difference between the total effect and these 3 effects equals

$$E\left[\sum_{m_1}\sum_{m_2} E\left(Y_{am_1m_2}|c\right)\{P(M_{1a}=m_1,M_{2a}=m_2|c)-P(M_{1a}=m_1|c)P(M_{2a}=m_2|c)\right.$$
$$\left.-P(M_{1a^*}=m_1,M_{2a^*}=m_2|c)+P(M_{1a^*}=m_1|c)P(M_{2a^*}=m_2|c)\}\right]. \quad (8)$$

This captures the indirect effect resulting from the effect of exposure on the dependence between the counterfactuals M_{1a} and M_{2a}, given C. This effect would be zero when both mediators are conditionally independent[21], given exposure and covariates, but also under much weaker conditions. Under linear models, for instance, this effect can only be non-zero when both mediators interact in their effect on the outcome and, moreover, one of the mediators interacts with the exposure in its effect on the other mediator. Because of this, we would often expect (8) to be much closer to zero than the other components (6) and (7) of the indirect effect, though not always (see Section 4).

In some cases, the effect (8) may be of primary scientific interest. For instance, consider the mediating roles of cancer stage at diagnosis and treatment in the effect of SES on 1-year survival in breast cancer patients. Suppose that the treatment decision process takes cancer stage into account in a manner that may be different for women with high versus low SES. The resulting effect of SES on 1-year survival that is mediated by this possibly differential decision process is encoded in (8).

Regardless of whether the component (8) is of scientific interest, it is important to consider it when expressing how much of the exposure effect is explained by specific pathways. For instance, in utero tobacco smoke exposure M_1 is known to have an effect on asthma and wheeze only in children with the GSTM1-null genotype M_2[22]. If an intervention to reduce smoking during pregnancy were only effective in mothers of infants without the GSTM1-null genotype, then the intervention would have no indirect effect via smoking. Yet, the indirect effect (6) would be non-zero because it would consider the characteristics M_1 and M_2 independently. Only by acknowledging that part of the indirect effect via M_1 is also expressed by the term (8) may valid conclusions be drawn.

3.3 Estimation

Under assumptions (i'), (ii') and (iii'), the effects (5), (6), (7) and (8) can be identified upon substituting $E\left(Y_{am_1m_2}|c\right)$ by $E\left(Y|a,m_1,m_2,c\right)$ and $P(M_{ja}=m_j|c)$ for $j=1,2$ by $P(M_j=m_j|a,c)$ in the above expressions. Suppose for instance that the outcome obeys model

$$E(Y|a,m_1,m_2,c) \;=\; \theta_0+\theta_1a+\theta_2m_1+\theta_3m_2+\theta_4m_1m_2+\theta_5am_1+\theta_6am_2+\theta_7c$$

and that the mediators (M_1, M_2), conditional on A and C, have means

$$E(M_j|a,c) \;\; = \;\; \beta_{0j} + \beta_{1j}a + \beta_{2j}c,$$

with residual variances σ_j^2, $j = 1, 2$, and covariance σ_{12}. Then the interventional direct effect (5) is given by

$$\begin{aligned} &E\left[\{\theta_1 + \theta_5(\beta_{01} + \beta_{11}a^* + \beta_{21}C) + \theta_6(\beta_{02} + \beta_{12}a^* + \beta_{22}C)\}(a - a^*)\right] \\ &= \{\theta_1 + \theta_5(\beta_{01} + \beta_{11}a^* + \beta_{21}E(C)) + \theta_6(\beta_{02} + \beta_{12}a^* + \beta_{22}E(C))\}(a - a^*). \end{aligned}$$

It equals $\theta_1(a - a^*)$ in the absence of exposure-mediator interactions. Upon fitting the appropriate regression models to the observed data, thus obtaining estimates of the above parameters, these estimates can be plugged in to the expression above to obtain an estimate of the interventional direct effect. The interventional indirect effect (6) via M_1 equals

$$\{\theta_2 + \theta_4(\beta_{02} + \beta_{12}a^* + \beta_{22}E(C)) + \theta_5 a\}\beta_{11}(a - a^*),$$

which is $\theta_2\beta_{11}(a - a^*)$ in the absence of exposure-mediator and mediator-mediator interactions. The interventional indirect effect (7) via M_2 is

$$\{\theta_3 + \theta_4(\beta_{01} + \beta_{11}a + \beta_{21}E(C)) + \theta_6 a\}\beta_{12}(a - a^*).$$

Finally, the indirect effect (8) resulting from the effect of exposure on the mediators' dependence is $\theta_4\sigma_{12} - \theta_4\sigma_{12} = 0$. The total effect can thus be decomposed into the direct effect and the two indirect effects defined above. If instead, A and M_1 interacted in their effect on M_2 in the sense that

$$E(M_2|m_1, a, c) = \beta_{02} + \beta_{12}a + \beta_{22}c + \beta_{32}m_1 + \beta_{42}am_1,$$

then (8) would evaluate to $\sigma_1^2\theta_4\beta_{42}(a - a^*)$.

This regression approach has the drawback that it requires a new derivation each time a different outcome or mediator model is considered. This can be remedied via a Monte-Carlo approach, which involves sampling counterfactual values of the mediators from their respective distributions. For instance, to evaluate the first component

$$E\left[\sum_{m_1}\sum_{m_2} E\left(Y_{am_1m_2}|c\right)P(M_{1a} = m_1|c)P(M_{2a^*} = m_2|c)\right],$$

of (6), one may take a random draw $M_{2a^*,i}$ for each subject i from the (fitted) distribution $P(M_2|a^*, c_i)$. Next, one takes a random draw $M_{1a,i}$ for each subject i from the (fitted) distribution $P(M_1|a, c_i)$. Finally, one may predict the outcome as the expected outcome under a suitable model with exposure set to a, M_1 set to $M_{1a,i}$, M_2 set to $M_{2a^*,i}$, and covariate C_i. The average of these fitted values across subjects then estimates the above component. Its performance can be improved by repeating the random sampling many times and averaging the results across the different Monte-Carlo runs. In practice, we recommend the bootstrap for inference.

4 A health disparity analysis

We illustrate our proposal using data for all 29,580 women diagnosed with malignant, invasive breast cancer from 2000 to 2006 in the Northern and Yorkshire Cancer Registry Information Service (NYCRIS) – a population-based cancer registry covering 12% of the English population – who have information on cancer stage at diagnosis recorded. Our aim is to investigate possible explanations for the disparity in breast cancer survival between women of higher and lower SES; 95.9% (64.7%) of women with higher SES survive to one (five) year(s) after diagnosis, compared with 93.2% (54.1%) in the lower SES group. One possible explanation is that women with lower SES are less likely to attend screening and as a result, are more likely to be diagnosed when the disease is already more advanced. A difference in treatment choice is another possible explanation.

Our analyses are included mainly for illustration and some caution is warranted, as they involve several simplifications . In particular, we consider a binary SES exposure (A) which is whether or not the woman resides (at diagnosis) in an affluent area. The mediator M_1 comprises age at diagnosis and cancer stage at diagnosis, classified as early (TNM stage 1/2) or advanced (TNM stage 3/4). The mediator M_2 is a treatment variable that classifies women either as having 'major surgery' or 'minor or no surgery'. The outcome (Y) is one-year survival from the date of diagnosis. Calendar year at diagnosis and region are considered as baseline confounders (C).

All analyses assume that the causal diagram of Figure 4 holds, and are based on 6 million Monte-Carlo draws in total (to ensure that the results were free of Monte-Carlo error to the number of decimal places given), with the distribution of the two confounders equal to their empirical distribution. Standard errors are obtained using the nonparametric bootstrap, with 1,000 bootstrap samples. Stata code is given in eAppendix D.

4.1 Sequential mediation analysis

Details on the sequential mediation analysis of Section 3.1 are given in the eAppendix. The results in Table 1 suggest that, of the 2.8% (95% CI 2.3%–3.4%) total difference in survival probability, about half of this (1.4%, 95%CI 1.1%–1.6%) is mediated by some combination of age and stage at diagnosis and treatment. Assuming that there are no unmeasured common causes of age/stage at diagnosis and treatment (i.e. no U in Figure 4), we can further decompose this indirect effect into an effect through age/stage (some of which may also act through treatment) (1.0%, 95% CI 0.8%–1.2%) and an effect through treatment alone (0.3%, 95% CI 0.2%–0.5%), thus indicating that only a small proportion of the effect is through the treatment variable alone.

4.2 Multiple mediator analysis based on interventional effects

Without relying on any cross-world assumptions nor any assumptions about the causal structure of the mediators, thus allowing U in Figure 4, the results in Table 2 (obtained as detailed in the eAppendix) suggest that, of the 2.8% (95% CI 2.3%–3.4%) total difference in survival probability, about a quarter of this (0.7%, 95%CI 0.5%–0.9%) is mediated by the dependence of treatment on stage and age at diagnosis, i.e. (8). Recall that we expected this effect to be small, except when there are particular interactions present, as is the case here (see eTable 2). Among women of a lower SES, there is a strong negative association between stage and treatment, meaning that those diagnosed at an advanced stage are less likely to receive major surgery. One possible interpretation would be that doctors and/or patients decide that treatment is not likely to be beneficial for patients with advanced disease, or that surgical treatment is substantially delayed for these patients due to tumor-reducing treatments such as chemotherapy being prioritised first. We see from eTable 2 that this negative association is much less pronounced for women of higher SES. Therefore, we would interpret this estimated 0.7% as the increase in survival that would be expected if the treatment decision, as a function of stage and age at diagnosis (and baseline confounders), would be made for poorer women as it is currently made for higher SES women. There is little evidence of further mediation through the treatment variable (estimated effect 0.02%, 95% CI: –0.05, 0.08%), and evidence of an effect through age and stage at diagnosis (estimated effect 0.7%, 95%CI 0.5%–0.8%). This would suggest that an additional 0.7% reduction in one-year mortality for lower SES women could be achieved if the distribution of age and stage at diagnosis (given year of diagnosis and region) were changed from that seen in lower SES women to that of higher SES women, a change that could perhaps be affected by encouraging better uptake of screening and other health-seeking behaviour among lower SES women.

5 Conclusions

Most mediation analyses involve multiple mediators, either because of scientific interest in multiple pathways, or because certain confounders are mediators at the same time. When the mediators are independent[21] or can be causally ordered[12], but share no (unmeasured) common causes, then distinct pathways via those mediators can be identified. We have shown that progress can be made even in the likely event that mediators share unmeasured common causes, or when the direction of causality is unknown. This is possible by redirecting the focus on less ambitious interventional (in)direct effects. In this article, we have focused on effects defined on the additive scale. We refer to eAppendix A for similar result for effects on other (e.g. multiplicative) scales.

The proposed effect decomposition is relatively easy to perform via a (Monte-Carlo based) regression approach. It delivers effects mediated via each of the mediators separately, but also via the mediators' dependence.

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Effect	Interpretation	Estimate	Bootstrap SE	95% CI lower	95% CI upper
$E(Y_1 - Y_0)$	Total causal effect	0.028	0.0028	0.023	0.034
$E(Y_{1M_{10}M_{20}} - Y_{0M_{10}M_{20}})$	Direct effect not through $\{M_1, M_2\}$	0.013	0.0028	0.008	0.018
$E(Y_{1M_{11}M_{21}} - Y_{1M_{10}M_{20}})$	Indirect effect through $\{M_1, M_2\}$	0.014	0.0014	0.011	0.016
$E(Y_{1M_{10}} - Y_{0M_{10}})$	Direct effect not through M_1	0.017	0.0028	0.011	0.022
$E(Y_{1M_{11}} - Y_{1M_{10}})$	Indirect effect through M_1	0.010	0.0011	0.008	0.012
$E(Y_{1M_{10}} - Y_{1M_{10}M_{20}})$	Indirect effect through M_2 only	0.003	0.0008	0.002	0.005

Table 1: Results of sequential mediation analysis

Effect	Estimate	Bootstrap SE	95% CI lower	95% CI upper
Total causal effect	0.028	0.0028	0.023	0.034
Interventional direct effect not through $\{M_1, M_2\}$ (5)	0.013	0.0027	0.008	0.018
Interventional indirect effect through M_1 (6)	0.007	0.0008	0.005	0.008
Interventional indirect effect through M_2 (7)	0.0002	0.0003	–0.0005	0.0008
Interventional indirect effect through the dependence of M_2 on M_1 (8)	0.007	0.0009	0.005	0.009

Table 2: Results of multiple mediator analysis based on interventional effects

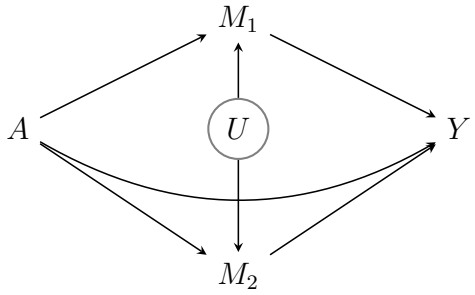

Figure 1: Causal diagram 1: M_1 and M_2 share an unmeasured common cause.

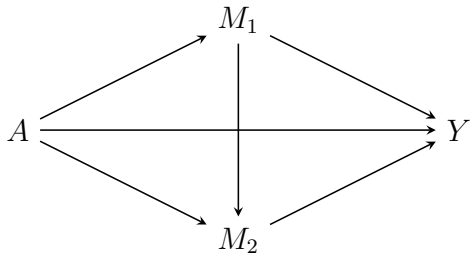

Figure 2: Causal diagram 2: M_1 affects M_2.

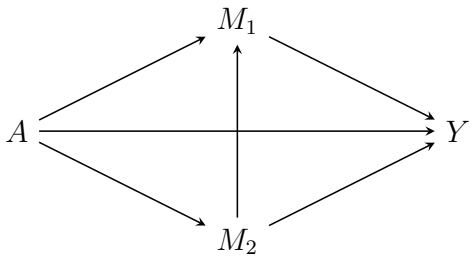

Figure 3: Causal diagram 3: M_2 affects M_1.

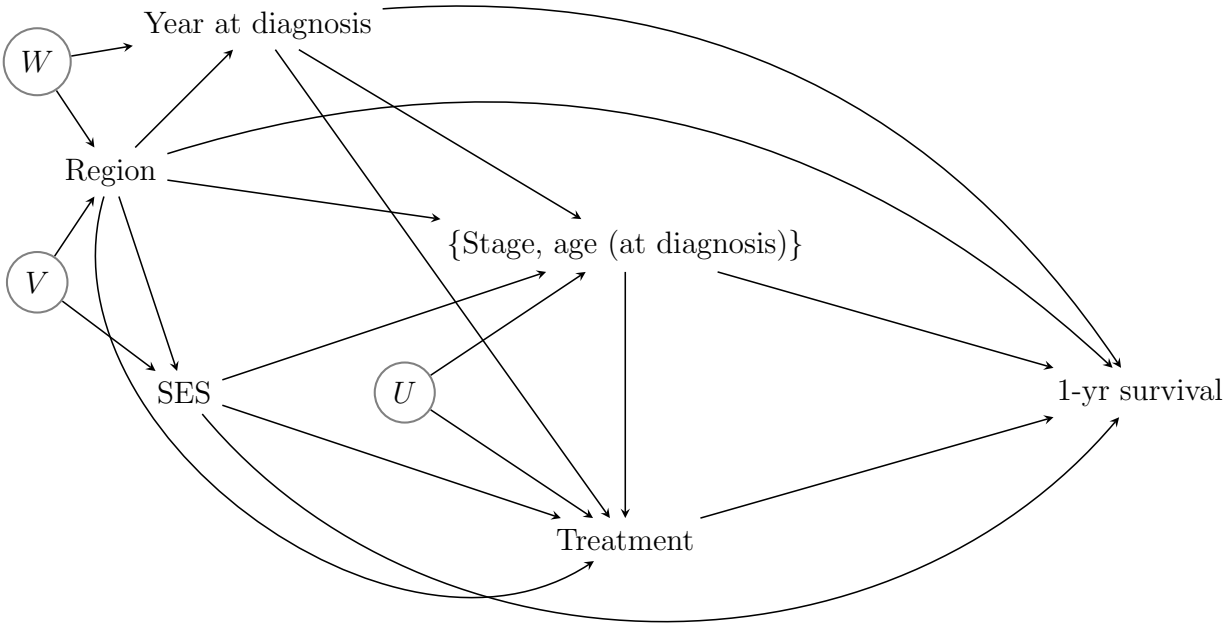

Figure 4: Causal diagram 4: data example.

Interventional effects for mediation analysis with multiple mediators: Supplementary Materials

March 22, 2016

eAppendix A: Other scales

All results in the article extend immediately to other scales. Let Y be a dichotomous outcome coded 0 or 1. Then the effect (5) can be written as

$$\frac{E\left[\sum_{m_1}\sum_{m_2} E\left(Y_{am_1m_2}|c\right) P(M_{1a^*}=m_1, M_{2a^*}=m_2|c)\right]}{E\left[\sum_{m_1}\sum_{m_2} E\left(Y_{a^*m_1m_2}|c\right) P(M_{1a^*}=m_1, M_{2a^*}=m_2|c)\right]}$$

on the relative risk scale, or as

$$\frac{E\left[\sum_{m_1}\sum_{m_2} E\left(Y_{am_1m_2}|c\right) P(M_{1a^*}=m_1, M_{2a^*}=m_2|c)\right]}{E\left[\sum_{m_1}\sum_{m_2} E\left(Y_{a^*m_1m_2}|c\right) P(M_{1a^*}=m_1, M_{2a^*}=m_2|c)\right]} \times \frac{E\left[\sum_{m_1}\sum_{m_2} E\left(1-Y_{a^*m_1m_2}|c\right) P(M_{1a^*}=m_1, M_{2a^*}=m_2|c)\right]}{E\left[\sum_{m_1}\sum_{m_2} E\left(1-Y_{am_1m_2}|c\right) P(M_{1a^*}=m_1, M_{2a^*}=m_2|c)\right]}$$

on the odds ratio scale. The effect (6) can be written as

$$\frac{E\left[\sum_{m_1}\sum_{m_2} E\left(Y_{am_1m_2}|c\right) P(M_{1a}=m_1|c)P(M_{2a^*}=m_2|c)\right]}{E\left[\sum_{m_1}\sum_{m_2} E\left(Y_{am_1m_2}|c\right) P(M_{1a^*}=m_1|c)P(M_{2a^*}=m_2|c)\right]}$$

on the relative risk scale, or as

$$\frac{E\left[\sum_{m_1}\sum_{m_2} E\left(Y_{am_1m_2}|c\right) P(M_{1a}=m_1|c)P(M_{2a^*}=m_2|c)\right]}{E\left[\sum_{m_1}\sum_{m_2} E\left(Y_{am_1m_2}|c\right) P(M_{1a^*}=m_1|c)P(M_{2a^*}=m_2|c)\right]} \times \frac{E\left[\sum_{m_1}\sum_{m_2} E\left(1-Y_{am_1m_2}|c\right) P(M_{1a^*}=m_1|c)P(M_{2a^*}=m_2|c)\right]}{E\left[\sum_{m_1}\sum_{m_2} E\left(1-Y_{am_1m_2}|c\right) P(M_{1a}=m_1|c)P(M_{2a^*}=m_2|c)\right]}$$

on the odds ratio scale. The effect (7) can likewise be computed. Finally, the effect (8) can be written as

$$\frac{E\left[\sum_{m_1}\sum_{m_2}E\left(Y_{am_1m_2}|c\right)P(M_{1a}=m_1,M_{2a}=m_2|c)\right]}{E\left[\sum_{m_1}\sum_{m_2}E\left(Y_{am_1m_2}|c\right)P(M_{1a}=m_1|c)P(M_{2a}=m_2|c)\right]}$$
$$\times\frac{E\left[\sum_{m_1}\sum_{m_2}E\left(Y_{a^*m_1m_2}|c\right)P(M_{1a^*}=m_1|c)P(M_{2a^*}=m_2|c)\right]}{E\left[\sum_{m_1}\sum_{m_2}E\left(Y_{a^*m_1m_2}|c\right)P(M_{1a^*}=m_1,M_{2a^*}=m_2|c)\right]}$$

on the relative risk scale, and as

$$\frac{E\left[\sum_{m_1}\sum_{m_2}E\left(Y_{am_1m_2}|c\right)P(M_{1a}=m_1,M_{2a}=m_2|c)\right]}{E\left[\sum_{m_1}\sum_{m_2}E\left(Y_{am_1m_2}|c\right)P(M_{1a}=m_1|c)P(M_{2a}=m_2|c)\right]}$$
$$\times\frac{E\left[\sum_{m_1}\sum_{m_2}E\left(Y_{a^*m_1m_2}|c\right)P(M_{1a^*}=m_1|c)P(M_{2a^*}=m_2|c)\right]}{E\left[\sum_{m_1}\sum_{m_2}E\left(Y_{a^*m_1m_2}|c\right)P(M_{1a^*}=m_1,M_{2a^*}=m_2|c)\right]}$$
$$\times\frac{E\left[\sum_{m_1}\sum_{m_2}E\left(1-Y_{am_1m_2}|c\right)P(M_{1a}=m_1|c)P(M_{2a}=m_2|c)\right]}{E\left[\sum_{m_1}\sum_{m_2}E\left(1-Y_{am_1m_2}|c\right)P(M_{1a}=m_1,M_{2a}=m_2|c)\right]}$$
$$\times\frac{E\left[\sum_{m_1}\sum_{m_2}E\left(1-Y_{a^*m_1m_2}|c\right)P(M_{1a^*}=m_1,M_{2a^*}=m_2|c)\right]}{E\left[\sum_{m_1}\sum_{m_2}E\left(1-Y_{a^*m_1m_2}|c\right)P(M_{1a^*}=m_1|c)P(M_{2a^*}=m_2|c)\right]}$$

on the odds ratio scale. Each of the components of these effects can be calculated using the Monte-Carlo approach proposed in the main text of the article.

eAppendix B: More than two mediators

With more than two mediators $M_1,...,M_t$, the effect of exposure on outcome can be decomposed into many different path-specific effects. We choose not to infer all of these effects for the following two reasons. First, the scientific interest typically lies in knowing the effects that are mediated through each of the mediators, but rarely lies in all path-specific effects ways. Second, strong untestable assumptions are required to be able to infer all path-specific effects, such as assumptions about the direction of the causal effects between the various mediators, and about the absence of unmeasured common causes of all mediators. In this Appendix, we will therefore concentrate on the following pathways. We define the average interventional direct effect of exposure on outcome that is not via any of the mediators as:

$$E\left[\sum_{m_1}...\sum_{m_t}\left\{E\left(Y_{am_1...m_t}|c\right)-E\left(Y_{a^*m_1...m_t}|c\right)\right\}P(M_{1a^*}=m_1,...,M_{ta^*}=m_t|c)\right].$$

This expresses the effect of exposure on outcome when fixing the joint distribution of all mediators. It corresponds to the effect $A \rightarrow Y$ in the causal diagram of Figure 1 below.

For each mediator $M_s, s = 1, ..., t$, we further define the average interventional indirect effect via M_s (but not its descendants) as

$$E\left[\sum_{m_1}...\sum_{m_t} E\left(Y_{am_1...m_t}|c\right)\left\{P(M_{sa}=m_s|c)-P(M_{sa^*}=m_s|c)\right\}\right.$$
$$\left.\times P(M_{1a}=m_1,...,M_{s-1,a}=m_{s-1}|c)P(M_{s+1,a^*}=m_{s+1},...,M_{ta^*}=m_t|c)\right]. \quad (1)$$

For $s = 1$, this corresponds to the effect $A \to M_1 \to Y$ in the causal diagram of Figure 1 below; for $s = 2$, this captures the combined effect along the pathways $A \to M_2 \to Y$ and $A \to M_1 \to M_2 \to Y$; for $s = 3$, it captures the combined effect along the pathways $A \to M_3 \to Y$, $A \to M_2 \to M_3 \to Y$, $A \to M_1 \to M_3 \to Y$ and $A \to M_1 \to M_2 \to M_3 \to Y$. Finally, it is easily seen that the difference between the total effect and the sum of the average interventional direct effect and the average interventional indirect effect via each of the mediators, captures an indirect effect of the exposure on the dependence between the mediators. Further work is needed to understand if the latter effect can be further decomposed into effects mediated via the dependence between specific subsets of mediators.

eAppendix C: More details on the data analysis

Data

In this Section, we give more detailed information on the NYCRIS data. Our analyses are based on all 29,580 women diagnosed with malignant, invasive breast cancer from 2000 to 2006 (inclusive) in NYCRIS who have information on cancer stage at diagnosis recorded; a further 2,589 women are excluded since this information is missing. For simplicity, we consider a binary SES exposure (A) which is whether or not the woman resides (at diagnosis) in an area (Lower Super Output Area) classified as belonging to the two most affluent quintiles of the national income distribution as defined by the income domain of the Indices of Multiple Deprivation (IMD) 2001. Since we have no direct information on screening, our first mediator (M_1) is a vector comprising age at diagnosis and cancer stage at diagnosis, classified as early (TNM stage 1 or 2) or advanced (TNM stage 3 or 4), considered jointly. Age and stage at diagnosis are strongly associated, likely due to the influence of screening and (latent) age at onset. Information on surgical treatment, obtained from a routinely collected national hospital dataset (Hospital Episode Statistics or HES), allows us to classify women either as having 'major surgery' (axillary dissection or other axillary nodal procedures, breast conserving surgery, mastectomy, and plastic surgery) or 'minor or no surgery' (other surgical procedures and none). This is our second mediator, M_2. The considered outcome (Y) is one-year survival from the date of diagnosis.

Calendar year at diagnosis and region (Yorkshire and The Humber, North East or North West) are considered as baseline confounders (C). As regards the causal structure of the mediators, we know that M_1 precedes M_2 and yet we can't rule out that they share unmeasured common causes, thus a combination of Figure 1 and Figure 3 of the main paper might apply. A possible causal diagram for the NYCRIS data is shown in Figure 4 of the main paper.

Sequential mediation analysis

We begin by performing the sequential mediation analysis described at the beginning of Section 3.1. First we note that with $C = \{\text{Region, Year at diagnosis}\}$ in lieu of C, assumptions (i')-(iii') hold if Figure 4 represents the underlying causal diagram (with M_1 in lieu of M_1). If we additionally assume (iv'), then we can identify the natural direct effect not mediated through either M_1 or M_2 or both using (3) and the corresponding natural indirect effect through either M_1 or M_2 using (4). To estimate (3) and (4) using the Monte-Carlo approach of Section 3.3, we need to fit a series of associational models:

Model 1: We fit a logistic regression model to one-year survival (Y) conditional on SES (A), Stage and Age at diagnosis (M_1), Treatment (M_2), and Region and Year of diagnosis (C) with all interactions between A, M_1 and M_2 included.

Model 2: We also fit a logistic regression model to Treatment (M_2) conditional on SES (A), Stage and Age at diagnosis (M_1), and Region and Year of diagnosis (C) with all interactions between A and M_1 included.

Model 3: We also fit a logistic regression model to Stage at diagnosis (one component of M_1) conditional on SES (A), Age at diagnosis (the other component of M_1), and Region and Year of diagnosis (C) with the interaction between SES and Age at diagnosis included.

Model 4: Finally, we fit a linear regression model to Age at diagnosis conditional on SES and Region and Year of diagnosis.

Note that this particular mediation analysis (with M_1 and M_2 considered as joint mediators) does not require any assumptions about the causal structure of the mediators; however, our associational models need to allow for correlation between them, and this is why we include Age in the model for Stage and Age and Stage in the model for Treatment. Also note that due to the very large sample size, there is little benefit in terms of precision (and a potential danger in terms of bias) in trying to find more parsimonious associational models than the above. Finally note that when using these results in the Monte-Carlo simulations to estimate (3), we will use not only the fitted value of the conditional expectation of age at diagnosis given SES and the confounders, but also the assumption that the errors from this model follow a normal distribution.

Tables 1–4 below give the full results of the individual regression models fitted to M_1, M_2 and Y. We use these results as described in Section 3.3 to estimate (3) and (4). Under assumptions (i)–(iv) with M_1 in lieu of M, we can additionally perform a mediation analysis with M_1 as the only mediator. Note that this involves assuming that U in Figure 4 does not exist. For this mediation analysis, models 3 and 4 above are used again, together with:

Model 1': A logistic regression model for one-year survival (Y) conditional on SES (A), Stage and Age at diagnosis (M_1), and Region and Year of diagnosis (C) with all interactions between A and M_1 included.

Models 1 and 1' are likely incompatible. We do not consider this to be of grave additional concern in practice, over and above the already substantial concern over parametric model misspecification in general.

We then use a Monte-Carlo approach to estimate the right-hand side of (1) in the main text with L empty and M_1 in lieu of M, which, under assumptions (i)–(iv) is the natural direct effect not through M_1. By subtracting from this the estimate of the natural direct effect not through either or both of the mediators, we obtain our sequential mediation analysis estimate of the natural indirect effect through M_2 alone.

Multiple mediator analysis based on interventional effects

We now perform the multiple mediator analysis described in Section 3.2, again using Monte-Carlo simulation as described at the end of Section 3.3. Details are given in the eAppendix. We make assumptions (i')–(iii'). In addition to models 1–4 above, we also now use:

Model 2': A logistic regression model for treatment (M_2) conditional on SES (A) and Region and Year of diagnosis (C).

The reason for specifying this model – which may be incompatible with model 2 – is that (6)–(8) all involve the distribution of M_{2a} given C, which can be substituted by the distribution of M_2 given A and C under assumption (iii). Displays (5), on the other hand, involves model 2, and (8) involves both. The results are given in Table 2.

Limitations

Our analyses are included mainly for illustration, to show how the proposed method can be applied in a realistic setting, and to show that even the most complicated effect, namely the mediated dependence (8), can have a meaningful interpretation when considered in an applied context. In order to focus on these interpretational issues, we made several simplifications that could be relaxed in future analyses of these data to gain a deeper and more reliable understanding of the reasons underlying socio-economic discrepancies in

breast cancer survival. Dichotomising both mediators has likely led to diluting the indirect effects and inflating the direct effect. In addition, dichotomising SES, the exposure, may have led to missing some more subtle effects across the income distribution. Focussing only on one-year survival may also mean that a different picture relating to longer term survival has been missed. In future work, we plan to relax all these simplifications in a more comprehensive substantive analysis, which will also involve sensitivity analyses to assess the impact of dropping women with unobserved stage at diagnosis. Another important limitation is the likely presence of unmeasured confounding, particularly of M_1 and Y by the latent age at disease onset, and of M_2 and Y by comorbidities, not available to us in the NYCRIS data. Sensitivity analyses to detect the plausible impact of such unmeasured confounding, as well as the robustness to the choice of a normality assumption for the errors from the model for age at diagnosis should also be explored.

eAppendix D: Stata code for the data analysis

```
gen xm1a=x*m1a
gen xm1b=x*m1b
gen xm2=x*m2
gen m1ab=m1a*m1b
gen m1am2=m1a*m2
gen m1bm2=m1b*m2
gen xm1ab=x*m1a*m1b
gen xm1am2=x*m1a*m2
gen xm1bm2=x*m1b*m2
gen m1abm2=m1a*m1b*m2
gen xm1abm2=x*m1a*m1b*m2

logit y x m1a m1b m2 xm1a xm1b xm2 m1ab m1am2 m1bm2 xm1ab xm1am2 xm1bm2 m1abm2 xm1abm2 i.c1 i.c2
logit m2 x m1a m1b xm1a xm1b m1ab xm1ab i.c1 i.c2
logit m1b x m1a xm1a i.c1 i.c2
reg m1a x i.c1 i.c2

cap program drop seqMC
cap program define seqMC, rclass
cap drop m1a_0-tce
qui set obs 6000000
qui replace c1=c1[_n-29580] if c1==.
qui replace c2=c2[_n-29580] if c2==.

qui reg m1a x i.c1 i.c2
qui gen m1a_0 = _b[_cons]+_b[2.c1]*(c1==2)+_b[3.c1]*(c1==3)+_b[2001.c2]*(c2==2001)+_b[2002.c2]*(c2==2002)
+_b[2003.c2]*(c2==2003)+_b[2004.c2]*(c2==2004) +_b[2005.c2]*(c2==2005)+_b[2006.c2]*(c2==2006)
+e(rmse)*rnormal()
qui gen m1a_1 = _b[_cons]+_b[2.c1]*(c1==2)+_b[3.c1]*(c1==3)+_b[2001.c2]*(c2==2001)+_b[2002.c2]*(c2==2002)
+_b[2003.c2]*(c2==2003)+_b[2004.c2]*(c2==2004) +_b[2005.c2]*(c2==2005)+_b[2006.c2]*(c2==2006)+_b[x]
+e(rmse)*rnormal()

qui logit m1b x m1a xm1a i.c1 i.c2
qui gen m1b_0 = runiform()<1/(1+exp(-(_b[_cons]+_b[2.c1]*(c1==2)+_b[3.c1]*(c1==3)+_b[2001.c2]*(c2==2001)
+_b[2002.c2]*(c2==2002)+_b[2003.c2]*(c2==2003)
+_b[2004.c2]*(c2==2004)+_b[2005.c2]*(c2==2005)+_b[2006.c2]*(c2==2006)+_b[m1a]*m1a_0)))
qui gen m1b_1 = runiform()<1/(1+exp(-(_b[_cons] +_b[2.c1]*(c1==2)+_b[3.c1]*(c1==3)+_b[2001.c2]*(c2==2001)
+_b[2002.c2]*(c2==2002)+_b[2003.c2]*(c2==2003)
+_b[2004.c2]*(c2==2004)+_b[2005.c2]*(c2==2005)+_b[2006.c2]*(c2==2006)+_b[x]+(_b[m1a]+_b[xm1a])*m1a_1)))
```

```
qui logit m2 x m1a m1b xm1a xm1b m1ab xm1ab i.c1 i.c2
qui gen m2_0 = runiform()<1/(1+exp(-(_b[_cons]+_b[2.c1]*(c1==2)+_b[3.c1]*(c1==3)+_b[2001.c2]*(c2==2001)
+_b[2002.c2]*(c2==2002)+_b[2003.c2]*(c2==2003) +_b[2004.c2]*(c2==2004)+_b[2005.c2]*(c2==2005)
+_b[2006.c2]*(c2==2006)+_b[m1a]*m1a_0+_b[m1b]*m1b_0+_b[m1ab]*m1a_0*m1b_0)))
qui gen m2_1 = runiform()<1/(1+exp(-(_b[_cons]+_b[2.c1]*(c1==2)+_b[3.c1]*(c1==3)+_b[2001.c2]*(c2==2001)
+_b[2002.c2]*(c2==2002)+_b[2003.c2]*(c2==2003) +_b[2004.c2]*(c2==2004)+_b[2005.c2]*(c2==2005)
+_b[2006.c2]*(c2==2006)+_b[x]+(_b[m1a]+_b[xm1a])*m1a_1+(_b[m1b]+_b[xm1b])*m1b_1
+(_b[m1ab]+_b[xm1ab])*m1a_1*m1b_1)))

qui gen m2_01 = runiform()<1/(1+exp(-(_b[_cons]+_b[2.c1]*(c1==2)+_b[3.c1]*(c1==3)+_b[2001.c2]*(c2==2001)
+_b[2002.c2]*(c2==2002)+_b[2003.c2]*(c2==2003) +_b[2004.c2]*(c2==2004)+_b[2005.c2]*(c2==2005)
+_b[2006.c2]*(c2==2006)+_b[m1a]*m1a_1+_b[m1b]*m1b_1+_b[m1ab]*m1a_1*m1b_1)))
qui gen m2_10 = runiform()<1/(1+exp(-(_b[_cons]+_b[2.c1]*(c1==2)+_b[3.c1]*(c1==3)+_b[2001.c2]*(c2==2001)
+_b[2002.c2]*(c2==2002)+_b[2003.c2]*(c2==2003) +_b[2004.c2]*(c2==2004)+_b[2005.c2]*(c2==2005)
+_b[2006.c2]*(c2==2006)+_b[x]+(_b[m1a]+_b[xm1a])*m1a_0+(_b[m1b]+_b[xm1b])*m1b_0+(_b[m1ab]
+_b[xm1ab])*m1a_0*m1b_0)))

qui logit y x m1a m1b m2 xm1a xm1b xm2 m1ab m1am2 m1bm2 xm1ab xm1am2 xm1bm2 m1abm2 xm1abm2 i.c1 i.c2
*M1 and M2 as joint mediators
qui gen y_00 = 1/(1+exp(-(_b[_cons]+_b[2.c1]*(c1==2)+_b[3.c1]*(c1==3)+_b[2001.c2]*(c2==2001)
+_b[2002.c2]*(c2==2002)+_b[2003.c2]*(c2==2003)+_b[2004.c2]*(c2==2004)+_b[2005.c2]*(c2==2005)
+_b[2006.c2]*(c2==2006)+_b[m1a]*m1a_0+_b[m1b]*m1b_0+_b[m2]*m2_0+_b[m1ab]*m1a_0*m1b_0
+_b[m1am2]*m1a_0*m2_0+_b[m1bm2]*m1b_0*m2_0+_b[m1abm2]*m1a_0*m1b_0*m2_0)))
qui gen y_10 = 1/(1+exp(-(_b[_cons]+_b[2.c1]*(c1==2)+_b[3.c1]*(c1==3)+_b[2001.c2]*(c2==2001)
+_b[2002.c2]*(c2==2002)+_b[2003.c2]*(c2==2003)+_b[2004.c2]*(c2==2004)+_b[2005.c2]*(c2==2005)
+_b[2006.c2]*(c2==2006)+_b[x]+(_b[m1a]+_b[xm1a])*m1a_0+(_b[m1b]+_b[xm1b])*m1b_0+(_b[m2]
+_b[xm2])*m2_0+(_b[m1ab]+_b[xm1ab])*m1a_0*m1b_0+(_b[m1am2]+_b[xm1am2])*m1a_0*m2_0+
(_b[m1bm2]+_b[xm1bm2])*m1b_0*m2_0+(_b[m1abm2]+_b[xm1abm2])*m1a_0*m1b_0*m2_0)))
qui gen y_01 = 1/(1+exp(-(_b[_cons]+_b[2.c1]*(c1==2)+_b[3.c1]*(c1==3)+_b[2001.c2]*(c2==2001)
+_b[2002.c2]*(c2==2002)+_b[2003.c2]*(c2==2003)+_b[2004.c2]*(c2==2004)+_b[2005.c2]*(c2==2005)
+_b[2006.c2]*(c2==2006)+_b[m1a]*m1a_1+_b[m1b]*m1b_1+_b[m2]*m2_1+_b[m1ab]*m1a_1*m1b_1
+_b[m1am2]*m1a_1*m2_1+_b[m1bm2]*m1b_1*m2_1+_b[m1abm2]*m1a_1*m1b_1*m2_1)))
qui gen y_11 = 1/(1+exp(-(_b[_cons]+_b[2.c1]*(c1==2)+_b[3.c1]*(c1==3)+_b[2001.c2]*(c2==2001)
+_b[2002.c2]*(c2==2002)+_b[2003.c2]*(c2==2003) +_b[2004.c2]*(c2==2004)+_b[2005.c2]*(c2==2005)
+_b[2006.c2]*(c2==2006)+_b[x]+(_b[m1a]+_b[xm1a])*m1a_1+(_b[m1b]+_b[xm1b])*m1b_1+(_b[m2]
+_b[xm2])*m2_1+(_b[m1ab]+_b[xm1ab])*m1a_1*m1b_1+(_b[m1am2]+_b[xm1am2])*m1a_1*m2_1+
(_b[m1bm2]+_b[xm1bm2])*m1b_1*m2_1+(_b[m1abm2]+_b[xm1abm2])*m1a_1*m1b_1*m2_1)))

*M1 as the only mediator
qui gen y_10_b = 1/(1+exp(-(_b[_cons]+_b[2.c1]*(c1==2)+_b[3.c1]*(c1==3)+_b[2001.c2]*(c2==2001)
+_b[2002.c2]*(c2==2002)+_b[2003.c2]*(c2==2003)+_b[2004.c2]*(c2==2004)+_b[2005.c2]*(c2==2005)
+_b[2006.c2]*(c2==2006)+_b[x]+(_b[m1a]+_b[xm1a])*m1a_0+(_b[m1b]+_b[xm1b])*m1b_0
+(_b[m2]+_b[xm2])*m2_10+(_b[m1ab]+_b[xm1ab])*m1a_0*m1b_0+(_b[m1am2]+_b[xm1am2])*m1a_0*m2_10
+(_b[m1bm2]+_b[xm1bm2])*m1b_0*m2_10+(_b[m1abm2]+_b[xm1abm2])*m1a_0*m1b_0*m2_10)))

qui gen NDE_M1M2=y_10-y_00
qui gen NIE_M1M2=y_11-y_10
qui gen NDE_M1=y_10_b-y_00
qui gen NIE_M1=y_11-y_10_b
qui gen NIE_M2alone=y_10_b-y_10

qui logit y x i.c1 i.c2
qui gen y1=1/(1+exp(-(_b[_cons]+_b[x]+_b[2.c1]*(c1==2)+_b[3.c1]*(c1==3)+_b[2001.c2]*(c2==2001)
+_b[2002.c2]*(c2==2002)+_b[2003.c2]*(c2==2003)+_b[2004.c2]*(c2==2004)+_b[2005.c2]*(c2==2005)
+_b[2006.c2]*(c2==2006))))
qui gen y0=1/(1+exp(-(_b[_cons]+_b[2.c1]*(c1==2)+_b[3.c1]*(c1==3)+_b[2001.c2]*(c2==2001)
+_b[2002.c2]*(c2==2002)+_b[2003.c2]*(c2==2003)+_b[2004.c2]*(c2==2004)
+_b[2005.c2]*(c2==2005)+_b[2006.c2]*(c2==2006))))
qui gen tce=y1-y0
qui summ tce
return scalar tce=r(mean)
```

```
qui summ NDE_M1M2
return scalar NDE_M1M2=r(mean)
qui summ NIE_M1M2
return scalar NIE_M1M2=r(mean)
qui summ NDE_M1
return scalar NDE_M1=r(mean)
qui summ NIE_M1
return scalar NIE_M1=r(mean)
qui summ NIE_M2alone
return scalar NIE_M2alone=r(mean)
end


cap program drop MMintMC
cap program define MMintMC, rclass
cap drop m1a_0-tce
qui set obs 6000000
qui replace c1=c1[_n-29580] if c1==.
qui replace c2=c2[_n-29580] if c2==.

qui reg m1a x i.c1 i.c2
qui gen m1a_0 = _b[_cons]+_b[2.c1]*(c1==2)+_b[3.c1]*(c1==3)+_b[2001.c2]*(c2==2001)
+_b[2002.c2]*(c2==2002)+_b[2003.c2]*(c2==2003)+_b[2004.c2]*(c2==2004)+_b[2005.c2]*(c2==2005)
+_b[2006.c2]*(c2==2006)+e(rmse)*rnormal()
qui gen m1a_1 = _b[_cons]+_b[2.c1]*(c1==2)+_b[3.c1]*(c1==3)+_b[2001.c2]*(c2==2001)
+_b[2002.c2]*(c2==2002)+_b[2003.c2]*(c2==2003)+_b[2004.c2]*(c2==2004)+_b[2005.c2]*(c2==2005)
+_b[2006.c2]*(c2==2006)+_b[x]
+e(rmse)*rnormal()

qui logit m1b x m1a xm1a i.c1 i.c2
qui gen m1b_0 = runiform()<1/(1+exp(-(_b[_cons]+_b[2.c1]*(c1==2)+_b[3.c1]*(c1==3)+_b[2001.c2]*(c2==2001)
+_b[2002.c2]*(c2==2002)+_b[2003.c2]*(c2==2003)+_b[2004.c2]*(c2==2004)+_b[2005.c2]*(c2==2005)
+_b[2006.c2]*(c2==2006)+_b[m1a]*m1a_0)))
qui gen m1b_1 = runiform()<1/(1+exp(-(_b[_cons]+_b[2.c1]*(c1==2)+_b[3.c1]*(c1==3)+_b[2001.c2]*(c2==2001)
+_b[2002.c2]*(c2==2002)+_b[2003.c2]*(c2==2003)+_b[2004.c2]*(c2==2004)+_b[2005.c2]*(c2==2005)
+_b[2006.c2]*(c2==2006)+_b[x]+(_b[m1a]+_b[xm1a])*m1a_1)))

qui logit m2 x m1a m1b xm1a xm1b m1ab xm1ab i.c1 i.c2
qui gen m2_0_cond = runiform()<1/(1+exp(-(_b[_cons]+_b[2.c1]*(c1==2)+_b[3.c1]*(c1==3)+_b[2001.c2]*(c2==2001)
+_b[2002.c2]*(c2==2002)+_b[2003.c2]*(c2==2003)+_b[2004.c2]*(c2==2004)+_b[2005.c2]*(c2==2005)
+_b[2006.c2]*(c2==2006)+_b[m1a]*m1a_0+_b[m1b]*m1b_0+_b[m1ab]*m1a_0*m1b_0)))
qui gen m2_1_cond = runiform()<1/(1+exp(-(_b[_cons]+_b[2.c1]*(c1==2)+_b[3.c1]*(c1==3)+_b[2001.c2]*(c2==2001)
+_b[2002.c2]*(c2==2002)+_b[2003.c2]*(c2==2003)+_b[2004.c2]*(c2==2004)+_b[2005.c2]*(c2==2005)
+_b[2006.c2]*(c2==2006)+_b[x]+(_b[m1a]+_b[xm1a])*m1a_1+(_b[m1b]+_b[xm1b])*m1b_1
+(_b[m1ab]+_b[xm1ab])*m1a_1*m1b_1)))

qui logit m2 x i.c1 i.c2
qui gen m2_0_marg = runiform()<1/(1+exp(-(_b[_cons]+_b[2.c1]*(c1==2)+_b[3.c1]*(c1==3)+_b[2001.c2]*(c2==2001)
+_b[2002.c2]*(c2==2002)+_b[2003.c2]*(c2==2003)+_b[2004.c2]*(c2==2004)+_b[2005.c2]*(c2==2005)
+_b[2006.c2]*(c2==2006))))
qui gen m2_1_marg = runiform()<1/(1+exp(-(_b[_cons]+_b[2.c1]*(c1==2)+_b[3.c1]*(c1==3)+_b[2001.c2]*(c2==2001)
+_b[2002.c2]*(c2==2002)+_b[2003.c2]*(c2==2003)+_b[2004.c2]*(c2==2004)+_b[2005.c2]*(c2==2005)
+_b[2006.c2]*(c2==2006)+_b[x])))

qui logit y x m1a m1b m2 xm1a xm1b xm2 m1ab m1am2 m1bm2 xm1ab xm1am2 xm1bm2 m1abm2 xm1abm2 i.c1 i.c2
qui gen y_000_7 = 1/(1+exp(-(_b[_cons]+_b[2.c1]*(c1==2)+_b[3.c1]*(c1==3)+_b[2001.c2]*(c2==2001)
+_b[2002.c2]*(c2==2002)+_b[2003.c2]*(c2==2003)+_b[2004.c2]*(c2==2004)+_b[2005.c2]*(c2==2005)
+_b[2006.c2]*(c2==2006)+_b[m1a]*m1a_0+_b[m1b]*m1b_0+_b[m2]*m2_0_cond
+_b[m1ab]*m1a_0*m1b_0+_b[m1am2]*m1a_0*m2_0_cond+_b[m1bm2]*m1b_0*m2_0_cond
+_b[m1abm2]*m1a_0*m1b_0*m2_0_cond)))
qui gen y_100_7 = 1/(1+exp(-(_b[_cons]+_b[2.c1]*(c1==2)+_b[3.c1]*(c1==3)+_b[2001.c2]*(c2==2001)
```

```
+_b[2002.c2]*(c2==2002)+_b[2003.c2]*(c2==2003)+_b[2004.c2]*(c2==2004)+_b[2005.c2]*(c2==2005)
+_b[2006.c2]*(c2==2006)+_b[x]+(_b[m1a]+_b[xm1a])*m1a_0+(_b[m1b]+_b[xm1b])*m1b_0
+(_b[m2]+_b[xm2])*m2_0_cond+(_b[m1ab]+_b[xm1ab])*m1a_0*m1b_0+(_b[m1am2]
+_b[xm1am2])*m1a_0*m2_0_cond+(_b[m1bm2]+_b[xm1bm2])*m1b_0*m2_0_cond+
(_b[m1abm2]+_b[xm1abm2])*m1a_0*m1b_0*m2_0_cond)))

qui gen y_110_8 = 1/(1+exp(-(_b[_cons]+_b[2.c1]*(c1==2)+_b[3.c1]*(c1==3)+_b[2001.c2]*(c2==2001)
+_b[2002.c2]*(c2==2002)+_b[2003.c2]*(c2==2003)/// +_b[2004.c2]*(c2==2004)+_b[2005.c2]*(c2==2005)
+_b[2006.c2]*(c2==2006)+_b[x]+(_b[m1a]+_b[xm1a])*m1a_1+(_b[m1b]+_b[xm1b])*m1b_1
+(_b[m2]+_b[xm2])*m2_0_marg+(_b[m1ab]+_b[xm1ab])*m1a_1*m1b_1
+(_b[m1am2]+_b[xm1am2])*m1a_1*m2_0_marg+(_b[m1bm2]
+_b[xm1bm2])*m1b_1*m2_0_marg+(_b[m1abm2]+_b[xm1abm2])*m1a_1*m1b_1*m2_0_marg)))
qui gen y_100_8 = 1/(1+exp(-(_b[_cons]+_b[2.c1]*(c1==2)+_b[3.c1]*(c1==3)+_b[2001.c2]*(c2==2001)
+_b[2002.c2]*(c2==2002)+_b[2003.c2]*(c2==2003)+_b[2004.c2]*(c2==2004)+_b[2005.c2]*(c2==2005)
+_b[2006.c2]*(c2==2006)+_b[x]+(_b[m1a]+_b[xm1a])*m1a_0+(_b[m1b]+_b[xm1b])*m1b_0
+(_b[m2]+_b[xm2])*m2_0_marg+(_b[m1ab]+_b[xm1ab])*m1a_0*m1b_0
+(_b[m1am2]+_b[xm1am2])*m1a_0*m2_0_marg+(_b[m1bm2]+_b[xm1bm2])*m1b_0*m2_0_marg
+(_b[m1abm2]+_b[xm1abm2])*m1a_0*m1b_0*m2_0_marg)))

qui gen y_101_9 = 1/(1+exp(-(_b[_cons]+_b[2.c1]*(c1==2)+_b[3.c1]*(c1==3)+_b[2001.c2]*(c2==2001)
+_b[2002.c2]*(c2==2002)+_b[2003.c2]*(c2==2003)+_b[2004.c2]*(c2==2004)+_b[2005.c2]*(c2==2005)
+_b[2006.c2]*(c2==2006)_b[x]+(_b[m1a]+_b[xm1a])*m1a_0+(_b[m1b]+_b[xm1b])*m1b_0
+(_b[m2]+_b[xm2])*m2_1_marg+(_b[m1ab]+_b[xm1ab])*m1a_0*m1b_0
+(_b[m1am2]+_b[xm1am2])*m1a_0*m2_1_marg+(_b[m1bm2]+_b[xm1bm2])*m1b_0*m2_1_marg
+(_b[m1abm2]+_b[xm1abm2])*m1a_0*m1b_0*m2_1_marg)))

qui gen y_111_10cond = 1/(1+exp(-(_b[_cons]+_b[2.c1]*(c1==2)+_b[3.c1]*(c1==3)+_b[2001.c2]*(c2==2001)
+_b[2002.c2]*(c2==2002)+_b[2003.c2]*(c2==2003)+_b[2004.c2]*(c2==2004)+_b[2005.c2]*(c2==2005)
+_b[2006.c2]*(c2==2006)+_b[x]+(_b[m1a]+_b[xm1a])*m1a_1+(_b[m1b]+_b[xm1b])*m1b_1
+(_b[m2]+_b[xm2])*m2_1_cond+(_b[m1ab]+_b[xm1ab])*m1a_1*m1b_1
+(_b[m1am2]+_b[xm1am2])*m1a_1*m2_1_cond+(_b[m1bm2]+_b[xm1bm2])*m1b_1*m2_1_cond
+(_b[m1abm2]+_b[xm1abm2])*m1a_1*m1b_1*m2_1_cond)))
qui gen y_111_10marg = 1/(1+exp(-(_b[_cons]+_b[2.c1]*(c1==2)+_b[3.c1]*(c1==3)+_b[2001.c2]*(c2==2001)
+_b[2002.c2]*(c2==2002)+_b[2003.c2]*(c2==2003)+_b[2004.c2]*(c2==2004)+_b[2005.c2]*(c2==2005)
+_b[2006.c2]*(c2==2006)+_b[x]+(_b[m1a]+_b[xm1a])*m1a_1+(_b[m1b]+_b[xm1b])*m1b_1
+(_b[m2]+_b[xm2])*m2_1_marg+(_b[m1ab]+_b[xm1ab])*m1a_1*m1b_1
+(_b[m1am2]+_b[xm1am2])*m1a_1*m2_1_marg+(_b[m1bm2]+_b[xm1bm2])*m1b_1*m2_1_marg
+(_b[m1abm2]+_b[xm1abm2])*m1a_1*m1b_1*m2_1_marg)))

*display 7
qui gen d7=y_100_7-y_000_7

*display 8
qui gen d8=y_110_8-y_100_8

*display 9
qui gen d9=y_101_9-y_100_8

*display 10
qui gen d10=y_111_10cond-y_111_10marg-y_100_7+y_100_8

qui logit y x i.c1 i.c2
qui gen y1=1/(1+exp(-(_b[_cons]+_b[x]+_b[2.c1]*(c1==2)+_b[3.c1]*(c1==3)+_b[2001.c2]*(c2==2001)
+_b[2002.c2]*(c2==2002)+_b[2003.c2]*(c2==2003)+_b[2004.c2]*(c2==2004)+_b[2005.c2]*(c2==2005)
+_b[2006.c2]*(c2==2006))))
qui gen y0=1/(1+exp(-(_b[_cons]+_b[2.c1]*(c1==2)+_b[3.c1]*(c1==3)+_b[2001.c2]*(c2==2001)
+_b[2002.c2]*(c2==2002)+_b[2003.c2]*(c2==2003)+_b[2004.c2]*(c2==2004)+_b[2005.c2]*(c2==2005)
+_b[2006.c2]*(c2==2006))))
qui gen tce=y1-y0
qui summ tce
return scalar tce=r(mean)
```

```
qui summ d7
return scalar d7=r(mean)
qui summ d8
return scalar d8=r(mean)
qui summ d9
return scalar d9=r(mean)
qui summ d10
return scalar d10=r(mean)
end

bootstrap r(tce) r(d7) r(d8) r(d9) r(d10), reps(1000): MMintMC
bootstrap r(tce) r(NDE_M1M2) r(NIE_M1M2) r(NDE_M1) r(NIE_M1) r(NIE_M2alone), reps(1000): seqMC
```

	Estimate	SE	95% CI	
			lower	upper
Baseline odds*	23.74	3.51	17.77	31.72
Conditional odds ratios				
SES				
higher	1.871	0.411	1.216	2.877
Age at diagnosis (yrs)**	0.931	0.005	0.920	0.942
Stage				
advanced	0.060	0.009	0.045	0.079
Treatment				
major	2.975	0.443	2.222	3.984
SES×Agediag	0.988	0.010	0.968	1.009
SES×Stage	0.657	0.164	0.402	1.073
SES×Treat	0.954	0.257	0.563	1.617
Agediag×Stage	1.056	0.008	1.041	1.071
Agediag×Treat	1.008	0.009	0.992	1.025
Stage×Treat	2.140	0.409	1.472	3.111
SES×Agediag×Stage	1.003	0.013	0.978	1.028
SES×Agediag×Treat	1.002	0.016	0.971	1.033
SES×Stage×Treat	1.090	0.376	0.555	2.142
Agediag×Stage×Treat	0.978	0.011	0.956	1.001
SES×Agediag×Stage×Treat	1.012	0.022	0.970	1.056
Region				
North-West	0.774	0.115	0.579	1.035
Yorks	0.991	0.059	0.881	1.114
Year of diagnosis				
2001	0.830	0.088	0.674	1.022
2002	0.942	0.102	0.762	1.165
2003	1.019	0.109	0.827	1.256
2004	0.954	0.103	0.772	1.180
2005	1.006	0.108	0.815	1.243
2006	1.092	0.120	0.879	1.355

Table 1: Results of logistic regression of one-year survival (Y) on SES (A), Stage and Age at diagnosis (M_1), Treatment (M_2), and Region and Year of diagnosis (C) with all interactions between A, M_1 and M_2. One-yr survival is coded 1 for survival and 0 for death.

* estimated odds of survival for women diagnosed in the North East region in 2000, with low SES, age at diagnosis 62 years, early stage and minor or no surgery

** centred at the mean age at diagnosis (61.8 years)

	Estimate	SE	95% CI	
			lower	upper
Baseline odds*	4.796	0.226	4.373	5.261
Conditional odds ratios				
SES				
higher	0.725	0.026	0.677	0.777
Age at diagnosis (yrs)**	0.937	0.002	0.934	0.941
Stage				
advanced	0.186	0.009	0.169	0.205
SES×Agediag	1.033	0.003	1.027	1.038
SES×Stage	1.799	0.152	1.525	2.123
Agediag×Stage	1.014	0.004	1.007	1.021
SES×Agediag×Stage	0.974	0.006	0.962	0.985
Region				
North-West	1.806	0.155	1.526	2.138
Yorks	0.795	0.025	0.747	0.846
Year of diagnosis				
2001	1.089	0.061	0.976	1.214
2002	1.119	0.062	1.003	1.249
2003	1.248	0.069	1.120	1.390
2004	1.429	0.081	1.280	1.596
2005	1.411	0.079	1.265	1.575
2006	1.442	0.082	1.291	1.611

Table 2: Results of logistic regression of Treatment (M_2) on SES (A), Stage and Age at diagnosis (M_1), and Region and Year of diagnosis (C) with all interactions between A and M_1. Treatment is coded 1 for major surgery and 0 for minor or no surgery.
* estimated odds of major surgery for women diagnosed in the North East region in 2000, with low SES, age at diagnosis 62 years and early stage.
** centred at the mean age at diagnosis (61.8 years)

	Estimate	SE	95% CI	
			lower	upper
Baseline odds*	0.164	0.009	0.148	0.182
Conditional odds ratios				
SES				
higher	0.757	0.029	0.702	0.816
Age at diagnosis (yrs)**	1.020	0.002	1.017	1.023
SES×Agediag	1.002	0.003	0.996	1.007
Region				
North-West	0.655	0.066	0.538	0.797
Yorks	1.059	0.040	0.985	1.140
Year of diagnosis				
2001	0.917	0.062	0.804	1.047
2002	0.950	0.064	0.833	1.083
2003	0.951	0.062	0.837	1.082
2004	0.845	0.057	0.741	0.965
2005	0.872	0.058	0.765	0.994
2006	0.909	0.061	0.798	1.036

Table 3: Results of logistic regression of Stage at diagnosis (one component of M_1) on SES (A), Age at diagnosis (the other component of M_1), and Region and Year of diagnosis (C) including the interaction between SES and age at diagnosis. Stage at diagnosis is coded 1 for advanced and 0 for early.

* estimated odds of being diagnosed at an advanced stage for women diagnosed in the North East region in 2000, with low SES and aged 62 years at diagnosis.

** centred at the mean age at diagnosis (61.8 years)

	Estimate	SE	95% CI	
			lower	upper
Baseline mean (intercept)*	61.36	0.247	60.88	61.85
Mean differences / slopes				
SES				
higher	–1.53	0.168	–1.86	–1.20
Region				
North-West	–0.488	0.383	–1.24	0.262
Yorks	0.442	0.170	0.109	0.775
Year of diagnosis				
2001	0.616	0.309	0.011	1.22
2002	0.620	0.309	0.014	1.22
2003	1.36	0.303	0.765	1.95
2004	0.737	0.303	0.142	1.33
2005	1.13	0.302	0.542	1.73
2006	0.958	0.305	0.360	1.56
Residual standard deviation				
	13.87			

Table 4: Results of linear regression of Age at diagnosis (one component of M_1, in years) on SES (A) and Region and Year of diagnosis (C).
* estimated mean age at diagnosis for women diagnosed in the North East region in 2000, with low SES.

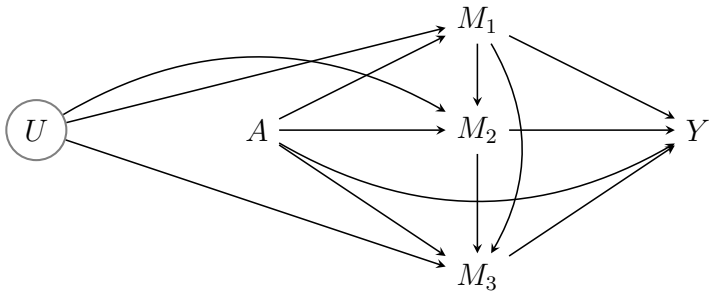

Figure 1: Causal diagram 5: multiple mediators.