Using dynamic path analysis to estimate a mediation effect through a survival variable

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Declaration

I, Felicity Clemens, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

Time-to-event composite outcomes are common in clinical trials. Reporting guidelines recommend that the treatment effect estimate for each component event be reported. In the setting with two components, when one precedes the other, there may be interest in estimating the indirect effect of treatment on the final event through the intermediate one. This thesis proposes a pragmatic solution to this problem.

The motivating example is a dataset pooled from three clinical trials investigating a treatment effect on time to cancer progression or death in patients with advanced non-small cell lung cancer. There is interest in exploring whether treatment had an indirect effect on death through its effect on progression. This problem could be addressed by implementing dynamic path analysis, which combines linear regression and additive hazards models to estimate the indirect effect of an exposure on a time-to-event outcome. However, it is only appropriate for settings with continuous intermediate variables. The thesis therefore suggests an extension dealing with settings where both intermediate and final events are time-to-event variables. This extension is described and tested using simulation studies. The results suggest that this method gives rise to results very close to those predicted, when the rate of the intermediate event is not very fast relative to the final event rate. When the intermediate event occurs much more quickly than the final event, depletion of individuals from the risk set by experiencing the final event causes divergence between the estimated and expected indirect treatment effects.

The extension of dynamic path analysis is implemented for the clinical trials dataset, showing a protective indirect effect of treatment on death through cancer progression.

The thesis concludes that the extension of dynamic path analysis to settings with a time-to-event intermediate outcome is feasible, although some results should be interpreted with care.

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Dedication

This thesis is dedicated to my parents, Bev and Herb Clemens, who taught me never to give up; to my husband Peter, who is my rock; and to my children, Theresa and Edmund, who make everything worthwhile.

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1 Introduction

1.1 Composite outcomes in clinical trials

Composite outcomes are commonly used in randomised clinical trials to increase the expected number of events observed during a selected follow-up period and therefore the power of the trial [1-3]. A composite outcome combines two or more events of interest into a single endpoint, so that the endpoint is achieved if one or more of these component events has occurred by the end of follow-up.

The component events chosen to form a composite outcome often represent related aspects of a disease [4, 5]. To aid interpretation it is generally recommended that the analysis of trials with a composite outcome report both the estimated treatment effect on the composite outcome, and cause-specific treatment effects for each component event. This addresses the possibility that a treatment may affect one component event differently from the other(s), thus leading to misleading inferences if the difference is ignored [1, 3, 6]. It also ensures that the effect of a treatment on different aspects of a disease can be captured [5, 7].

Time-to-event composite outcomes in clinical trials arise when a trial endpoint consists of the timing of the first of a number of events of interest. They are commonly used in clinical areas where the rate of occurrence of major events such as death is low [1-3]. For example, Lim et al [6] conducted a survey of clinical trial reports in the area of cardiovascular medicine, identifying 304 trials published between 2000 and 2007 that used composite outcomes, of which 226 (73.7%) had a time-to-event composite outcome.

Component events chosen to form a time-to-event composite outcome are often causally linked steps in the same disease process. In this case, considering a composite outcome defined by two components, they comprise a final and an intermediate event, with the latter likely to be a strong predictor of the final event [5]. In general, occurrence of the intermediate event does not prevent occurrence of the final event. The intermediate event may be referred to as the proximal event, and the final event the distal event.

1.2 Motivating example: the Zactima trials

This thesis is motivated by the analysis of the Zactima trials, a suite of three randomised controlled trials funded and carried out by AstraZeneca. The trials aimed to estimate the effect of a treatment, Zactima, for non-small-cell lung cancer (NSCLC) patients. The trials were carried out between 2006 and 2008, and results were published between 2010 and 2012 [8-10]. Zactima is the trade name for vandetanib, which had previously been licensed for use in medullary thryroid cancer.

The trials divided patients into a treatment group receiving Zactima administered together with an established treatment, and a placebo group receiving placebo therapy and the same established treatment. The three trials differed principally in terms of the established treatment offered, respectively docetaxel, pemetrexed and best supportive care (see [11, 12]). In addition, the trial offering best supportive care recruited patients who had failed one or two prior chemotherapy regimens, while the other two trials recruited patients who had failed first-line therapy only. The primary outcome for two of the three trials (and a secondary outcome for the third trial) was a composite of time to cancer progression or death, whichever came first, referred to as progression-free survival (PFS).

Two of the three trials found a statistically significant protective effect of Zactima on PFS with hazard ratios of 0.79 (97.6% CI 0.70, 0.90) and 0.63 (95.2% CI 0.54, 0.74) respectively [8, 9]; the third trial found a borderline effect of Zactima on PFS with a hazard ratio of 0.86 (97.6% CI 0.69, 1.06) [10]. All three trials found that the effect of Zactima on death was protective but not statistically significant [8-10].

The authors inferred from these results that Zactima might have a protective effect on cancer progression, but not on death. However further investigation is called upon to support this, and also whether the effect of treatment on death is or is not transmitted through its effect on cancer progression. The first question would involve the study of the cause specific effects on treatment on the components of the composite outcome, and the second the study of the treatment effect on death through its effect on cancer progression.

1.3 Cause-specific analysis of treatment effects in the Zactima trials

The first step in investigating the effects of treatment in the Zactima trials is to pool the data from the three trials, given their design similarities (but also considering whether treatment effects are homogeneous across the trials), and estimate the effects of treatment on the rate of cancer progression, and separately on the rate of death, following recommendations about reporting the cause-specific effects of treatment on the component events of a composite outcome [1, 3, 6]. This analysis can be performed in the first instance using the familiar Cox proportional hazards model [13] with treatment as the explanatory variable and cancer progression or death as the outcome, in each case controlling for systematic differences across the three trials by including specific trial indicators (and assessing whether there is evidence of treatment-trial interaction). Assuming no treatment-trial interaction, and proportionality of effects, the first model would give rise to the estimated (adjusted) hazard ratio for the effect of treatment on cancer progression, conditional on surviving; the second to the estimated (adjusted) hazard ratio for the effect of treatment on death. The model for the mortality rate defined above does not include cancer progression, therefore its estimate represents the overall effect of treatment on death, in the sense that it does not control for the possible mediating role played by cancer progression.

This approach, however, ignores the association between cancer progression and death. As discussed above, the presence of two time-to-event component events, one of which can only precede the other, and which are both manifestations of the disease process, suggests that secondary analyses should also examine the relationship between cancer progression and death. By partitioning the overall effect into indirect and indirect effects, mediation analysis can be used to address this problem.

1.4 Outline of mediation analysis

The general setting for mediation analysis considers an exposure or treatment (henceforward referred to as a treatment, for simplicity), an outcome, and a mediator, which may be affected by treatment and itself precedes and affects the outcome (see for example [14, 15]). In the

present context, where the outcome and mediator are both time-to-event variables, the mediator may be referred to as an event mediator.

The overall effect of treatment on an outcome, as described in the previous section, can be thought of as its effect working both through a mediator and along a pathway that does not include the mediator. The direct effect of treatment on an outcome is the effect of treatment working through a pathway that does not include the mediator. Conversely, the indirect effect of treatment on the outcome is that part of the effect of treatment which works specifically through the mediator (see for example [14, 16]).

As described above, the overall effect of treatment on death can be estimated in the Zactima trials by fitting a Cox proportional hazards with treatment as the explanatory variable and death as the outcome (controlling for trial characteristics). By analogy, one might infer that the direct effect of treatment on death could be estimated by fitting the same model but additionally adjusting for cancer progression. In general, although this strategy is commonly recommended as means of estimating a direct effect [17], the inclusion of cancer progression as a covariate does not necessarily guarantee the estimation of the direct effect of treatment because the hazard ratio is non-collapsible and therefore conditioning on the mediator does not lead to the direct effect of the exposure [14, 18].

Similarly, the Cox proportional hazards model cannot be used to estimate the indirect effect of treatment on death through progression by adopting the multiplication of coefficients method used in traditional mediation analysis deriving from the path tracing rules of path analysis (even if this were carried out using the log hazard ratios). This is because the multiplication of coefficients derives from rules that implement the partitioning of correlations, and hence of relations among normally distributed variables [14, 17, 19, 20].

In fact, there are no general statistical methods specifically developed for estimating the direct and indirect treatment effect on a time-to-event outcome through a time-to-event mediator in classical mediation analysis. Solutions have been proposed within the framework of counterfactual-based mediation analysis [14, 16, 21-23], although only recently and with a wide range of definitions. For example, natural direct effects are defined in terms of how much the average outcome would change if treatment were set at different levels (possibly contrary to fact) while the mediator were set at the level that it would take had exposure been set at its reference value (possibly contrary to fact). Natural indirect effects are defined in terms of the average change in outcome that would occur if treatment were set at the exposed value (possibly contrary to fact) while the mediator were changed from the level it would take if treatment were set at the exposure value, to its level if treatment were set to the non-

exposure value (possibly contrary to fact) (see [14, 16, 23, 24]). Further definitions have been offered, such as controlled direct effects (see [14, 16, 23, 24]), but, in general, estimation for settings where the outcome is a time-to-event variable are complex to implement and the results are difficult to explain (see [25-27]). Furthermore, there is very little specific guidance in the literature for estimating an indirect treatment effect when both mediator and outcome are time-to-event variables [28].

This thesis suggests a pragmatic approach to solving this problem that could be useful in a wide variety of clinical settings. As noted above, composite time-to-event outcomes are widely used in clinical trials, so it is reasonable to infer that a means of partitioning the direct and indirect treatment effects of a treatment would be beneficial. As an example, Cannon [5] implicitly discussed an indirect treatment effect in outlining the results of the ISIS-2 trial [29], noting that treatment with aspirin prevented myocardial infarction (MI), and that this reduction in MI itself led to a lower death rate in the aspirin group. However, no attempt was made to quantify the indirect effect of aspirin treatment on death rates through its effect on MI.

1.5 Dynamic path analysis as a solution

The approach proposed in this thesis uses as a starting point the dynamic path analysis method of Fosen, Aalen et al [20, 30, 31]. This is a simple method of mediation analysis that belongs to the more traditional (as opposed to counterfactual-based) path analysis approach to mediation analysis that has developed from the structural equation models literature (see for example [32-35]) and Wright's path analysis [36, 37]. The path analysis approach to mediation analysis relies on the linearity of all the models involved [14, 20]. The interpretation of model coefficients refers back to the assumptions encoded in the models [34], in contrast with the counterfactual approach, where causal effects are defined in terms of potential outcomes inferred from relations observed within datasets [20, 34]. From Aalen [20], "The idea is… to follow the idea that events and processes influence one another".

Dynamic path analysis [20, 30, 31] extends path analysis to the setting of a (possibly time-varying) continuous mediator and a time-to-event outcome. It combines a linear regression model for the mediator with an additive hazards model for the hazard of the outcome [20, 38, 39]. The models are estimated at the time of each event occurrence. Multiplying the estimates

of the treatment effect on the mediator and the mediator effect on the hazard of the event leads to estimates of the indirect effect of treatment on the time-to-event outcome using path tracing rules [15, 37, 40], subject to the assumption that the models are correctly specified [14, 15, 19, 32, 33, 41]. To aid interpretability, these indirect effect estimates are usually summed over time and reported graphically as cumulative effects [20, 30, 31, 42].

This thesis extends the dynamic path analysis approach to the setting where both the mediator and the outcome are time-to-event variables. As with both path analysis and dynamic path analysis, the estimated direct and indirect effects are interpreted with regard to the causal assumptions underlying the regression models used [20, 34]. The clinical trials setting of this thesis lends some plausibility to these causal assumptions and therefore justifies its application.

1.6 Aim and objectives of the thesis

Motivated by the difficulties of conducting secondary analysis of treatment effects on the component events of a time-to-event composite outcome, the main aim of this thesis is to extend dynamic path analysis to the setting where both outcome and mediator are time-to-event variables. To achieve this aim, the following objectives are identified:

1) To introduce the dynamic path analysis method of Fosen, Aalen et al [20, 30, 31] as a means of estimating the indirect effect of a treatment on a time-to-event outcome via a continuous mediator, and to verify its properties;
2) To extend dynamic path analysis, and investigate the properties of this extension, to the setting where the outcome and mediator are time-to-event variables;
3) To apply this extension to the Zactima trials dataset, estimating the indirect effect of treatment on death through its effect on cancer progression.

1.7 Structure of the thesis

Chapter 2 describes the Zactima trials referred to above, and confirms the main published findings of each trial. The effects of treatment on the component events of the composite outcome are estimated on a pooled dataset using the Cox proportional hazards model [13].

Chapter 3 introduces the additive hazards model of Aalen [20, 38, 39] and uses simulation studies to verify the performance of the additive hazards model in simple settings with time-fixed explanatory variables. A range of metrics is used to evaluate the performance of the model over time.

In Chapter 4, the additive hazards model is used to estimate the effects of treatment on each of the component events of the composite outcome in the Zactima trials, and a mechanism of action of treatment is proposed that works through the intermediate event of cancer progression.

Chapter 5 outlines some concepts of mediation analysis, and introduces dynamic path analysis. The proposed extension of dynamic path analysis from the setting with a continuous mediator and a time-to-event outcome to the setting informed by the Zactima trials, where both the proximal and distal events are time-to-event variables, is described.

Chapter 6 conducts and reports simulation studies to verify that traditional dynamic path analysis with a continuous mediator gives rise to unbiased estimates of the indirect effect of treatment.

The performance of the proposed extension to the dynamic path analysis estimator is examined under varying conditions using simulation studies in Chapter 7.

The method is then applied to the pooled Zactima trials dataset to estimate an indirect effect of treatment on death through cancer progression in Chapter 8.

Chapter 9 considers to what extent these aims of the thesis have been met and proposes directions for future research in this area.

2 Treatment effects on the component events of a composite outcome: the Zactima trials

2.1 Introduction

As discussed in chapter 1, a key recommendation in the reporting of treatment effect estimates on composite outcomes is that, in addition to the main results, event rates and treatment effects be reported separately for every component of a composite outcome [1, 3, 6]. This chapter reports the decomposition of a composite outcome and the estimation of treatment effects on the component events of a composite outcome for the motivating example of this thesis, the Zactima trials [8-10].

2.1.1 Aims

This chapter will present details of the Zactima trials [8-10], the motivating example of this thesis, and preliminary analyses of the data with respect to their treatment effect estimates.

More specifically, the aims of the chapter are:

1) To describe the three Zactima trials and summarise their published findings
2) To estimate the effects of treatment on the component events of the composite outcome in each of the three trial datasets;
3) To pool the data from the three trials, giving rise to more precise estimates of treatment effects on the component events, and carry out exploratory analysis to investigate possible mechanisms of action of the treatment.

2.2 The Zactima trials

2.2.1 Introduction

The three trials presented here, Zodiac [8], Zephyr [9] and Zeal [10], were randomised parallel-group double-blind placebo-controlled trials for the use of an existing drug, vandetanib (Zactima), in patients with stage III and IV non-small cell lung cancer (NSCLC). The trials were funded and conducted by AstraZeneca between May 2006 and November 2008. Vandetanib had previously been approved for use in medullary thryroid cancer. Vandetanib works both by inhibiting the growth of tumour cells and by slowing down tumour angiogenesis, the process by which tumours are vascularised [43].

The primary outcome for two of the three trials, Zodiac and Zeal, was progression-free survival (PFS). This was defined as a composite of time to either cancer progression or death, whichever happened first, including only deaths which occurred within 3 months of the final assessment for progression. The secondary outcome for these trials was overall survival, defined as time between randomisation and any death. Conversely, the primary outcome for the Zephyr trial was overall survival, and the secondary outcome was PFS. The exclusion of deaths which occurred more than 3 months after the final progression assessment led to a total of 86 fewer deaths being included in the PFS outcome than the overall survival outcome (which counted all deaths) across all three trials.

The populations of interest in the three trials consisted of patients aged over 18, with locally advanced or metastatic stage IIIB or IV NSCLC (see [44]) and a life expectancy of at least 12 weeks. Zodiac and Zeal patients had failed first-line therapy (see [11, 12]). Zephyr patients had failed one or two prior chemotherapy regimens, and prior treatment with an EGFR tyrosine kinase inhibitor (commonly used as both first and second line therapy in patients with advanced disease [12]). Zephyr had a treatment: placebo randomisation ratio of 2:1, while the other two trials had a 1:1 ratio. In Zodiac, patients were randomised to receive either oral vandetanib (Zactima) with intravenous (IV) docetaxel (see [11, 12]), or placebo with IV docetaxel. Docetaxel is a cytotoxic drug which inhibits tumour cell division [45]. In Zephyr, patients were randomised to receive either oral vandetanib (Zactima) and best supportive care or placebo and best supportive care. In Zeal, patients were randomised to receive either oral vandetanib (Zactima) with IV pemetrexed (see [11, 12]), or placebo with IV pemetrexed. Pemetrexed is a chemotherapy drug used to prevent the formation of DNA in tumour cells

[45]. Treatment in all three trials was stopped when patients experienced cancer progression (see [46]). Progression assessments took place every 6 weeks in the Zodiac and Zeal trials, and every 8 weeks in the Zephyr trial. Follow-up ended in the Zodiac trial at 24 months, in the Zephyr trial at 34 months, and in the Zeal trial at 18 months (see Figure 2-1 for the Kaplan-Meier estimates of survivor function).

Each of the three trials used Zactima together with accepted therapies in order to look for evidence that it provided an additional protective effect. The published trial papers [8-10] tested for an effect of treatment on the primary outcome (PFS for Zodiac and Zeal, and overall survival for Zephyr) using log-rank tests (see [47]), and estimated the adjusted effects of treatment on PFS and overall survival by fitting Cox models which included baseline covariates, some of which were common across trials and some of which were unique to each trial. The published papers did not report the estimated effects of treatment on cancer progression.

2.2.2 Estimated effects of treatment on PFS

Table 2-1 shows the published estimates of the effect of treatment on PFS [8-10] obtained by fitting Cox models adjusted for the baseline variables listed in the table.

Table 2-1 Numbers of patients and PFS events, and estimated adjusted HRs for the effect of treatment on PFS for each of the three trials

Trial	Number of patients included in the analysis	Number of PFS events	Baseline variables included in the Cox model	Estimated HR for treatment, [CI[1]]
Zodiac	1391	1205	Tumour stage, number of organs involved, histology, smoking, sex, ethnicity, EGFR-expression, -amplification and –mutation, and previous failure of bevacizumab	0.79, [0.70, 0.90]
Zephyr	924	834	Tumour stage, number of organs involved, histology, smoking, sex, ethnicity, EGFR-expression, -amplification and –mutation, prior TKI therapy, and WHO performance status	0.63, [0.54, 0.74]
Zeal	534	443	Tumour stage, number of organs involved, histology, smoking, sex, ethnicity, EGFR-expression, -amplification and –mutation, and previous failure of bevacizumab	0.86, [0.69, 1.06]

[1] The CIs reported in the published papers were adjusted to allow for interim analyses. The Zodiac trial reports a 97.6% CI, the Zephyr trial reports a 95.2% CI and the Zeal trial reports a 97.6% CI.

The trial-specific results presented in Table 2-1 indicate that treatment has a statistically significant protective effect on PFS in the Zodiac and Zephyr trials, and a protective but not statistically significant effect on PFS in the Zeal trial.

2.3 Trial-specific analysis of the effects of treatment on component events

This section presents a reanalysis of the Zactima trials datasets, focusing on treatment effects on the component events of cancer progression and death. A consideration of treatment effects on all component events of a composite outcome allows the implicit assumption of homogeneity of treatment effects to be explored [1-3]. It may also provide some insight into the mechanism of action of treatment.

The datasets used in this chapter were provided by AstraZeneca. The Zodiac trial dataset provided for analysis had been updated since the published trial results.

2.3.1 Methods for trial-specific analysis

The descriptive analyses comprised number of patients randomised to each group, and the number of cancer progressions and deaths (by treatment group and overall). Kaplan-Meier curves (see [47, 48]) were used to describe the survival experience by treatment group with respect to cancer progression and death.

In line with the published results, Cox proportional hazards models were used to estimate the effects of treatment on each outcome adjusting for baseline covariates. Cox models are fitted via partial likelihood estimation which leads to estimating covariate effects while allowing the baseline hazard function to vary freely over time and to remain unspecified. The key feature of the Cox model is the assumption of proportionality, under which the ratio of hazards for two individuals with different covariate values is constant over time [20, 49].

All deaths were included in the analyses presented in this chapter.

The Cox models fitted to each trial dataset are specified in Table 2-2 below. In the models shown in the table:

- $\alpha_{prog}(t)$ represents the hazard of progression at time t;
- $\alpha_{prog.0}(t)$ represents the hazard of progression at time t in the baseline group, in which the value of all covariates is set to 0;
- T_{prog} is the random variable representing time to progression;
- $\alpha_{dth}(t)$ represents the hazard of death at time t;
- $\alpha_{dth.0}(t)$ represents the hazard of death at time t in the baseline group, in which the value of all covariates is set to 0;
- T_{dth} is the random variable representing time to death;
- *treat* is a fixed binary variable indexing treatment group (0=placebo, 1=Zactima);
- the vector **W** includes the following fixed baseline covariates, common to all trials:
    - tumour stage;
    - number of organs involved at baseline;
    - histology;
    - smoking;
    - sex;
    - ethnicity;
    - EGFR-expression, -amplification and -mutation (see [8])

  These variables are coded as categorical variables with observed values **w**.

Including the covariates **W** as adjustment variables ensures that the estimated treatment effects are controlled for any chance imbalances across treatment group with respect to these variables and improves precision of the estimates.

Table 2-2 Cox models fitted to the Zactima trials data to estimate treatment effects on progression and death in each trial separately.

Outcome	Model[1]	Model number
Progression	$\alpha_{\text{prog}}(t) = \alpha_{\text{prog.0}}(t)\exp(\beta_1^{(1)}\text{treat} + \mathbf{\beta}_2^{(1)\mathbf{T}}\mathbf{w})$	2-1
Death	$\alpha_{\text{dth}}(t) = \alpha_{\text{dth.0}}(t)\exp(\beta_1^{(2)}\text{treat} + \mathbf{\beta}_2^{(2)\mathbf{T}}\mathbf{w})$	2-2

[1] The superscript **T** denotes the transpose of a vector

For each model, proportionality of the effect of treatment was checked by visual examination of Nelson-Aalen plots of the cumulative hazards by treatment group [50]. A test of proportionality based on Schoenfeld residuals was also carried out [50, 51]. Under proportionality, the sum of the (time-specific) scaled Schoenfeld residuals specific to the treatment variable and the estimated treatment effect, should be constant over time. Therefore, regressing time on this sum should give a regression coefficient equal to 0 if proportionality with respect to treatment holds. A statistically significant regression coefficient provides evidence of non-proportionality [50, 51]. Proportionality was checked for the other baseline covariates, and the models re-fitted using any non-proportional baseline covariates as stratification variables [50].

2.3.2 Results of trial-specific analysis

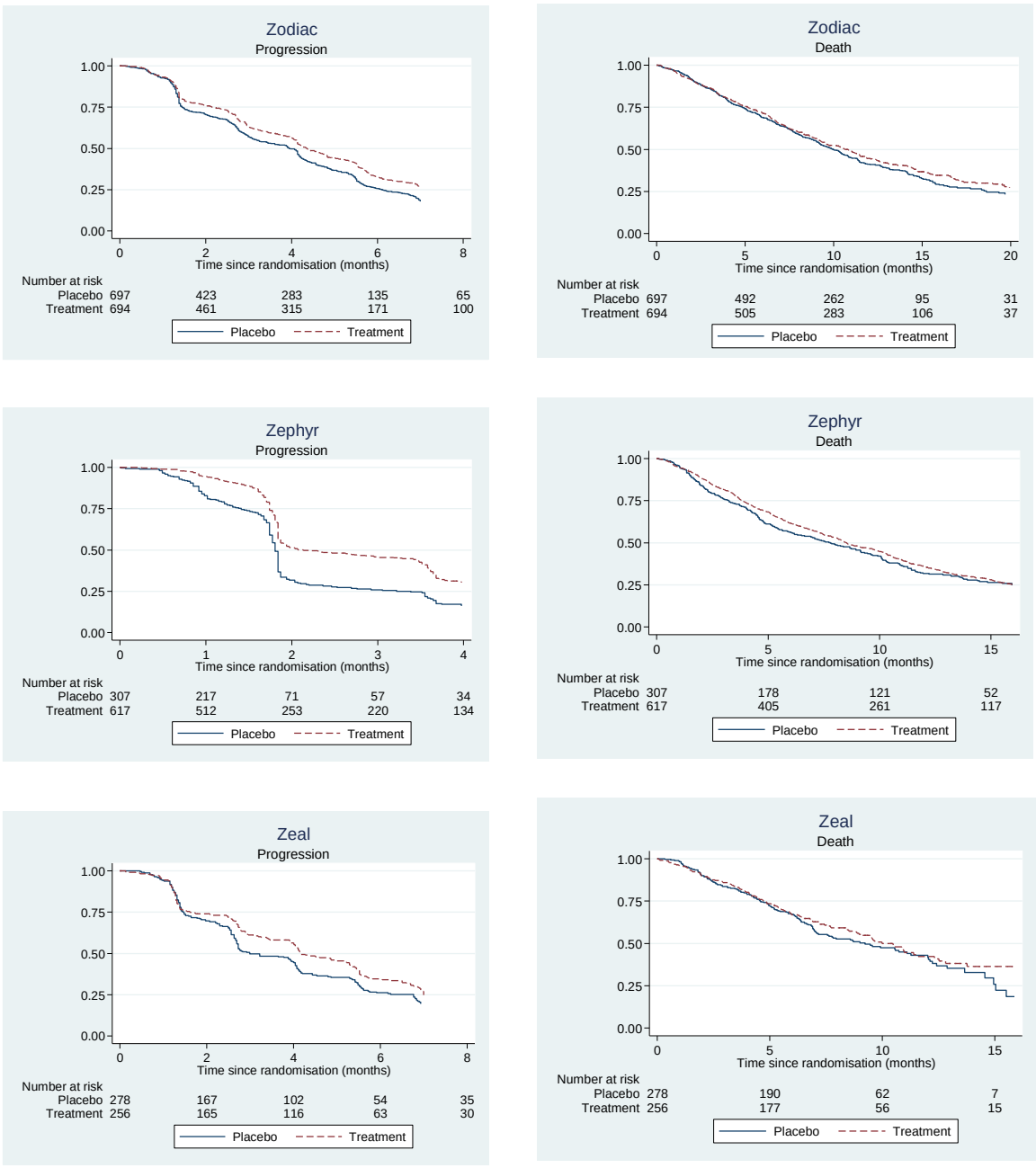
Table 2-3 shows the number of patients randomised to each group, and the numbers of cancer progressions and deaths experienced by treatment group and overall for the three trials.

Table 2-3 Numbers of patients randomised and outcomes by treatment group and overall for all three trials

Outcome	N (%)		
	Placebo group	Treatment group	Overall
Zodiac trial			
Number randomised (%)	697 (100)	694 (100)	1391 (100)
Number of progressions	547 (78)	504 (73)	1051 (76)
Median time to progression in months [IQR]	4.0 [1.4, 6.1]	4.4 [2.2, 7.1]	4.1 [1.7, 6.8]
Number of deaths	418 (60)	403 (58)	821 (59)
Median time to death in months [IQR]	10.0 [4.8, 18.6]	10.6 [5.2, 20.7]	10.3 [5.0, 20.2]
Number of deaths after progression	332 (48)	299 (43)	631 (45)
Zephyr trial			
Number randomised (%)	307 (100)	617 (100)	924 (100)
Number of progressions	238 (78)	463 (75)	701 (76)
Median time to progression in months [IQR]	1.8 [1.4, 3.4]	2.1 [1.7, 5.3]	1.8 [1.7, 4.2]
Number of deaths	234 (76)	471 (76)	705 (76)
Median time to death in months [IQR]	7.8 [3.2, 15.9]	8.5 [3.8, 15.9]	8.4 [3.7, 15.9]
Number of deaths after progression	179 (58)	353 (57)	532 (58)
Zeal trial			
Number randomised (%)	278 (100)	256 (100)	534 (100)
Number of progressions	207 (74)	180 (70)	387 (72)
Median time to progression in months [IQR]	3.0 [1.5, 6.8]	4.2 [1.6, 7.0]	4.0 [1.5, 7.0]
Number of deaths	147 (53)	122 (48)	269 (50)
Median time to death in months [IQR]	9.2 [4.6, 15.0]	10.5 [4.7, 17.5]	9.6 [4.7, 16.5]
Number of deaths after progression	115 (41)	88 (34)	203 (38)

Figure 2-1 shows Kaplan-Meier estimates of the survivor function by treatment group for cancer progression (left) and death (right). The x-axis is truncated at the 75th percentile of follow-up time, which for progression is approximately 7 months in Zodiac and Zeal, and 4 months in Zephyr. For death, the 75th percentile of time is approximately 20 months in the Zodiac trial, and 16 months in Zephyr and Zeal. This truncation is line with truncation of the results of additive hazards models reported in chapter 4.

Figure 2-1 Kaplan-Meier estimates of survivor function by treatment group for progression (left) and death (right) for all three trials



In the left-hand column of the figure, the Kaplan-Meier curves exhibit a stepped shape which reflects the scheduled progression assessments, which took place every 6 weeks in the Zodiac and Zeal trials, and every 8 weeks in the Zephyr trial.

In the Zodiac trial (first row of figure), survival appears better in the treatment group for progression from 1.5 months. There is a less clear survival advantage for death, which becomes more apparent only after 10 months of follow-up.

The treatment group in the Zephyr trial (second row) shows a marked survival advantage for progression from 0.5 months, and a survival advantage for death from 1 month.

The Zeal trial (third row) shows a survival advantage in the treatment group for progression from 1.5 months. Survival for death is similar across treatment groups, with a small survival advantage in the treatment group appearing between about 7 and 10 months after randomisation.

Table 2-4 below reports the adjusted hazard ratios and 95% confidence intervals for the effects of treatment on progression and death estimated by fitting the Cox models shown in Table 2-2. Note that interpretation of the hazard ratios for progression is conditional on survival.

Table 2-4 Estimated adjusted hazard ratios [95% CI] for the effect of treatment on progression and death for all three trials

Trial	Progression	Death
Zodiac	0.74 [0.66, 0.85]	0.92 [0.80, 1.06]
Zephyr	0.65 [0.55, 0.76]	0.97 [0.83, 1.14]
Zeal	0.85 [0.69, 1.04]	0.82 [0.64, 1.05]

An examination of the Nelson-Aalen plots of cumulative hazards (not shown) indicated that the hazards of progression were proportional by treatment group for Zodiac, Zephyr and Zeal.

For death, cumulative hazards by treatment group are very close for the first 8 and 6 months respectively in the Zodiac and Zeal trials. The cumulative hazards then diverge and appear proportional. In Zephyr, the difference in the cumulative hazards again appears constant, suggesting that the hazards might not be proportional.

Table 2-5 shows the chi-squared test statistic and P value associated with the regression tests for proportionality in the treatment variable.

Table 2-5 Results of proportionality tests of treatment effect for the progression and death outcomes, by trial

Trial	Progression	Death
Zodiac	χ^2_1=2.21, P=0.14	χ^2_1=0.60, P=0.44
Zephyr	χ^2_1=3.51 P=0.06	χ^2_1=3.76, P=0.05
Zeal	χ^2_1=1.38, P=0.24	χ^2_1=2.01, P=0.16

In the Zephyr trial, there is borderline statistically significant evidence against proportionality for progression and for death. The lack of proportionality of treatment in the Zephyr trial may indicate that use of a hazard ratio to estimate the effect of treatment in Zephyr is inappropriate. However, in the other trials there is a lack of evidence against proportionality.

Global tests for proportionality indicated that some of the baseline explanatory variables included in Model 2-1 showed non-proportionality. Re-fitting the models and stratifying on these explanatory variables did not result in any marked changes to the estimated treatment effects on progression (the estimated hazard ratios and 95% CIs for Zodiac, Zephyr and Zeal became respectively 0.77 [0.68, 0.88], 0.64 [0.54, 0.75] and 0.84 [0.68, 1.03]. The treatment effect estimates were therefore robust to some model misspecification. Similarly, for the death outcome, stratifying on variables showing evidence of non-proportionality did not result in significant changes to the estimated treatment effects in Model 2-2, with the hazard ratio and 95% CI for Zephyr becoming 0.98 [0.84, 1.15]. Variables included in Model 2-2 for the Zodiac and Zeal trials showed no evidence of non-proportionality.

2.3.3 Summary of trial-specific analysis

In summary, all three trials demonstrated a reduction in the hazard ratio of progression associated with the use of Zactima. In all three trials, the effect of treatment on death was protective but not statistically significant. The confidence intervals for all the hazard ratios presented in Table 2-4 are quite wide, indicating a lack of precision of the estimate. The proportional hazards assumption of the Cox model appeared to be upheld in the Zodiac and Zeal trial, but was questionable in the Zephyr trial.

2.4 Pooling the Zactima trials datasets

2.4.1 Introduction

An issue arising from the analyses presented above is that of obtaining accurate estimates of the effects of treatment on cancer progression and death in the Zactima trials. The Zodiac and Zephyr trials report quite different point estimates for the effect of treatment on progression compared to the effect of treatment on death (see Table 2-4). This could call into question the interpretation of treatment effects which use the composite outcome PFS. However, the confidence intervals reported in Table 2-4 are wide, so it is not clear whether the treatment effects are truly heterogeneous across the component events.

An analysis of the effect of treatment using data pooled from all three trials increases the number of events available, which should increase both power to detect treatment effects and the precision of treatment effect estimates, assuming homogeneity of effect across the three populations of patients.

2.4.2 Methods for the pooled analysis

The datasets provided for each trial were merged and a categorical variable defined to index the trials. Kaplan-Meier curves (see [47, 48]) were used to estimate the survivor function in the pooled dataset by treatment group for progression and death. The stratified Cox models [13] specified in Table 2-6, with strata defined by trial, were fitted to estimate the effects of treatment on progression and death. Stratification by trial allows estimation of a common treatment effect, without assuming that baseline hazards are proportional across trials [50].

The Cox models for progression and death include the baseline variables common to the three trials (in line with the methods presented in section 2.3.1). Estimates of treatment effect are therefore adjusted to account for possible imbalances across treatment groups with respect to these variables [52].

Table 2-6 below specifies the Cox models fitted to the pooled dataset. Notation from section 2.3.1 is extended to include:

- *k*=1,2,3 indicating trial;
- *prog(t)*, a binary time-updated variable indicating whether progression had occurred by time t (0=no progression, 1=progression);
- *treat*prog(t)* is an interaction term taking the value at time t of 1 if *treat*=1 and *prog(t)*=1, and 0 otherwise.

Table 2-6 Cox models fitted to the Zactima trials data to estimate treatment effects on progression and death

Outcome	Description	Model	Model number
Progression	Effect of treatment on progression	$\alpha_{\text{prog.k}}(t) = \alpha_{\text{prog.k.0}}(t)\exp(\beta_1^{(3)}\text{treat} + \boldsymbol{\beta}_4^{(3)\mathbf{T}}\mathbf{w})$	2-3
Death	Overall effect of treatment on death	$\alpha_{\text{dth.k}}(t) = \alpha_{\text{dth.k.0}}(t)\exp(\beta_1^{(4)}\text{treat} + \boldsymbol{\beta}_4^{(4)\mathbf{T}}\mathbf{w})$	2-4
	Effect of treatment on death, controlled for progression	$\alpha_{\text{dth.k}}(t) = \alpha_{\text{dth.k.0}}(t)\exp(\beta_1^{(5)}\text{treat} + \beta_2^{(5)}\text{prog}(t) + \boldsymbol{\beta}_4^{(5)\mathbf{T}}\mathbf{w})$	2-5
	Effect of treatment on death with a treatment-progression interaction	$\alpha_{\text{dth.k}}(t) = \alpha_{\text{dth.k.0}}(t)\exp(\beta_1^{(6)}\text{treat} + \beta_2^{(6)}\text{prog}(t) + \beta_3^{(6)}\text{treat} * \text{prog}(t) + \boldsymbol{\beta}_4^{(6)\mathbf{T}}\mathbf{w})$	2-6

As in section 2.3.1, the vector **W** includes fixed baseline covariates common to all trials.

Model 2-3 is the analogue of Model 2-1 fitted on the pooled dataset, estimating the effect of treatment on progression adjusted for baseline covariates. Similarly, Model 2-4 is the analogue of Model 2-2, estimating the effect of treatment on death adjusted for baseline covariates.

Model 2-5 is fitted to investigate whether the effect of treatment on death adjusted for progression, $\beta_1^{(5)}$, is different from the effect of treatment on death unadjusted for progression, $\beta_1^{(4)}$. The use of the pooled dataset should give this investigation more power than if it had been carried out on the individual trial datasets. This strategy is commonly employed to determine whether the effect of an exposure such as treatment on an outcome such as death is mediated through an intermediate variable such as exposure (see for example [32, 40, 41] and chapter 5). The drawbacks of this approach are outlined in section 5.2.1.

Model 2-6 investigates whether the effect of treatment on death involves progression. The parameter $\beta_1^{(6)}$ represents the effect of treatment on death at time t if prog(t)=0, while the parameter $\beta_3^{(6)}$ is interpreted as the additional effect of treatment on death at time t if *prog(t)*=1.

The assumption of homogeneity of the treatment effect across trials was checked by adding interaction terms $treat*I_{k=2} + treat*I_{k=3}$ to Models 2-3, 2-4 and 2-5 [50]. The statistical significance of these terms was tested by comparing the log-likelihood ratio of models including the interactions with that of models excluding them.

The assumption of proportionality in the treatment variable for Models 2-3, 2-4 and 2-5 was investigated using Nelson-Aalen plots and the regression-based test of proportionality using the sum of the scaled Schoenfeld residuals and estimated treatment effect (described in section 2.3.1). Proportionality was not checked for treatment in Model 2-6, because the inclusion of an interaction term *treat*prog(t)* means that the model does not assume proportionality with respect to treatment [47, 48]. As before, global tests were carried out to investigate the assumption of proportionality with respect to the fixed baseline covariates.

2.4.3 Results for the pooled analysis

2.4.3.1 Descriptive results

Table 2-7 below shows the number of patients randomised to each group, and numbers of outcomes experienced by treatment group and overall in the pooled dataset.

Table 2-7 Numbers of patients randomised and outcomes by treatment group and overall in the pooled dataset

Descriptor	N (%)		
	Placebo group	Treatment group	Overall
Number randomised	1282	1567	2849
Number of progressions	992 (77)	1147[1] (73)	2139 (75)
Median time to progression in months [IQR]	2.9 [1.4, 5.6]	3.6 [1.8, 6.6]	3.4 [1.7, 5.9]
Number of deaths	799 (62)	996 (64)	1795 (63)
Median time to death in months [IQR]	9.3 [4.3, 17.6]	9.7 [4.5, 19.3]	9.6 [4.4, 18.0]
Number of deaths after progression	626 (49)	740 (47)	1366 (48)

[1] There were more individuals in the treatment group than the placebo group because of the 2:1 randomisation ratio used in Zephyr.

Figure 2-2 below shows numbers of deaths by treatment group and progression status, together with median event times in months. The data are not differentiated by trial in this figure.

Figure 2-2 Summary of outcomes and follow-up time by treatment group for the pooled dataset. Times are given in months (mo)

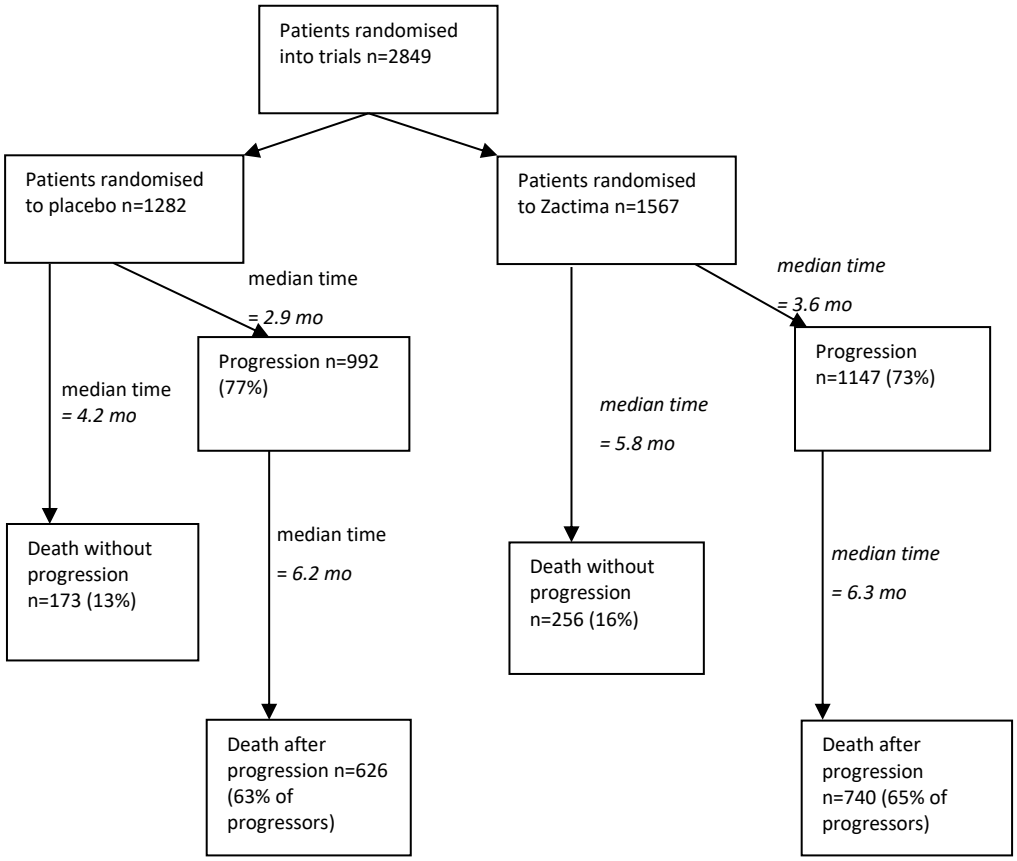
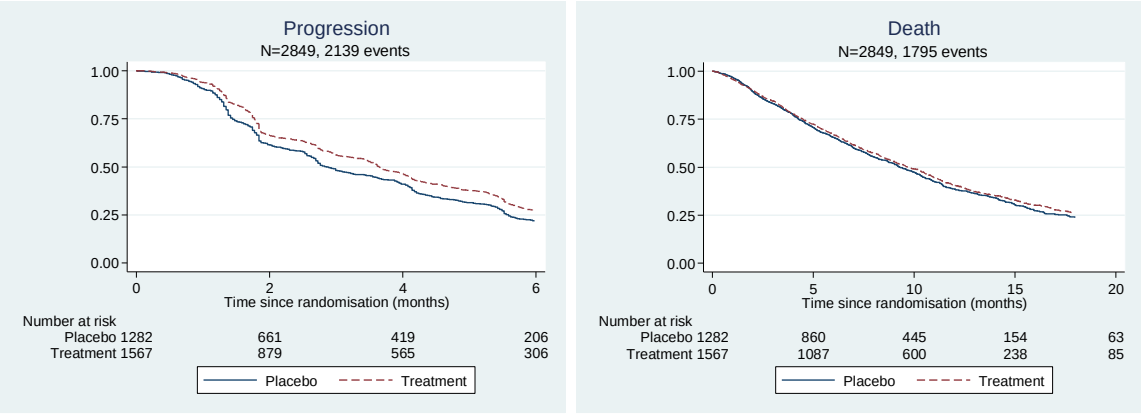


Figure 2-2 shows that median times to progression and death are longer in the treatment group. However, time between progression and death is similar in the treatment and placebo groups, which may indicate that treatment, which is discontinued at progression, does not have a lasting effect, or affects progression alone.

Figure 2-3 shows Kaplan-Meier estimates of the survivor function by treatment group for progression (left) and death (right). The x-axis is truncated at the pooled 75th percentile of follow-up time, which for progression is approximately 6 months and for death is approximately 18 months.

Figure 2-3 Kaplan-Meier estimates of survivor function by treatment group for progression (left) and death (right)



For cancer progression, there is a clear survival advantage in the treatment group. For death, there a minimal survival advantage in the treatment group is apparent after 6 months post-randomisation.

2.4.3.2 Results from fitting Cox models

Table 2-8 shows the estimated effects of treatment obtained by fitting the stratified Cox models specified in Table 2-6. The right-hand column reports results for the likelihood ratio test of statistical significance of the coefficient for the treatment effect [47, 49].

Table 2-8 Estimated hazard ratios for the effects of treatment

Outcome	Description	Model number	Estimated HR	95% CI for HR	X^2, P for inclusion in the model
Progression	Effect of treatment on progression	2-3	0.74	[0.68, 0.81]	X^2_1=45.4, P<0.001
Death	Overall effect of treatment on death	2-4	0.92	[0.84, 1.01]	X^2_1=2.9, P=0.09
	Effect of treatment on death, controlled for progression	2-5	1.00	[0.91, 1.10]	X^2_1<0.001, P= 0.96
	Effect of treatment on death with a progression interaction: effect of treatment before progression	2-6	1.01	[0.83, 1.23]	X^2_2=0.02, P=0.99
	Effect of treatment on death with a progression interaction: effect of treatment after progression		1.00	[0.90, 1.11]	

The results reported in Table 2-8 confirm that the estimated effect of treatment on progression is protective and statistically significant. The overall effect of treatment on death estimated by fitting Model 2-4 is protective with HR=0.92, but of borderline statistical significance, P=0.09. When the effect of progression on death is taken into account by fitting Model 2-5, the protective effect of treatment disappears, with HR=1.00, P=0.96.

The interaction term in Model 2-6 is not statistically significant, χ^2_1=0.01, P=0.91. This implies that there is no evidence that the effect of treatment on death differs according to progression at time t.

The addition of interaction terms between treatment and trial to each model indicate a lack of evidence that the effect of treatment is different by trial, χ^2_2=3.39, P=0.18 for Model 2-3, χ^2_2=1.64, P=0.44 for Model 2-4 and χ^2_2=2.35, P=0.31 for Model 2-5. It is therefore reasonable to assume that the effects of treatment are homogeneous across the three datasets.

An examination of the Nelson-Aalen plots of cumulative hazard by treatment group (not shown) indicates that the hazards of progression appear proportional. For the death outcome,

the hazards are very close for the first 6 months. After this time, the hazards appear proportional.

Table 2-9 shows the results of the regression-based proportionality test for the treatment effect in Models 2-3, 2-4 and 2-5. A statistically significant result indicates evidence against proportionality in treatment [50, 51].

Table 2-9 Results of the proportionality tests for treatment applied to the pooled dataset

Outcome	Description	Model number	χ^2, P for test of proportionality of treatment effect
Progression	Effect of treatment on progression	2-3	χ^2_1=0.24, P=0.62
Death	Overall effect of treatment on death	2-4	χ^2_1=0.40, P=0.53
	Effect of treatment on death, controlled for progression	2-5	χ^2_1=0.11, P=0.74

In the pooled dataset, there is insufficient evidence against the assumption of proportionality with respect to treatment. For the progression outcome, there is some evidence against proportionality for some of the fixed baseline covariates. Stratifying on these covariates and re-fitting Model 2-3 did not materially change inferences about the treatment effect, with the hazard ratio and 95% CI becoming 0.74 [0.68, 0.81]. For the death outcome, there is some evidence against proportionality for one of the baseline covariates in Model 2-4. Stratification did not materially affect inferences about treatment effects, with the hazard ratio and 95% CI becoming 0.92 [0.84, 1.02]. For Model 2-5, there is no evidence against proportionality for the fixed baseline covariates.

2.5 Discussion

Pooling the datasets from the three trials increases the numbers of observations available to estimate treatment effects on the component events of the composite outcome. However, as noted in section 2.4.1, there is an assumption of homogeneity of treatment effects across the three trials. Even though the trial-specific treatment effect estimates reported in Table 2-4 appear to differ across trials, these between-trial differences are shown to be not statistically significant (see text below Table 2-8), justifying the pooling of the trials datasets.

The trial-specific analyses indicate that treatment is protective of progression in all three trials, but this effect is statistically significant in only two of the three trials. The effect of treatment on death appears to be protective, but is not statistically significant in any of the three trials. The datasets were pooled to increase the precision of the treatment effect estimates.

Treatment is found in the pooled dataset to be significantly protective of progression. This is consistent with the results of the Zodiac and Zephyr trials.

In the pooled dataset, the estimated overall effect of treatment on death is protective, but not statistically significant. This could be a result of low power in the data to detect a treatment effect on one component of a composite outcome.

The addition of a treatment-progression interaction in Model 2-6 is not statistically significant, indicating a lack of evidence that the effect of treatment on death depends on whether progression has occurred (see Table 2-8). This is in spite of the fact that treatment stopped when progression was detected.

The difference in the estimated treatment effects obtained by fitting Model 2-4, which does not adjust for progression, and Model 2-5, which does adjust for progression, suggests that there is some effect of treatment on death that works through the progression event (see for example [40, 41]).

Investigating the existence of such an indirect effect in the context of the component events of a composite time-to-event outcome forms a major part of this thesis, and is addressed in chapters 5, 6 and 7. In chapter 8, the indirect effect of treatment on death through its effect on cancer progression is estimated in the Zactima trials dataset.

3 The additive hazards model

3.1 Introduction

Aalen [38] identifies two major drawbacks of proportional hazards models, a class which includes both fully parametric models such as the exponential and Weibull models (see for example [48]) and the semi-parametric Cox model. The first is that in a situation with multiple explanatory variables, the proportional hazards assumption for a given variable may depend on which other variables are included in the model [38, 50]. The second is that the proportional hazards assumption may hold for a given continuous variable under some variable transformations but not others; the proportionality assumption is linked to correct specification of the model. A consequence of this is that time-varying effects (non-proportionality of hazards) may be identified under one variable transformation but not another [38, 53].

A model that relaxes the assumption of proportionality of hazards is the additive hazards model proposed by Aalen, using counting process notation for time-to-event outcomes [38, 53]. As well as not assuming proportionality of hazards, this model easily accommodates time-varying covariate effects, so can be very flexible [20, 38]. The additive hazards model estimates coefficients representing differences in hazards, rather than the hazard ratios estimated by the Cox model [38, 53]. It shares some of the properties of linear regression models, which allow the effect of an explanatory variable on a time-to-event outcome to be partitioned into a direct effect and an indirect effect working through a mediator variable (see chapter 5). Such a decomposition is not in general possible when the time to event outcome is modelled with a non-linear model such as the Cox model (see [17, 20, 32] and chapter 5).

3.1.1 Aims

This chapter introduces the additive hazards model, which will be used in mediation analysis in future chapters (see chapters 5, 7 and 8). It also reports the results of simulation studies

conducted to verify that the model estimates are unbiased when applied to simple situations with a single time-fixed explanatory variable (either binary or continuous) and a time-to-event outcome.

The aims of the chapter are:

1. To introduce the terminology of counting processes, which is used to define the additive hazards model;
2. To introduce the additive hazards model for survival data;
3. To use simulation studies to verify that the estimation of the additive hazards model described by Aalen produces unbiased estimates of the cumulative hazard coefficients with good coverage in a simple setting with a single time-fixed explanatory variable. Further simulations are presented in chapters 6 and 7 to examine the behaviour of the additive hazards model in more complex situations.

The time-to-event setting considered here involves a single absorbing event, a state which, when entered, cannot be left. Hereafter this event is referred to as death. The notation used to denote the main variables referred to in this chapter are:

- N(t), the counting process associated with death [20], which records the number of deaths that have occurred up to and including time t;
- dN(t), the increment of N(t), a binary variable indicating whether or not a death is observed within the very small time interval [t, t+dt) [20];
- T_D, the random variable representing time to death;
- An explanatory variable (or vector of explanatory variables), which, depending on the context, is specified as:
    - A vector of k explanatory variables whose values may vary over time, written as $\mathbf{X}(t)=(X_1(t), X_2(t)\ldots X_k(t))^T$, where the T superscript denotes transposition;
    - X_{trt}, binary explanatory variable indicating treatment;
    - X_{cont}, continuous explanatory variable representing the level of some exposure or biomarker.

To keep the notation simple, in this chapter we assume that observations are not affected by censoring. However, Aalen [20] shows that the form of the intensity process described in the next section is preserved under independent censoring.

3.2 Introduction to counting processes

This section provides a non-technical introduction to the key concepts in counting processes as applied to a survival data setting, and is based largely on Hosmer [49] and Aalen [20].

Consider a single individual in a study who is under observation from time t=0 until death. The random variable denoting the individual's survival time is T_D. Using standard survival analysis notation, the individual's hazard of death at time t is given by:

$$\alpha(t)dt = \Pr\left(t \leq T_D < t + dt | T_D \geq t\right) \quad \text{3-1}$$

Formally, the conditioning in expression 3-1 above, and elsewhere, includes changes in covariate values over time, and number of events before time t; however, throughout this chapter the simpler notation $T_D \geq t$ is used. In this same setting, the counting process for a given individual records the number of deaths that have occurred up to time t with:

$$N(t) = I(T_D \leq t) \quad \text{3-2}$$

This is equivalent to recording whether death has occurred by time t given that death can only occur once and thus, just before the event occurs, N(t)=0. At the time of the event, the value of N(t) jumps from 0 to 1 and stays at 1 for the rest of the of the study. The increment of this process dN(t) is a binary variable indicating whether or not an event is observed within the very small time interval [t, t+dt) [20].

The at-risk process Y(t) for the individual indicates whether he is still at risk of death at time t:

$$Y(t) = I(T_D \geq t) \quad \text{3-3}$$

For times t when the individual has not yet experienced the event, and is therefore at risk of the event, Y(t)=1. Once the event has occurred, the individual is no longer at risk, and Y(t)=0.

The intensity process expresses the expected change in number of deaths during the very small interval [t, t+dt), given the history up to time t. This is equivalent to the conditional probability that an event occurs in [t, t+dt), given that the event has not yet occurred [20]. The intensity process can thus be written as:

$$\lambda(t)dt = P(dN(t) = 1 | T_D \geq t) \quad \text{3-4}$$

Given the definition of hazard in expression 3-1, and linking standard to counting processes notation, the intensity process is given by:

$$\lambda(t)dt = P(dN(t) = 1|T_D \geq t) = P(t \leq T_D < t + dt|T_D \geq t) = Y(t)\alpha(t)dt \quad \text{3-5}$$

from Aalen [20].

The total number of expected events for the individual up to and including time t is given by the cumulative intensity, Λ(t), which is obtained by integrating the intensity process λ(t)dt over the interval [0, t]:

$$\Lambda(t) = \int_0^t \lambda(u)du = \int_0^t Y(u)\alpha(u)\,du \quad \text{3-6}$$

The difference between the counting process and the cumulative intensity is a quantity analogous to a residual, with expected value 0, defined as a martingale M(t):

$$M(t) = N(t) - \Lambda(t) \quad \text{3-7}$$

[54]. Expression 3-7 can be rearranged to give an expression for the counting process N(t) in terms of its expected value Λ(t) and the martingale M(t):

$$N(t) = \Lambda(t) + M(t) \quad \text{3-8}$$

and similarly, the increment of the counting process dN(t) can be written as

$$dN(t) = \lambda(t)dt + dM(t) \quad \text{3-9}$$

so that at time t, the increment dN(t) represents an outcome with expected component λ(t)dt and residual dM(t) [20]. The predictable component of this formulation, the intensity process λ(t)dt, can be modelled using a linear approach [20]. The additive hazards model introduced in section 3.3 below is one of a class of models that takes this approach [20, 53].

3.3 Introduction to the additive hazards model

Consider a vector of k explanatory variables $\mathbf{X}(t)$ as defined in section 3.1.1. Observed values of the explanatory variables at time t are $\mathbf{x}(t) = \left(x_1(t), \ldots, x_k(t)\right)^T$. These values may be time-varying or fixed. The hazard function $\alpha(t|\mathbf{x}(t))$ can be expressed as a function of the observed values of $\mathbf{x}(t)$. The effects of the explanatory variables on the intensity process can be modelled by writing the intensity process in terms of the hazard function using expression 3-5:

$$\lambda(t|\mathbf{x}(t))dt = Y(t)\alpha(t|\mathbf{x}(t))dt \quad \text{3-10}$$

The hazard function $\alpha(t|\mathbf{x}(t))$ is defined by Aalen [20] as an additive function of $\mathbf{x}(t)$ as follows:

$$\alpha(t|\mathbf{x}(t)) = \gamma_0(t) + \gamma_1(t)x_1(t) + \cdots + \gamma_k(t)x_k(t) \qquad 3\text{-}11$$

The covariate coefficients $\gamma_g(t)$, g=0,1,…, k may vary freely over time [20, 38, 39].

The estimation procedure for the additive hazards model focuses on the cumulative regression functions, $\Gamma_g(t) = \int_0^t \gamma_g(u)du$, g=0,1,…, k, because estimating $\gamma_g(t)$, g=0,1,…k at every time t would be imprecise [20].

The cumulative regression coefficients are estimated as described in the following text. Using expressions 3-9 and 3-10, and writing $\gamma_g(t)dt = d\Gamma_g(t)$ for notational consistency:

$$dN(t) = Y(t)\big(d\Gamma_0(t) + d\Gamma_1(t)x_1(t) + \cdots + d\Gamma_k(t)x_k(t)\big) + dM(t) \qquad 3\text{-}12$$

Expression 3-12 takes the form of an ordinary linear regression model [20, 38], because it is written with the outcome expressed in terms of observed data $dN(t)$. This can be written in matrix notation. From Aalen [20], $\mathbf{N}(t) = \big(N_1(t), \dots, N_n(t)\big)^T$ is the vector of observed counting process outcomes for individuals i=1,2… n. The vector of cumulative regression functions is $\mathbf{\Gamma}(t) = \big(\Gamma_0(t), \dots, \Gamma_k(t)\big)^T$, and the vector of martingales is $\mathbf{M}(t) = \big(M_1(t), \dots, M_n(t)\big)^T$. The $(nx(k+1))$ matrix $\mathbf{X}^*(t)$ combines covariates and at-risk indicators, such that the ith row of the matrix is given by $\big(Y_i(t), Y_i(t)x_{i1}(t), \dots Y_i(t)x_{ik}(t)\big)$. Model 3-12 can now be written as

$$d\mathbf{N}(t) = \mathbf{X}^*(t)d\mathbf{\Gamma}(t) + d\mathbf{M}(t) \qquad 3\text{-}13$$

Ordinary least squares regression can be used to obtain estimates of the regression coefficients, $d\hat{\mathbf{\Gamma}}(t)$ [20, 38, 39]. If $\mathbf{X^*}(t)$ has full rank, meaning that its columns are linearly independent, then the inverse of $(\mathbf{X^*}(t)^T\mathbf{X^*}(t))$ exists. The estimator of $d\mathbf{\Gamma}(t)$ is then given by:

$$d\hat{\mathbf{\Gamma}}(t) = \Big(\mathbf{X}^*(t)^T\mathbf{X}^*(t)\Big)^{-1}\mathbf{X}^*(t)^T d\mathbf{N}(t) \qquad 3\text{-}14$$

This is the estimator familiar from ordinary least-squares regression (see for example [55]).

At time t, the estimator of the cumulative regression functions $\mathbf{\Gamma}(t)$ is given by:

$$\hat{\mathbf{\Gamma}}(t) = \int_0^t \Big(\mathbf{X}^*(u)^T\mathbf{X}^*(u)\Big)^{-1}\mathbf{X}^*(u)^T d\mathbf{N}(u) = \sum_{t_j \le t}\Big(\mathbf{X}^*(t_j)^T\mathbf{X}^*(t_j)\Big)^{-1}\mathbf{X}^*(t_j)^T\Delta\mathbf{N}(t_j) \qquad 3\text{-}15$$

with the sum including only those t_j when an event occurs and $\mathbf{X'}(t_j)$ has full rank. $\Delta\mathbf{N}(t_j)$ relates to event times t_j and consists of a vector of 0s, with a single 1 in the position

corresponding to the individual who has the event at time t_j. The estimator is unbiased if there is a high probability that $\mathbf{X}^*(t)$ has full rank at time t [20, 30, 31, 38].

The resulting estimates are usually presented as a plot of $\hat{\Gamma}_g(t)$ against t, for g=0,1,…,k. Because the plot shows a cumulative estimate $\hat{\Gamma}_g(t)$, covariate effects are represented by the slope of the estimated curve, and time-varying effects are represented by changes in this slope [20, 38, 42]. The graphical format has the advantage of clearly showing changes in covariate effects over time, reflecting one of the strengths of the additive hazards model.

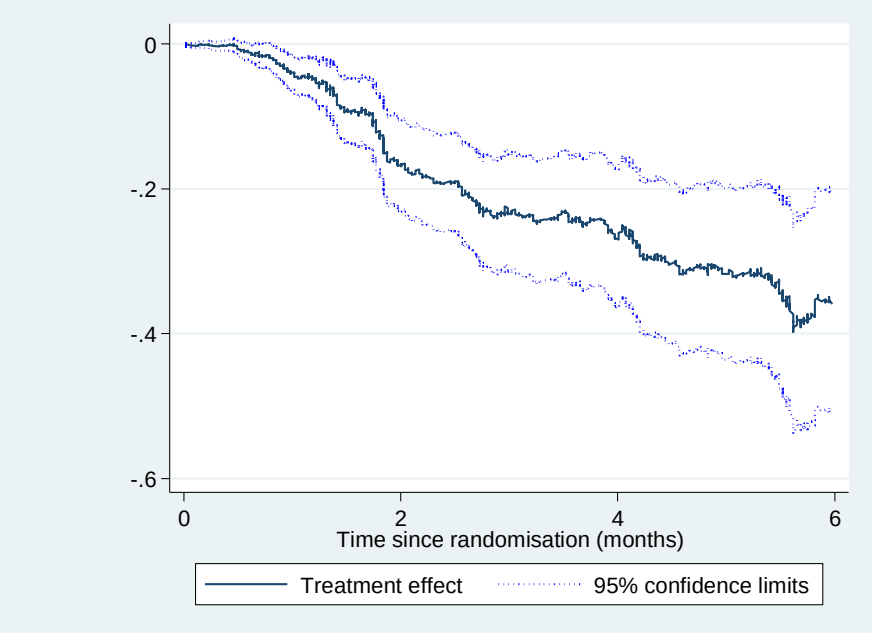
Hosmer and Royston [56] show that the variance of $\hat{\Gamma}_g(t)$ can be estimated by $\widehat{\mathrm{Var}}\left(\hat{\Gamma}_g(t)\right) = \sum_{t_j \le t} \widehat{\gamma_g^2}\left(t_j\right)$. From this expression, pointwise 95% confidence limits can be derived and plotted [56].

Illustrative example 3-1

Figure 3-1 below is an example of a plot of a cumulative regression coefficient over time, namely of a treatment effect. To obtain the plot the following additive hazards model was fitted to the pooled Zactima trials dataset to estimate the effect of treatment (treat) on the outcome of cancer progression, adjusting for trial type (**trial**) and baseline covariates (**W**):

$$\alpha(t|\text{treat}, \mathbf{trial}, \mathbf{w}) = \gamma_0(t) + \gamma_1(t)\text{treat} + \boldsymbol{\gamma}_2^{\mathrm{T}}(t)\mathbf{trial} + \boldsymbol{\gamma}_3^{\mathrm{T}}(t)\mathbf{w} \qquad \text{3-16}$$

Figure 3-1 Estimated cumulative regression coefficient $\widehat{\Gamma_1}(t)$ for the effect of treatment on progression with 95% pointwise confidence limits



From Figure 3-1, the slope of the cumulative regression coefficient is negative, meaning that treatment has a protective effect on cancer progression. There is no apparent effect of treatment on progression at the very start of follow-up. From about 0.5 months to about 5 months, the effect of treatment on progression is approximately constant, because the slope of the plot is approximately a straight line.

This analysis is presented fully in chapter 4.

Tests of the null hypothesis that $\Gamma_g(t)=0$ at all t, meaning that $X_g(t)$ has no effect on death, $g=1,\ldots k$, have been proposed [38, 39, 53, 56, 57]. In general, the tests involve the time-specific parameter estimates $\hat{\gamma}_g(t)$ being weighted with some function, then summed over event times. The result is scaled by the estimates of the time-specific standard errors, and referred to a standard normal distribution [53, 56]. Suitable weighting functions include:

- weights equal to the number of individuals in each risk set;
- weights equal to the square root of the inverse of the variance;
- weights equal to the Kaplan-Meier estimate of the survival function just before each event time;
- weights=1

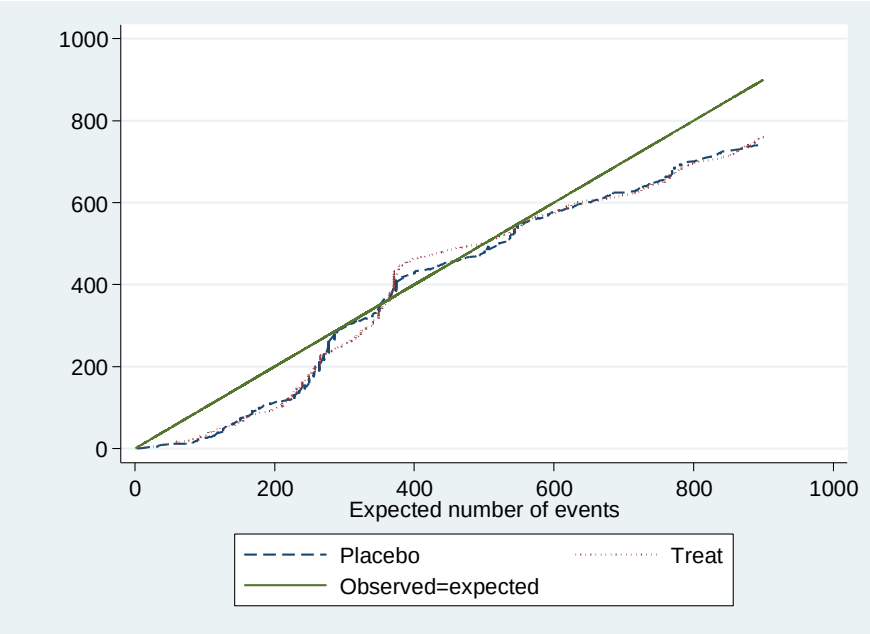
[38, 56, 57]. There is no consensus on which weighting method to use.

A simple method for checking the fit of the additive hazards model has been adapted from Arjas [58] by Aalen [20, 38, 58]. In brief, estimated cumulative intensity processes $\Lambda(t)$ are aggregated over suitable subgroups defined by key covariates and compared to the counting processes N(t) aggregated over the same subgroups. This is equivalent to a plot of observed against expected numbers of events within each subgroup [20]. As the Arjas plot does not involve a time dimension, it is used to evaluate model fit as events accrue, and does not specifically refer to model fit as time passes [20].

Illustrative example 3-2

Figure 3-2 below is an example of an Arjas plot. The additive hazards model described in illustrative example 3-1 was fitted to the pooled Zactima trials dataset to estimate the effect of treatment on the outcome of cancer progression. The plot is obtained by graphing observed against expected numbers of events in each treatment group. The reference line y=x indicates that the model perfectly predicts the numbers of events experienced within each treatment group.

Figure 3-2 Arjas plot of observed against expected number of events by treatment group



The plots of observed against expected cumulative numbers of progressions are close to a straight line along y=x passing through the origin. This means that the cumulative numbers of progressions predicted by the model are close to the observed cumulative numbers of progressions, and therefore that the model provides a good fit to the data.

This analysis is presented fully in chapter 4.

In summary, regression coefficients in the additive hazards model can be estimated by fitting a least-squares regression model for the effect of the covariates on d**N**(t) at each event time t, d**N**(t) consisting of a vector of 0s for each individual in the risk set just before time t, and a 1 corresponding to the individual who experiences the event at time t. The estimates are then summed over time to give rise to a cumulative estimate for the effect of each covariate over

time. The model can be fitted in Stata using the `stlh` command written by Hosmer and Royston [56]. Tied event times are dealt with sequentially [56].

The following section 3.4 investigates the behaviour of the additive hazards model using simulation studies.

3.4 Simulation studies to assess performance of the additive hazards model

The simulation studies presented in this section address aim 3) in section 3.1.1 of verifying that the additive hazards model produces unbiased estimates with good coverage of the cumulative regression coefficient when there is a single time-fixed explanatory variable X (which may be further specified as X_{trt} or X_{cont} as described in section 3.4.1 below). These simulations form a basis for simulations in later chapters which will evaluate dynamic path analysis and the proposed extension to dynamic path analysis.

The estimation model given in Table 3-1 below refers to a single time-fixed explanatory variable X. In Table 3-1 the model has parameters $\gamma_0(t)$ representing the baseline hazard of the event at time t and $\gamma_1(t)$ representing the increment in hazard of the event at time t for a unit increase in X. Interest in this section focuses on $\Gamma_1(t)$ (or $\Gamma_2(t)$, depending on context), the cumulative coefficient of X. Estimates $\widehat{\gamma_1}(t_D)$ are obtained as described in section 3.3 by fitting the model at each event time t_D. These estimates are summed over event times to give the cumulative estimate $\widehat{\Gamma_1}(t_D)$, using the estimator shown in Table 3-1.

Table 3-1 Additive hazards model to estimate the effect of a single time-fixed predictor

Setting	**Estimation model**	**Estimand** (Cumulative coefficient at time t)	**Estimator** (Estimator for cumulative coefficient at death time t_D)
Additive hazards model with a time-fixed X	$\alpha(t\|X) = \gamma_0(t) + \gamma_1(t)X$	$\Gamma_1(t) = \int_0^t \gamma_1(u)\,du$	$\widehat{\Gamma_1}(t_D) = \sum_{t_j \le t_D} \widehat{\gamma_1}(t_j)$

The $\widehat{\gamma_1}(t_j)$ are estimated by fitting a least-squares regression model at each event time t_j.

3.4.1 Data generation in the simulation studies

The simulations presented in this chapter consider three different scenarios where the explanatory variable has an additive effect on the baseline hazard:

a) a time-fixed binary explanatory variable X_{trt}, and constant baseline hazard function $\gamma_0(t)= \gamma_0$, so that T_D is exponentially distributed;
b) a time-fixed binary explanatory variable X_{trt}, and time-varying baseline hazard function $\gamma_0(t)$, so that T_D follows a Weibull distribution in the baseline group;
c) a time-fixed continuous explanatory variable X_{cont}, and constant baseline hazard function $\gamma_0(t)= \gamma_0$, leading to T_D being exponentially distributed.

Settings a) and c) correspond to the events occurring at a constant rate, given the value of X_{trt} or X_{cont}, throughout follow-up. The use of the Weibull distribution in setting b) is intended to check the performance of the estimates when the event occurs at a non-constant rate.

The strategy for carrying out the simulations is to generate the simulation datasets using the additive hazards models shown in Table 3-2, obtain the parameter estimates by fitting the additive hazards model (shown in Table 3-1) to the simulated data, and compare the estimate to the true value of the estimand.

Models used to generate the data are shown in Table 3-2 below. Throughout the rest of this chapter, the parameter values chosen as part of data generation are marked with an asterisk to emphasise that they are known.

Table 3-2 Data generation models for the additive hazards model with a single predictor

Setting	Data generation models	True value of the estimand
a) Additive hazards model with explanatory variable X_{trt}, T_D is exponentially distributed	$\alpha(t\|X_{trt}) = \gamma_0^*(t) + \gamma_1^* X_{trt}$ $\gamma_0(t) = \gamma_0^*$ $P(X_{trt} = 1) = p^*$	$\Gamma_1(t) = \int_0^t \gamma_1^* \, du = \gamma_1^* t$
b) Additive hazards model with explanatory X_{trt}, T_D follows a Weibull distribution in the baseline group	$\alpha(t\|X_{trt}) = \gamma_0^*(t) + \gamma_1^* X_{trt}$ $\gamma_0(t) = \nu^* \kappa^* t^{\nu^*-1}$ $P(X_{trt} = 1) = p^*$	$\Gamma_1(t) = \int_0^t \gamma_1^* \, du = \gamma_1^* t$
c) Additive hazards model with explanatory variable X_{cont}, T_D is exponentially distributed	$\alpha(t\|X_{cont}) = \gamma_0^*(t) + \gamma_2^* X_{cont}$ $\gamma_0(t) = \gamma_0^*$ $E(X_{cont}) = \delta_0^*$	$\Gamma_2(t) = \int_0^t \gamma_2^* \, du = \gamma_2^* t$

Event times T_D were generated using the Stata command `survsim` (see [59]) according to the models for $\alpha(t|X_{trt})$ and $\alpha(t|X_{cont})$ shown in Table 3-2. The command allows complex survival time data to be generated with user-defined hazard functions. These user-defined hazard functions comprised a baseline hazard $\gamma_0(t)$ and an effect representing the additive contribution to the hazard of X_{trt} or X_{cont}, given by γ_1^* or γ_2^* respectively. The baseline hazard was either set to a constant γ_0^* in setting a) or c), or given by $\gamma_0(t) = \nu^* \kappa^* t^{\nu^*-1}$ where $\kappa^*>0$ and $\nu^*>0$ in setting b). The binary treatment indicator X_{trt} was generated using a uniformly distributed random variable U_1 defined over the interval (0,1) with a cutoff $0<p^*<1$ such that $X_{trt}=0$ if $U_1<p^*$, $X_{trt}=1$ if $U_1 \geq p^*$.

Values of X_{cont} were drawn from a normal distribution with mean δ_0^* (see below) and standard deviation 0.2. The value of the standard deviation was chosen to ensure a reasonable spread of values of X_{cont} about δ_0^*.

Several values were specified for γ_1^* and γ_2^* (the coefficients for the explanatory variables X_{trt} and X_{cont} respectively). For simplicity, these parameters values are set to certain values in the interval (0,1]. Values of the baseline parameters γ_0^*, ν^* and κ^* were chosen so that:

a) the 75th percentile of survival time (when reporting ends in accordance with the recommendations of Hosmer and Royston [56]) would fall at time t=4; results of the simulations are reported at t=1,2,3,4 (see below);
b) the differences in hazards associated with the explanatory variables corresponded to plausible hazard ratios, because hazard ratios are a more familiar effect measure. For

example, in simulation setting 1 (see Table 3-3) the coefficient for X_{trt}, γ_1^*, was set to 0.2. The baseline hazard γ_0^* was set to 0.27, corresponding to a hazard ratio associated with X_{trt} of 1.74.

Parameter values chosen for the simulations are reported in Table 3-3 below.

Table 3-3 Simulation parameters for evaluation of the additive hazards model

	Explanatory variable X_{trt}			
Simulation setting number	1	2	3	4
Parameter				
$\gamma_0^*(t)$	0.27	0.20	-	-
κ*	-	-	0.40	0.25
ν*	-	-	0.70	0.85
γ_1^*	0.20	0.50	0.20	0.50
p*	0.5 for all settings 1-4			
	Explanatory variable X_{cont}			
Simulation setting number	5		6	
Parameter				
$\gamma_0^*(t)$	0.10		0.07	
γ_2^*	0.50		1.00	
δ_0^*	0.50		0.30	

In these simulations, administrative censoring was set to be minimal for simplicity. To achieve this, censoring time was chosen to be t=5 for all individuals. Given the choices of parameter values shown in Table 3-3, this means that death would be experienced by all but a handful of individuals. There was no censoring apart from this administrative censoring.

Each simulation generated 1000 datasets with N=3000 individuals. The dataset size of N=3000 was chosen to be similar to the size of the Zactima trials dataset (see chapter 2).

3.4.2 Evaluation of the model using the simulated datasets

The estimates obtained by fitted the additive hazards model using the methods described in section 3.3 were compared with the true values of the estimands using the metrics listed in

Table 3-4 below. The symbol τ refers generically to the true value of the parameter of interest ($\Gamma_1(t)$ or $\Gamma_2(t)$).

Table 3-4 Metrics reported for the additive hazards model simulations with a single explanatory variable

Metric[1]	**Interpretation**
τ	True value of the quantity of interest set in the data generation process
$\bar{\tau} = \frac{\sum_p \widehat{\tau_p}}{P}$	Mean value of the estimate of τ across simulation runs
$\frac{\bar{\tau} - \tau}{\tau} \times 100$	Percentage bias
Percentage of times the 95% confidence interval for $\hat{\tau}_p$ includes τ	95% coverage
$\frac{\sum_p SE(\widehat{\tau_p})}{P}$	Mean model-based standard error
$SE(\hat{\tau}) = \sqrt{\frac{1}{P-1}\sum_p (\widehat{\tau_p} - \bar{\tau})^2}$	Empirical standard error

[1]Note that $\hat{\tau}_p$ denotes the estimate from simulated data set p, p=1, … P; P=1000.

The choice of these metrics is based on Burton [60] and aims to provide quantitative evaluation of the model rather than the simple graphical comparison that is common in the literature (see for example [42]).

The metrics are reported at four timepoints, t=1,2,3,4. The last of the four timepoints represents the approximate 75th percentile of T_D, in accordance with Hosmer and Royston [56]. A graphical comparison of the estimands and mean values of the estimates over time (as used widely in the literature) is also provided for one simulation setting as an illustrative example.

Burton [60] recommends that coverage should be within approximately 2 standard errors of the nominal coverage probability q, $SE(q) = \sqrt{q(1-q)/P}$ to control the probability of type I error. The acceptable level of coverage for a 95% confidence interval based on 1000 repetitions is therefore between 93.6% and 96.4%. Percentage bias as defined in Table 3-4 should be low at each time point if the additive hazards model performs well in the settings shown in Table 3-2 and Table 3-3.

3.4.3 Results from the simulation studies

Table 3-5 shows results of simulation settings 1-4 evaluating the additive hazards model with a fixed binary explanatory variable X_{trt}. The table confirms good agreement of the estimates with the true values, with low percentage bias (below 1%) at each of the four evaluation timepoints. Coverage falls within the acceptable boundaries at each evaluation timepoint. The empirical and model-based standard errors of $\widehat{\Gamma_1}(t)$ are close, which according to Burton [60] signals a lack of bias in the estimated standard errors. By design, the final evaluation timepoint t=4 falls close to the mean of the 75th percentile of T_D across simulations.

Table 3-5 Evaluation of the performance of the additive hazards model with explanatory variable X_{trt}. The values of baseline parameters γ_0^* or κ* and ν* are given as footnotes. Results are based on 1000 simulated data sets of N=3000 individuals.

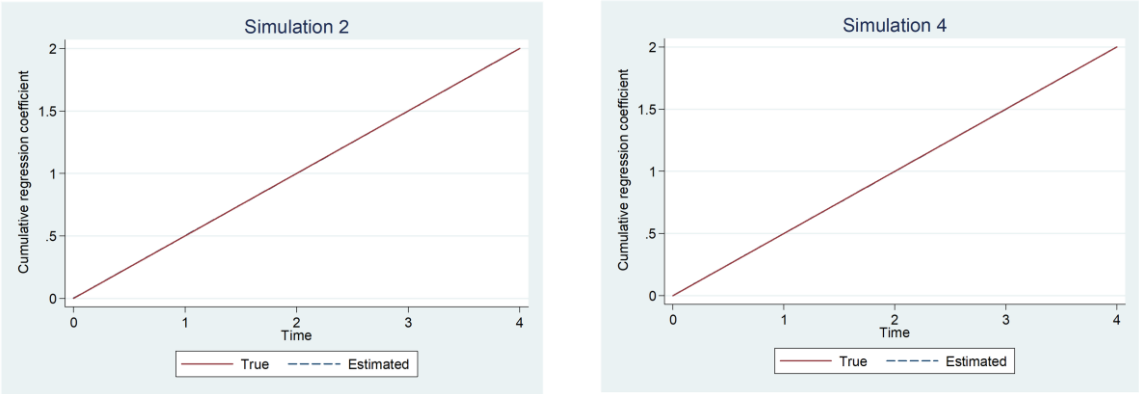
	Simulation setting	T_D follows an exponential distribution Time				Simulation setting	T_D follows a Weibull distribution in the baseline group Time			
		1	2	3	4		1	2	3	4
	1	γ_1^*=0.2[1]				3	γ_1^*=0.2[3]			
True value $\Gamma_1(t)$		0.2	0.4	0.6	0.8		0.2	0.4	0.6	0.8
Mean of estimates $\widehat{\Gamma_1}(t)$		0.199	0.399	0.598	0.798		0.200	0.400	0.599	0.798
Mean percentage bias		-0.09	-0.16	-0.27	-0.28		0.05	-0.11	-0.24	-0.22
Mean % of deaths in sample		30.6	51.3	65.5	75.4		38.9	56.3	67.3	74.7
95% coverage		95.7	95.0	94.8	95.8		95.2	94.6	95.3	95.4
Empirical / Model-based SE		0.024 /0.025	0.039 /0.039	0.053 /0.054	0.071 /0.071		0.029 /0.029	0.043 /0.043	0.055 /0.056	0.069 /0.069
	2	γ_1^*=0.5[2]				4	γ_1^*=0.5[4]			
True value $\Gamma_1(t)$		0.5	1.0	1.5	2.0		0.5	1.0	1.5	2.0
Mean of estimates $\widehat{\Gamma_1}(t)$		0.500	0.999	1.499	1.999		0.499	0.999	1.500	2.000
Mean percentage bias		0.04	-0.10	-0.05	-0.02		-0.14	-0.12	0.01	-0.02
Mean % of deaths in sample		34.2	54.1	66.4	74.5		37.4	56.4	67.6	74.8
95% coverage		95.4	94.9	95.1	94.8		95.4	94.7	95.1	94.9
Empirical/ Model-based SE		0.028 /0.029	0.049 /0.049	0.073 /0.073	0.108 /0.106		0.029 /0.030	0.049 /0.050	0.074 /0.075	0.109 /0.106

[1] γ_0^*=0.27 [2] γ_0^*=0.20 [3] κ*=0.40, ν*=0.70 [4] κ*=0.25, ν*=0.85

Illustrative example 3-3

Figure 3-3 shows graphs comparing the true cumulative regression coefficient for X_{trt}, $\Gamma_1(t)$, with the mean value of the estimates across simulations $\widehat{\Gamma_{1p}}(t), p = 1, \ldots 1000$, both plotted against time for simulation settings 2 and 4. The graph for simulation setting 2 provides an illustrative example of the performance of the estimator $\widehat{\Gamma_1}(t)$ when T_D is exponentially distributed, while the graph for simulation setting 4 provides an illustrative example when T_D follows a Weibull distribution in the baseline group. For each simulated dataset p of the 1000 generated, the value at evaluation timepoint t' of $\widehat{\Gamma_{1p}}(t')$ is taken as the value of $\widehat{\Gamma_{1p}}(t_D)$ estimated at the last event time before time t', so that very little time elapsed between the t_D and the corresponding t'. The values of the $\widehat{\Gamma_{1p}}(t')$ are then averaged over the 1000 simulations.

Figure 3-3 Example graphs showing the values of $\Gamma_1(t)$ and the mean $\widehat{\Gamma_1}(t)$ over time from simulation setting 2 (left) and simulation setting 4 (right). The dashed lines representing the mean of the $\widehat{\Gamma_1}(t)$ are hidden beneath the solid lines representing $\Gamma_1(t)$. In both of these examples $\gamma_1(t) = \gamma_1^* = 0.5$.



The graphs in Figure 3-3 indicate that the estimator provides unbiased estimates.

Table 3-6 shows results of the simulations for settings 5 and 6 evaluating the additive hazards model with a continuous explanatory variable X_{cont}. Percentage bias in the $\widehat{\Gamma_2}(t)$ is negligible (less than 1% at all evaluation timepoints) and coverage is inside the acceptable range at each evaluation timepoint. The empirical and model-based standard errors of the $\widehat{\Gamma_2}(t)$ are close at each timepoint, confirming a lack of bias in the estimates [60].

Table 3-6 Evaluation of the performance of the additive hazards model with explanatory variable X_{cont}. The values of baseline parameters γ_0^* and δ_0^* are given as footnotes. Results are based on 1000 simulated data sets of N=3000 individuals.

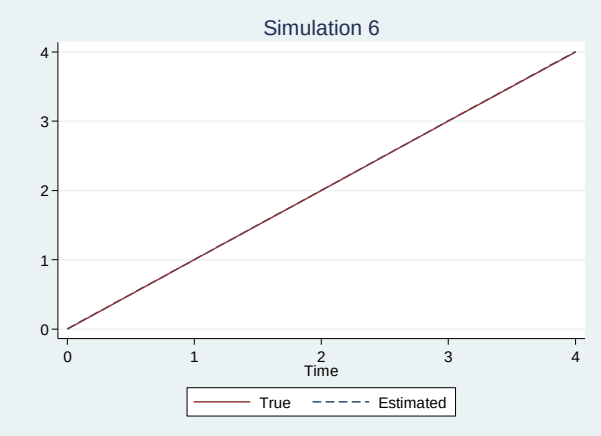
	Simulation setting	T_D follows an exponential distribution Time			
		1	2	3	4
	5	γ_2^*=0.5[5]			
True value $\Gamma_2(t)$		0.5	1.0	1.5	2.0
Mean of estimates $\widehat{\Gamma_2}(t)$		0.497	0.999	1.498	1.993
Mean percentage bias		-0.64	-0.04	-0.15	-0.36
Mean % of deaths in sample		29.2	49.3	63.4	73.3
95% coverage		95.8	95.0	95.2	95.5
Empirical / Model-based SE		0.058 /0.059	0.091 /0.091	0.123 /0.021	0.151 /0.052
	6	γ_2^*=1.0[6]			
True value $\Gamma_2(t)$		1	2	3	4
Mean of estimates $\widehat{\Gamma_2}(t)$		0.999	2.004	2.998	3.990
Mean percentage bias		-0.09	0.22	-0.06	-0.25
Mean % of deaths in sample		30.6	51.3	65.5	75.3
95% coverage		95.5	95.4	95.8	95.5
Empirical/ Model-based SE		0.124 /0.122	0.187 /0.188	0.251 /0.253	0.316 /0.321

[5] γ_0^*=0.1, δ_0^*=0.5 [6] γ_0^*=0.07, δ_0^*=0.3

Illustrative example 3-4

Figure 3-4 is a graphical example showing the true cumulative regression coefficient for X_{cont}, $\Gamma_2(t)$, with the mean value of the estimates across simulations $\widehat{\Gamma_{2p}}(t), p = 1, \ldots 1000$ plotted against time for simulation setting 6. The superimposition of the lines representing $\Gamma_2(t)$ and the mean of $\widehat{\Gamma_2}(t)$ indicate good agreement between the true values and the estimated values.

Figure 3-4 Example graph showing the values of $\Gamma_2(t)$ and the mean $\widehat{\Gamma_2}(t)$ over time from simulation setting 6. The dashed line representing the mean of the $\widehat{\Gamma_2}(t)$ are hidden beneath the solid line representing $\Gamma_2(t)$. In this example $\gamma_2(t) = \gamma_2^* = 1.0$.



From the results reported in Table 3-5 and Table 3-6, the additive hazards model seems to perform well for both continuous (X_{cont}) and binary (X_{trt}) explanatory variables.

3.5 Summary

In this chapter, the additive hazards model has been introduced using the counting process framework. Results presented in section 3.4.3 have confirmed the expectation that fitting the additive hazards model produces unbiased estimates of the cumulative regression coefficients in models with a single time-fixed explanatory variable in the settings investigated, when the data were generated using an additive hazards model. The simulations in this chapter have not been exhaustive, but have provided an illustration of how the additive hazards model works, and have demonstrated how the performance of simulations in this thesis can be evaluated.

Having established that the additive hazards model produces unbiased estimates that perform well in simple situations and with a realistic number of observations (N=3000), chapter 4 reports results from the analysis of the Zactima trials using additive hazards models.

4 Estimating treatment effects in the Zactima trials using the additive hazards model

4.1 Introduction

The analyses reported in chapter 2 indicate that treatment is protective of progression in the Zactima trials. A Cox model fitted on the pooled dataset to estimate the effect of treatment on death gives evidence of a borderline protective effect of treatment, which however disappears when progression is added to the model as an additional explanatory variable.

As noted in chapter 3, two drawbacks of the Cox model are its assumption of proportionality and the difficulty of identifying time-varying covariate effects (see [48, 50, 53] and section 3.1). The additive hazards model [53], in contrast, does not assume proportionality and allows covariate effects to vary freely over time. Using additive hazards models to investigate the effects of treatment on progression and death therefore allows the relationships between the explanatory variables and outcomes to be explored, without the limitations of the Cox model.

4.1.1 Aims

This chapter estimates cumulative regression coefficients associated with treatment in the Zactima trials by fitting additive hazards models. These estimates are compared with the results from the Cox models fitted in chapter 2.

The aims of the chapter are:

1. to demonstrate the implementation of additive hazards models in the pooled Zactima dataset by estimating the effects of treatment on:
    a. progression
    b. death, not adjusting for progression
    c. death, adjusting for progression by including progression as a time-updated explanatory variable;

2. to compare these treatment effect estimates with those obtained using Cox models, and determine whether the Cox model estimates adequately summarise treatment effects in the pooled Zactima trials.

4.2 Methods

The additive hazards models listed in Table 4-1 were fitted separately to estimate the effects of treatment on the outcomes of progression and death. All the additive hazards models include the fixed baseline covariates common to the three trials (specified in section 2.2). The covariate effects in the additive hazards model were allowed to vary with time (hence relaxing the proportional hazards assumption of the Cox model). Estimates of treatment effect therefore take into account possible imbalances across treatment groups with respect to these variables, and their time-varying effects [52]. In addition, and as for the Cox model specifications, the models control for heterogeneities across trials that may confound the effect of treatment on the outcomes (by using a trial indicator).

Using a similar notation to that adopted in earlier chapters:

- $\alpha_{prog}(t)$ represents the hazard of progression at time t;
- $\alpha_{dth}(t)$ represents the hazard of death at time t;
- *treat* is a binary variable indexing treatment group;
- *prog(t)* is a binary time-updated explanatory variable indicating progression, such that if $prog(t_j)$=1 then $prog(t_k)$=1 for all k>j;
- The vector **trial** includes two indicator variables for membership of the Zephyr and Zeal trials respectively. The vector of regression coefficients associated with these indicators at time *t* is written as $\boldsymbol{\gamma}_2(t)$;
- the vector **W** includes all nine fixed baseline explanatory variables common to all three trials specified in section 2.2. These variables are coded as categorical variables with observed values **w**. The vector of regression coefficients associated with these explanatory variables at time *t* is written as $\boldsymbol{\gamma}_4(t)$.

Table 4-1 Additive hazards models fitted to the Zactima trials data to estimate treatment effects on progression and death

Outcome	Description	Estimation model	Model number
Progression	Effect of treatment on progression	$\alpha_{\text{prog}}(t) = \gamma_0^{(1)}(t) + \gamma_1^{(1)}(t)\text{treat} + \boldsymbol{\gamma_2^{(1)\mathrm{T}}}(t)\mathbf{trial} + \boldsymbol{\gamma_4^{(1)\mathrm{T}}}(t)\mathbf{w}$	4-1
Death	Effect of treatment on death, not adjusting for progression	$\alpha_{\text{dth}}(t) = \gamma_0^{(2)}(t) + \gamma_1^{(2)}(t)\text{treat} + \boldsymbol{\gamma_2^{(2)\mathrm{T}}}(t)\mathbf{trial} + \boldsymbol{\gamma_4^{(2)\mathrm{T}}}(t)\mathbf{w}$	4-2
	Effect of treatment on death, adjusting for progression	$\alpha_{\text{dth}}(t) = \gamma_0^{(3)}(t) + \gamma_1^{(3)}(t)\text{treat} + \boldsymbol{\gamma_2^{(3)\mathrm{T}}}(t)\mathbf{trial} + \gamma_3^{(3)}(t)\text{prog}(t) + \boldsymbol{\gamma_4^{(3)\mathrm{T}}}(t)\mathbf{w}$	4-3

As described in chapter 3, the values of all regression coefficients $\gamma_{\cdot}^{(\cdot)}(t)$ may vary freely over time. $\gamma_0^{(\cdot)}(t)$represents the hazards at time t in the baseline treatment group, where the values of all covariates are set to the reference level. The parameters of interest in these analyses are the $\gamma_1^{(\cdot)}(t)$, which represent the additive effects of treatment at time t adjusted for trial, baseline covariates and, in Model 4-3, progression.

The estimates of treatment effect are reported as graphs of the cumulative regression coefficients $\widehat{\Gamma_1^{(\cdot)}}(t) = \sum_{t_j \le t} \widehat{\gamma_1^{(\cdot)}}(t_j)$ against time [20, 38, 42]. As recommended by Royston [56], the x-axes of all graphs presented in this chapter are truncated near the 75$^{\text{th}}$ percentile of follow-up time.

The 95% pointwise confidence limits for $\Gamma_1^{(\cdot)}(t)$ [20] are graphed together with estimates of $\widehat{\Gamma_1^{(\cdot)}}(t)$. The performance of the models is assessed by plotting observed against expected numbers of events in each treatment group using the method of Arjas [20, 53, 58] outlined in section 3.3. These plots are intended to provide an overview of how well the model predicts the total number of events experienced by time t. Model fit is investigated for different subgroups of interest (see section 3.3), in this case by treatment group. If the model perfectly predicts the numbers of events experienced within each treatment group, the plot will take the form of a straight line along y=x. Deviations from the line show where the model overestimates or underestimates the number of events in each group. The Arjas plot was chosen to assess model fit on the basis of a recommendation by Aalen et al in [20]. The simple strategy of comparing observed and expected numbers of events is appealing, and examining the model fit within subgroups adds an extra dimension of information. In addition, the Arjas plot allows model fit to be examined while events are accruing. However, because the

method considers total numbers of events in each subgroup, it is perhaps more suited to assessing overall model fit than to investigating the predictive ability of a single covariate (treatment) in the model. Additional drawbacks are the lack of an explicit time dimension to the plot, and a scarcity of guidance in the literature on how the plot can be produced for an additive hazards model.

4.3 Results

4.3.1 Estimated effect of treatment on progression, adjusting for trial and baseline covariates

The results reported in this section are obtained by fitting an additive hazards model for the effect of treatment on the outcome of progression, adjusting for trial and baseline covariates (Model 4-1).

As reported in Table 2-7, of 2849 patients, 2139 (75%) experienced progression. Of the 1282 patients in the placebo group, 992 patients (78%) experienced progression, while 1147 of the 1567 patients in the treatment group (73%) experienced progression. The median time to progression in the placebo group was 2.9 months, while in the treatment group it was 3.6 months (see Figure 2-2).

Figure 4-1 shows a plot of the estimated cumulative regression coefficient for the effect of treatment on progression, $\widehat{\Gamma_1^{(1)}}(t)$, against time. The x-axis is truncated at 6 months, corresponding approximately to the 75th percentile of time (see [56]). The 95% pointwise confidence limits exclude the null value of 0 after about 1 month, meaning that the cumulative effect of treatment on progression reaches statistical significance at around 1 month. At 1 months, the cumulative effect of treatment on progression is -0.042, with a 95% confidence interval of [-0.067, -0.018], meaning that treatment is protective of progression. At 3 months, the cumulative effect is -0.23 [-0.31, -0.15]. At 6 months, the cumulative effect is -0.36 [-0.51, -0.20]. The appearance of the slope of the plot is approximately linear after 1 month, meaning that the effect of treatment $\widehat{\gamma_1^{(1)}}(t)$ is constant over time [20, 53].

Figure 4-1 Estimated cumulative regression coefficient and 95% pointwise confidence limits for the effect of treatment on progression, adjusted for trial and baseline covariates (from Model 4-1)

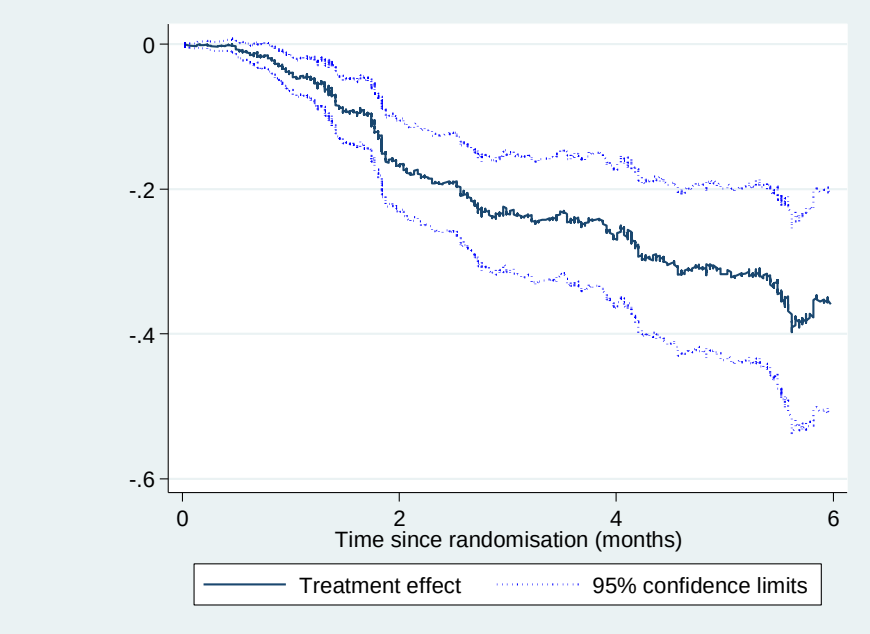
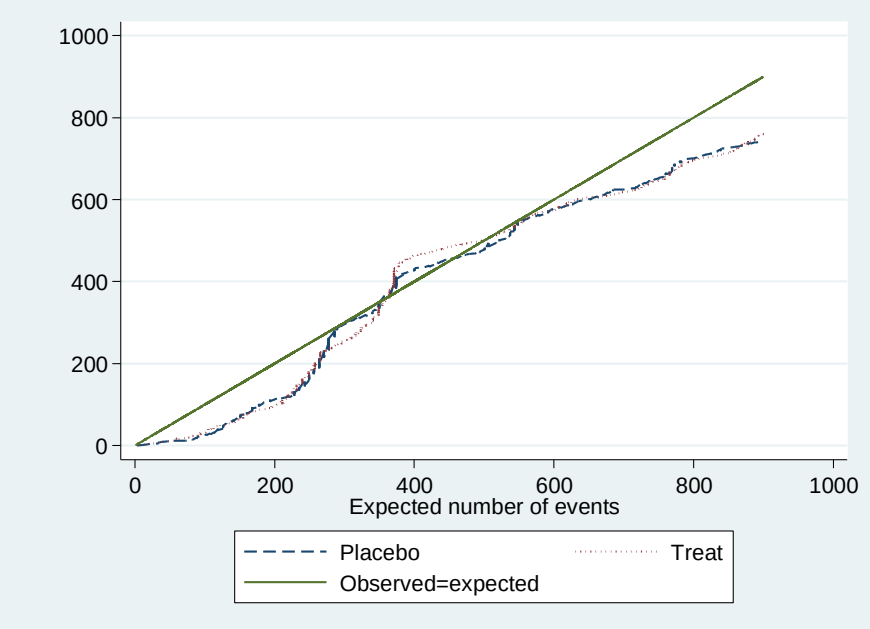


Figure 4-2 shows the Arjas plot of observed against expected number of events by treatment group corresponding to the fitted model. It is truncated at 900 events, which corresponds to approximately 6 months of follow-up time.

Figure 4-2 Arjas plot of observed against expected number of events by treatment group for Model 4-1



The observed and expected cumulative numbers of progressions are quite close, as demonstrated by the straight line passing through the origin. However, the model

overestimates the number of events up until about 250 events have been observed, and after 600 events have occurred. This could result from the omission of important explanatory covariates or interactions between covariates which affect the number of deaths predicted by the model while while not necessarily having much impact on the value of the cumulative regression coefficient for treatment.

4.3.2 Estimated effect of treatment on death, adjusting for trial and baseline covariates but not for progression

The results reported in this section are obtained by fitting Model 4-2.

From Table 2-7, of the total of 2849 patients, 1795 (63%) experienced a death. 799 of the 1282 patients in the placebo group (62%) experienced death, while 996 of 1567 patients in the treatment group (64%) experienced death. The median time to death in the placebo group was 9.3 months compared to 9.7 months in the treatment group. The 75th percentile of time to death was 18 months.

Figure 4-3 shows the cumulative regression coefficient and 95% pointwise confidence limits for the estimated effect of treatment on death not adjusting for progression $\widehat{\Gamma_1^{(2)}}(t)$. As before, the graph is truncated at approximately the 75th percentile of time (18 months after randomisation), as recommended by Hosmer and Royston [56]. The 95% pointwise confidence limits for $\Gamma_1^{(2)}(t)$ derived from Model 4-2 include the null value of 0 throughout the time interval [0, 18], meaning that the estimated effect of treatment on death does not reach statistical significance. The effect is protective, because the slope of the cumulative regression coefficient is negative, and linear after 2 months. At 2 months, the cumulative effect of treatment, $\widehat{\Gamma_1^{(2)}}(t)$, is -0.011 with a 95% confidence interval of [0.015, -0.037]. At 6 months, the cumulative effect is -0.050 [-0.106, 0.005]. At 12 months, the effect is -0.09 [-0.19, 0.02], and at 18 months it is -0.11 [-0.28, 0.07].

Figure 4-3 Estimated cumulative regression coefficient and 95% pointwise confidence limits for the overall effect of treatment on death, adjusting for trial and baseline covariates but not progression (from Model 4-2)

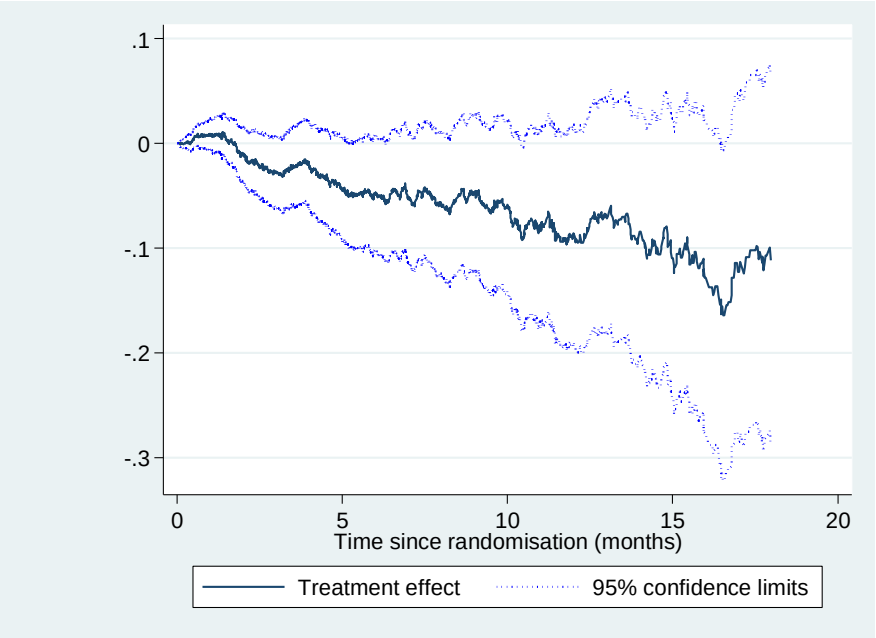
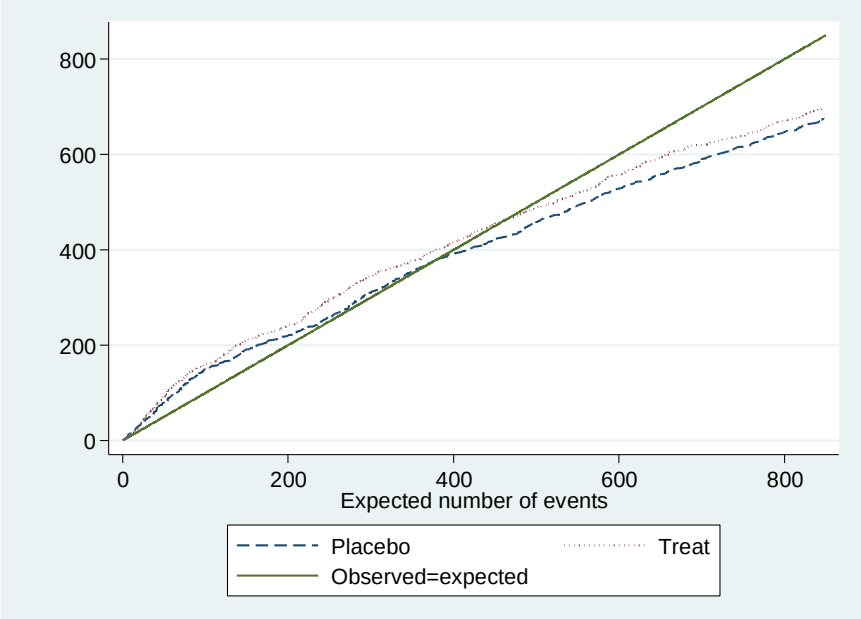


Figure 4-4 below shows an Arjas plot of observed against expected number of deaths from Model 4-2 by treatment group. The plot is truncated at 850 deaths, corresponding approximately to 18 months of follow-up time.

Figure 4-4 Arjas plot of observed against expected number of events by treatment group for Model 4-2



From Figure 4-4, the model appears in general to predict accurately the number of deaths in each treatment group. The model underestimates numbers of deaths in both treatment groups until 200 events have accrued in each group. After around 600 deaths have accrued in each group, the model slightly overestimates the number of deaths expected. This may be a

result of some individuals being more resistant than expected, so they experience death later than predicted by the model. As before, this effect could be explained by missing covariates or interactions which affect the total number of events accrued.

4.3.3 Estimated effect of treatment on death adjusting for trial, baseline covariates and progression

The results reported below are obtained by fitting Model 4-3, which adjusts for trial, baseline covariates and progression. The estimated effect of treatment on death, $\widehat{\Gamma_1^{(3)}}(t)$, represents the estimated effect of treatment on death while progression is held fixed (see chapter 3 and for example [14]).

Figure 4-5 shows the estimated cumulative regression coefficient $\widehat{\Gamma_1^{(3)}}(t)$ and 95% pointwise confidence limits for $\Gamma_1^{(3)}(t)$. As in section 4.3.2, the graph is truncated at 18 months, representing the 75th percentile of death time. The 95% pointwise confidence limits for $\Gamma_1^{(3)}(t)$ include the null value of 0 throughout follow-up, meaning that the effect of treatment on death is not statistically significant. Furthermore, the estimate of the cumulative regression coefficient for the effect of treatment $\widehat{\Gamma_1^{(3)}}(t)$ is close to 0 throughout follow-up, meaning that the estimated effect of treatment on death when trial, baseline covariates and progression are included in the model is negligible. For example, at 2 months the cumulative effect of treatment on death adjusted for progression is -0.0003 with 95% confidence interval [-0.027, 0.026]. At 6 months it is -0.009 [-0.064, 0.046], at 12 months it is -0.015 [-0.121, 0.089] and at 18 months it is -0.002 [-0.181, 0.177].

Figure 4-5 Estimated cumulative regression coefficient and 95% pointwise confidence limits for the effect of treatment on death, adjusting for trial, baseline covariates and progression (from Model 4-3)

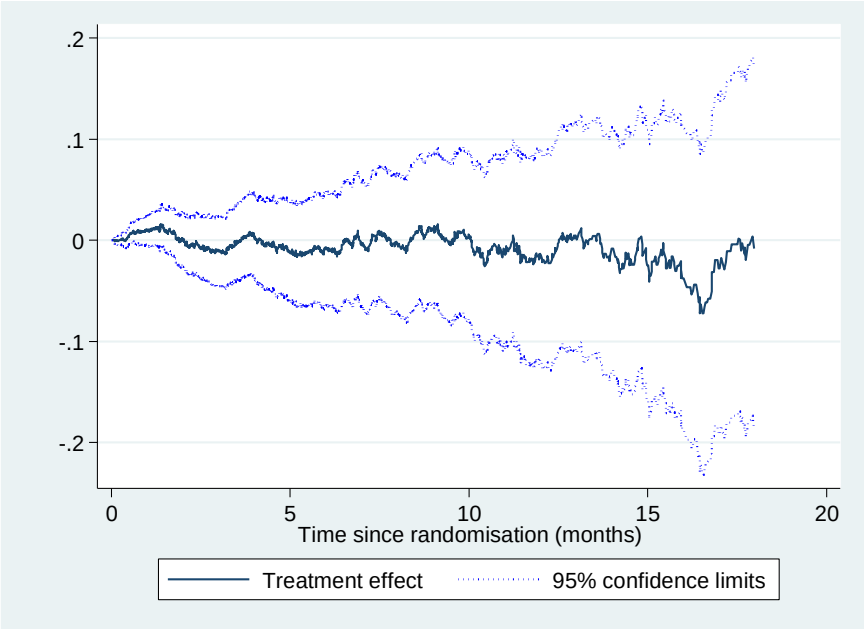


Figure 4-6 below shows an Arjas plot of observed against expected number of events by treatment group from Model 4-3. As for Figure 4-4, the plot is truncated at 850 events, corresponding approximately to 18 months of follow-up time.

Figure 4-6 Arjas plot of observed against expected number of events by treatment group for Model 4-3

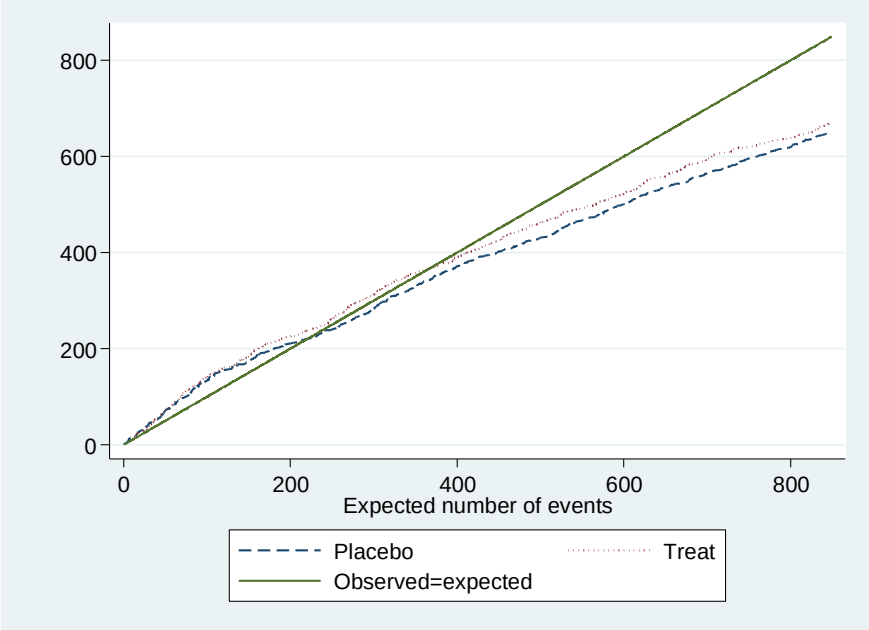


Figure 4-6 is similar to Figure 4-4 (the Arjas plot by treatment group derived from fitting Model 4-2). It indicates that Model 4-3 underestimates the numbers of deaths early in follow-up and overestimates the numbers of deaths later on when more than 600 deaths have accrued in each group.

4.3.4 Comparison of Cox and additive hazards model estimates of treatment effects

The findings reported so far can be summarised as follows:

- The estimated cumulative additive effect of treatment on the hazard of progression, adjusting for trial and baseline covariates, is protective and statistically significant over most of the follow-up time;
- The estimated cumulative additive effect of treatment on the hazard of death adjusting for trial and baseline covariates is protective but not statistically significant during any period of the follow-up;
- The estimated cumulative effect of treatment on death adjusting for trial, baseline covariates, and progression is virtually null over time;
- The effects referred to above are roughly constant over time.

These findings reflect results obtained by fitting Cox models to the pooled Zactima trials data.

The finding that the cumulative regression coefficient plots Figure 4-1, Figure 4-3 and Figure 4-5 show the effect of treatment as a roughly straight line provides some evidence that the effect of treatment is proportional [53, 61].

4.4 Discussion

This chapter has found that treatment has a protective and statistically significant effect on progression when expressed on an additive scale for the hazard. This supports previous findings reported in chapter 2. The change of the estimated effect of treatment on death from protective (though not statistically significant) when progression is not included in the model, to virtually null (and not statistically significant) when progression is added as an explanatory variable, suggests that some effect of treatment on death is working through the intermediate event of progression. This corroborates the findings reported in chapter 2 from fitting Cox models.

The performance of the additive hazards models set out in Table 4-1 in predicting the numbers of events has been assessed using Arjas plots. These indicate that the additive hazards models

for the effect of treatment on progression or death provide a good fit to the data for much of the follow-up time.

In general, there is no evidence of a time-varying effect of treatment on the outcomes of death or progression when expressed on an additive scale. This was also found on the hazard ratio scale. Hazard ratios estimated by fitting Cox models to the pooled trials datasets (as in chapter 2) would therefore be a simpler way of reporting the treatment effect estimates than the plots of the cumulative regression coefficients presented in this chapter. However, as there is a suggestion in this dataset that the effect of treatment on death may work through progression, the additive hazards model provides a basis for this indirect effect to be estimated using the method of dynamic path analysis [20, 30, 31].

5 Introduction to mediation analysis

5.1 Introduction

In clinical trials, the primary statistical analysis usually addresses a question about whether a treatment affects the primary outcome. Secondary analyses may investigate whether a treatment affects intermediate variables that in turn affect the outcome. This additional step helps elucidate whether and how the treatment works by considering the role of intermediate variables in mediating the treatment-outcome relationship, and therefore involves concepts and methods that belong to mediation analysis.

The history of mediation analysis is rooted in the social sciences and is linked to the path analysis approach of Wright [36, 37]. In the social sciences, path analysis is one approach to mediation analysis, while others include Baron and Kenny's causal steps [40, 41] and the difference method (see [23, 62, 63]). The terminology used in this chapter is based on this tradition, while other more recent approaches to mediation analysis use different vocabularies (see for example [21-23, 64-66]).

Path analysis was originally defined for continuous dependent variables, implying a setting with a continuous mediator and a continuous outcome. Dynamic path analysis is an adaptation of path analysis to settings with a continuous mediator and a survival outcome [20, 30, 31]. This chapter describes a novel extension of dynamic path analysis to a setting with a time-updated binary mediator (equivalent to a survival mediator) and a survival outcome. This extension is relevant for clinical settings, in particular clinical trials with a composite time-to-event outcome (see chapter 1).

5.1.1 Aims

The aims of this chapter are:

1) To describe traditional mediation analysis, and introduce path analysis as a means of estimating mediated effects;
2) To describe dynamic path analysis, which applies to the setting with a continuous mediator and a survival outcome;
3) To describe how dynamic path analysis can be extended to a setting with a time-updated binary (survival) mediator and a survival outcome.

5.2 Introduction to mediation analysis

The section first describes the causal steps framework introduced by Baron and Kenny [40, 41] to infer mediation [33], together with the method of difference of coefficients to estimate mediated effects. Path analysis is then introduced as another, related, method of estimating mediated effects. The section considers simple settings and concludes with comments on the implications and assumptions of traditional mediation analysis, as they have implications for the development proposed in this thesis.

The variables of interest in this setting are:

- X, a binary explanatory variable taken in this chapter to indicate treatment group;
- Y, a continuous outcome (equivalent to the distal event referred to in chapter 1);
- M, a continuous mediator variable (equivalent to the proximal event or intermediate variable referred to in chapter 1);
- Confounding variables denoted C. C_1 is a confounder of the X-Y relationship, C_2 is a confounder of the X-M relationship, C_3 is a confounder of the M-Y relationship, and C_4 is a confounder of the M-Y relationship that is affected by X (see Figure 5-2 and Figure 5-3). Whenever multiple confounders for each of these relationships are referred to, the vector notation $\mathbf{C}=(C_1, C_2, \ldots, C_k)$ is used.

The direct effect of X on Y is understood to represent the effect of X on Y when the level of M is held fixed. The indirect effect is thought of as that part of the effect of X on Y which

operates only through changing levels of M [14, 67]. Note that the direct and indirect effects terminology should be used in conjunction with a specified mediator M, as the direct effect of X on Y can include indirect effects mediated through variables other than M.

5.2.1 Baron and Kenny's causal steps

The framework of Baron and Kenny [40, 41], often referred to as the causal steps approach [33], is frequently used as a starting point in traditional mediation analysis [33]. By itself, it does not provide estimates of the size of mediated or unmediated treatment effects.

Assuming for simplicity that there are no confounders, the relationships between X, M and Y are described within this framework using the following linear regression models:

$$\mathrm{E}(\mathrm{Y}|\mathrm{X}) = \beta_0' + \beta_1'\mathrm{X} \quad \text{5-1}$$

$$\mathrm{E}(\mathrm{Y}|\mathrm{X},\mathrm{M}) = \beta_0 + \beta_1\mathrm{X} + \beta_2\mathrm{M} \quad \text{5-2}$$

$$\mathrm{E}(\mathrm{M}|\mathrm{X}) = \delta_0 + \delta_1\mathrm{X} \quad \text{5-3}$$

where E(..|..) denotes expectation.

The relationship between models 5-1, 5-2 and 5-3 and direct and indirect effects is specified later in this section.

The causal steps approach as described by Kenny [15] suggested consideration of the true values of the parameters in models 5-1, 5-2 and 5-3 to infer mediation. The following conditions must hold in order for M to be considered a mediator of the X-Y relationship [40, 41]:

1. X must have an overall effect on Y, meaning that $\beta_1' \neq 0$;
2. X must have an effect on M, meaning that $\delta_1 \neq 0$;
3. M must affect Y when X is controlled, meaning that $\beta_2 \neq 0$;
4. If M completely mediates the X-Y relationship, the effect of X on Y should be explained by M, so that $\beta_1 = 0$ when $\beta_1' \neq 0$ [15].

Some qualifications to these conditions have been proposed. Condition 1 does not necessarily need to hold for mediation to be present, because the overall effect of X expressed as β_1' comprises both the direct and indirect effects. If these effects have the same magnitude but

opposite sign [14] β_1' may equal zero in the presence of mediation [14, 32, 33, 67]. Condition 4 only needs to hold when there is complete mediation [15]; partial mediation occurs when $\beta_1 \neq 0$ but $|\beta_1'| > |\beta_1|$[14, 67]. Conditions 2 and 3, however, continue to be widely accepted as criteria for determining mediation [14, 15, 32].

In earlier work on the causal steps approach [40, 41], models corresponding to expressions 5-1, 5-2 and 5-3 were fitted and the statistical significance of the relevant parameter estimates considered [32, 40, 41, 68]. This approach was superseded, as using the statistical significance of parameter estimates to infer mediation is problematic because statistical significance is a function of sample size [15]. In addition, associations between variables may exist in the absence of statistical significance [14, 33, 67, 68], especially when the variables are highly correlated [33, 40, 41].

One important underlying assumption made when inferring mediation using the causal steps approach is that of temporal ordering [14], meaning that that X precedes M which precedes Y [14, 32, 33, 41]. This has implications for the analysis of data collected from certain study designs; for example, temporal ordering may be difficult to establish in a cross-sectional study.

Models 5-1, 5-2 and 5-3 are linear regression models. The interpretation of the parameters given above requires that both X and M have linear effects on Y and that X has a linear effect on M [14, 15, 19, 33]. The models assume that there is no interaction between X and M and no other non-linearities in these variables, and that the relationships between the variables are correctly specified. More generally, for the causal interpretation of the results, there should be no omitted confounders in the three models [14, 15, 32, 33, 40, 41] and all variables should be accurately measured [15, 40, 41]). The additional statistical assumption of independent error terms with constant variance is often quoted for inference but is not required for identification of the mediation parameters, as it is implicit in the causal assumptions given above [32].

The strength of the causal steps approach is in its simplicity. The equations can also be extended to include confounders [14, 32, 41]. However, it does not provide a numerical estimate of mediated and unmediated effects.

5.2.2 Estimation of mediation effects: the difference method

One way of obtaining a numerical estimate of the extent of mediation is to combine parameter estimates obtained by fitting models corresponding to 5-1, 5-2 and 5-3 using the method of difference in coefficients [19]. This method (also known as the difference method) has been described by Judd and Kenny [41], Baron and Kenny [40] and Mackinnon [19, 32, 33, 69].

The difference method relies on the decomposition of the total effect of X on Y into a direct and indirect effect [41]:

$$\text{Total effect} = \text{direct effect} + \text{indirect effect} \qquad \text{5-4}$$

In the absence of confounders, the total effect of X on Y in this framework is given by the coefficient β_1' in model 5-1. The direct effect of X on Y is given by the coefficient β_1 in model 5-2. The indirect effect using the difference method is given by $\beta_1' - \beta_1$, because the change in the coefficient for X from β_1' to β_1 reflects how much of the relationship between X and Y is explained by M [32]. The indirect effect is estimated by fitting models corresponding to 5-1 and 5-2 and calculating $\widehat{\beta_1'} - \widehat{\beta_1}$. The difference method is only valid for parameters from linear models, hence generally for continuous outcomes, or for binary outcomes modelled on the difference scale (such as risk differences in a linear model) [14, 20], and does not hold for binary outcomes modelled on a multiplicative scale (such as odds ratios in a logistic regression model) [14, 17, 19, 20]. The assumptions made when inferring mediation as described in the previous section also apply to the use of the difference method to derive mediated effects.

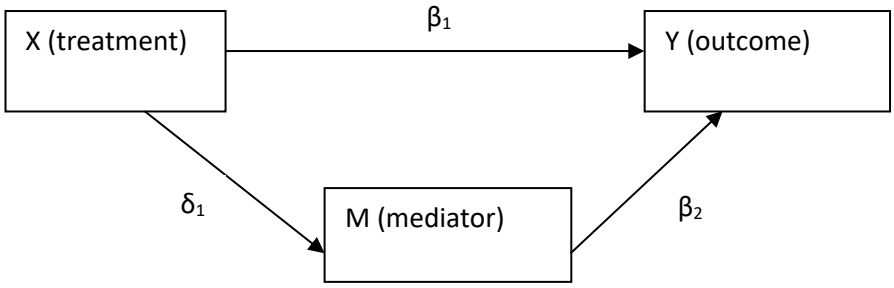
5.2.3 Estimation of mediation effects: path analysis

An alternative approach to estimating direct and indirect effects within the framework described above uses path analysis and is often referred to as the method of product of coefficients or the product method [19].

A path diagrams such as the simple example in Figure 5-1 below illustrates the relationships between X, M and Y. The arrows in the diagram are referred to as paths of influence [36, 37] or causal paths [40]. In Figure 5-1, the direct effect of X on Y is represented by a single arrow between X and Y, while the indirect effect is represented by the path composed of the arrow

from X to M and the arrow from M to Y (referred to as the X-M-Y pathway). Coefficients from models 5-2 and 5-3 are shown as path coefficients in Figure 5-1.

Figure 5-1 Path diagram showing the relationships between a treatment X, an outcome Y and a mediator M, with path coefficients (for simplicity assuming no confounders affecting these relationships)



Path analysis involves the multiplication of regression coefficients along pathways to estimate indirect effects [40]. In this example the indirect effect of X on Y is given by tracing the indirect path between X and Y and multiplying coefficients along the X-M-Y path [36, 37] to give $\delta_1\beta_2$ [40, 41]. The rationale behind this method is that is that a change in X will lead to a δ_1 change in M, and a δ_1 change in M will lead to a $\delta_1\beta_2$ change in Y [14, 19, 32, 33, 40, 41].

The indirect effect of X on Y is estimated by fitting regression models equivalent to models 5-2 and 5-3 and calculating $\widehat{\delta_1}\widehat{\beta_2}$ [14, 32]. The same assumptions concerning no unmeasured confounding of the X-M, X-Y, and M-Y relationships, temporality and correct specification of the regression models analysis apply to this method [32, 33]. For a continuous outcome, or a binary outcome measured on the difference scale, the difference method obtained using equations 5-1 and 5-2 coincides with the product method obtained by path analysis using the equations 5-2 and 5-3 [14, 32, 69]. The total effect of X on Y in the simple setting represented in Figure 5-1 is given by $\beta_1 + \delta_1\beta_2$, corresponding respectively to the direct and indirect effects [37] as in expression 5-4.

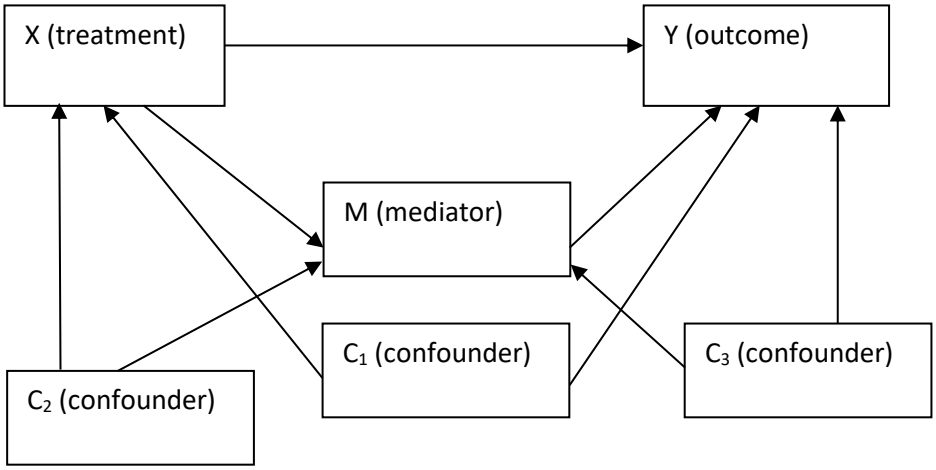
Path analysis can be extended to situations with multiple mediators and explanatory variables [37, 70], subject to additional assumptions about temporality, linearity, lack of interactions and no omitted confounders.

5.2.4 Confounding and mediation analysis

The assumption of no omitted confounders is necessary for implementing the methods discussed above [14, 32]. Confounders in the setting illustrated by Figure 5-1 are common causes of X and Y, or X and M, or M and Y. Failure to include such common causes in the regression models 5-1, 5-2 and 5-3 would lead to bias in the estimates of direct and indirect effects [14].

Considering the simple mediation setting shown in Figure 5-1, four different types of confounders are potentially problematic [14]. Three of these are shown in Figure 5-2. C_1 influences X and Y, C_2 influences X and M, and C_3 influences M and Y.

Figure 5-2 Path diagram showing associations between X, M and Y, and confounding by C_1, C_2 and C_3



In the setting shown in Figure 5-2, if a model corresponding to 5-1 is fitted to estimate the total effect of X on Y, ignoring the relevant confounders, $\widehat{\beta_1'}$ will comprise the direct X-Y effect, the indirect X-M-Y effect, the spurious X-C_1-Y effect which arises because C_1 is a cause of both X and Y, and the spurious X-C_2-M-Y effect which arises because C_2 is a cause of both X and M [24]. When estimating the total effect of X on Y, C_1 and C_2 must be included in the model to remove this confounding effect [16, 66] as shown below. In a randomised clinical trial, if randomisation is successful, levels of C_1 and C_2 are balanced across treatment groups, and confounding of the X-Y relationship would not occur.

Similarly, in the setting shown in Figure 5-2, if a model for Y that includes X and M (such as 5-2) is fitted to estimate the direct effect of X on Y, C_1 and C_3 must be included in this model as shown below so that the estimates of the coefficients of X and M are not confounded [14, 41].

However, because mediation analyses are often secondary analyses, data on potential M-Y confounder C_3 (or confounders $\mathbf{C_3}$) may not be routinely collected. In the context of a randomised trial, M-Y confounding is not usually avoided by randomisation of X [14, 32, 41].

In the same setting, a model for M that includes X (such as model 5-3) must include C_2 so that the estimated coefficient of X is unconfounded [14].

The models including confounders C_1, C_2 and C_3 are shown below:

$$\mathrm{E}(\mathrm{Y}|\mathrm{X}) = \beta_0' + \beta_1'\mathrm{X} + \beta_2'\mathrm{C}_1 + \beta_3'\mathrm{C}_2 \qquad \textbf{5-1 (b)}$$

$$\mathrm{E}(\mathrm{Y}|\mathrm{X},\mathrm{M}) = \beta_0 + \beta_1\mathrm{X} + \beta_2\mathrm{M} + \beta_3\mathrm{C}_1 + \beta_4\mathrm{C}_3 \qquad \textbf{5-2 (b)}$$

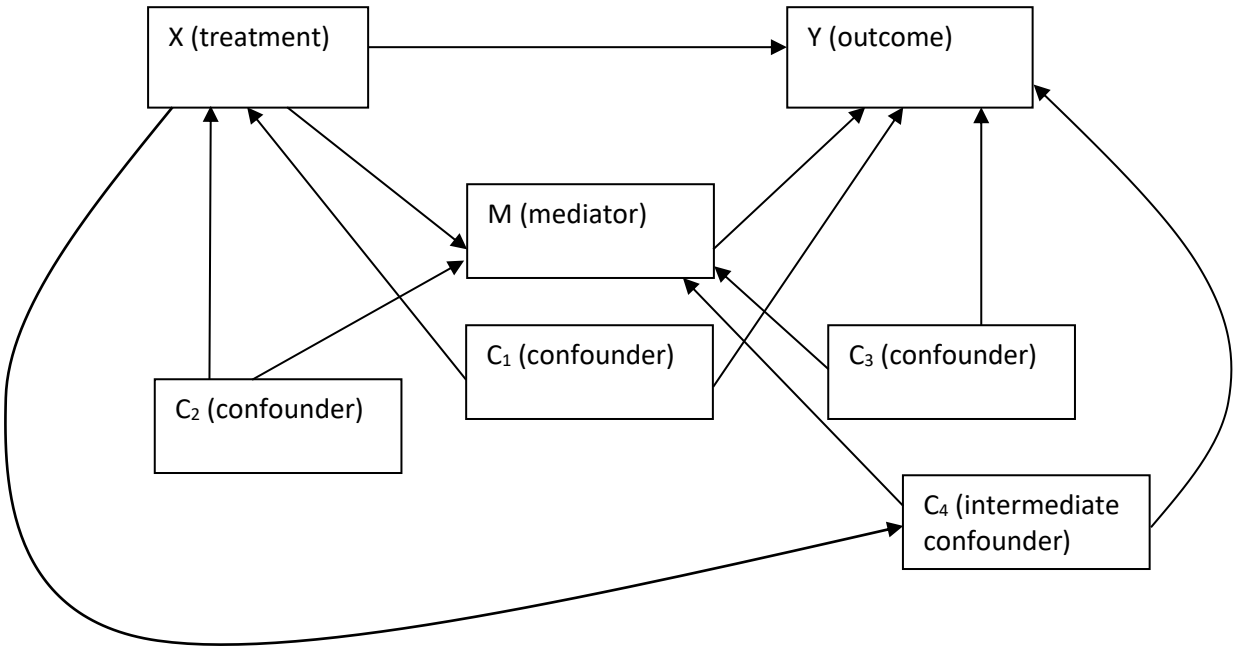
$$\mathrm{E}(\mathrm{M}|\mathrm{X}) = \delta_0 + \delta_1\mathrm{X} + \delta_2\mathrm{C}_2 \qquad \textbf{5-3 (b)}$$

Use of the difference method in mediation analysis requires estimation of β_1' and β_1, that is, the total effect of X on Y, and the direct effect of X on Y. If there are known confounders, this requires fitting models 5-1(b) and 5-2(b). The assumption of no unmeasured C_1, C_2 or C_3, meaning no unmeasured confounding of the X-Y, X-M and M-Y relationships is therefore required to implement the difference method.

Use of path analysis requires estimation of δ_1 and β_2. In the presence of known confounders, this requires fitting models 5-2(b) and 5-3(b). As before, the assumption of no unmeasured C_1, C_2 or C_3 is required to implement the method.

Figure 5-3 below shows a setting similar to the setting depicted in Figure 5-2, but with the addition of C_4, a so-called intermediate confounder that confounds the M-Y relationship and is itself affected by X.

Figure 5-3 Path diagram showing associations between X, M and Y, confounding by C_1, C_2 and C_3, and intermediate confounding by C_4



In this setting, a model for Y that includes X and M (similar to 5-2), if extended to include C_1 and C_3, would not accurately estimate the effect of M on Y, because C_4 is a confounder of the M-Y relationship. Including C_4 in the model will remove this bias, but will also mean that the direct effect of X on Y, which includes the X-C_4-Y path, will not be estimated by the regression coefficient for X [24]. The difference or product methods are thus not able to deal with intermediate confounding using the modelling framework specified in section 5.2.1 [24]. An additional assumption for both methods is therefore the assumption of no intermediate confounding.

5.2.5 Mediation analysis and interaction between X and M

The approaches to mediation analysis described so far require the assumption that models 5-1, 5-2 and 5-3 are correctly specified [14, 33, 40, 41]. One implication of this is that there must be no interaction between X and M or in other words, the change in the expected value of Y associated with M must not vary with differing levels of X [32].

If there were an interaction between X and M, model 5-2 would become:

$$E(Y|X,M) = \beta_0 + \beta_1 X + \beta_2 M + \beta_3 XM \qquad 5\text{-}5$$

where the XM component represents an interaction between X and M, and β_3 the interaction effect, that is, the additional effect of M on Y associated with a 1-unit increase in the value of X (or the additional effect of X on Y associated with a 1-unit increase in the value of M).

The causal steps approach of Baron and Kenny can be adapted to situations where there is an interaction between X and M [15, 40, 41]. However, using the difference method and path analysis for estimating the size of the indirect effect becomes infeasible because there is no clear way to handle the interaction term β_3 [14] when deriving the direct and indirect effects. It is therefore important to establish whether there is an interaction between X and M before using either method. This may be done by fitting a model corresponding to 5-5, and testing the statistical significance of $\widehat{\beta_3}$. However, VanderWeele [14] pointed out that interactions may be important even though the interaction term is not statistically significant. Instead, he suggested examining the magnitude of $\widehat{\beta_3}$ and the extent to which the other estimates in the model are changed by including an interaction term. If the interaction term is small in itself and its inclusion does not induce much change in $\widehat{\beta_1}$ or $\widehat{\beta_2}$, it can be left out of the estimation model with meaningful approximate mediation parameters derived [14].

In the presence of non-linear terms in X or M other than interactions, VanderWeele [14] proposed that path analysis may still be used to test for the presence of mediation. In this case, $\delta_1\beta_2$ can no longer be interpreted as the indirect effect of X on Y; however, if $\delta_1\beta_2 \neq 0$, the presence of an indirect effect could be inferred, under the assumptions of no omitted confounding discussed above [14]. This argument also applies to settings where a binary outcome is modelled using logistic regression. In this setting path analysis gives rise to estimates which cannot be interpreted as direct and indirect effects (see [14, 71]).

5.3 Introduction to dynamic path analysis

This section discusses dynamic path analysis, an extension of path analysis with a survival outcome and a continuous mediator proposed by Fosen, Aalen and colleagues [20, 30, 31]. The method draws on the concepts of path analysis and generalises them to a survival setting for

the outcome [20, 30, 31, 53]. The result is a method of estimating the indirect effect of an explanatory variable on a survival outcome through a continuous mediator. In clinical trials, dynamic path analysis has been used in secondary analysis aimed at exploring the mechanism of action of a treatment (see for example [30, 42, 72].

Dynamic path analysis is presented in this chapter using the counting process notation introduced in chapter 3. For this reason, the following variables are used in this section:

- N(t), the counting process associated with the event of interest [20];
- dN(t), the increment of N(t) [20];
- T_D, the random variable representing time to event;
- $M_{cont}(t)$, a continuous time-varying mediator variable. At event time t, $M_{cont}(t)$ refers to the value of M_{cont} just before time t in line with the usage of Aalen [20].

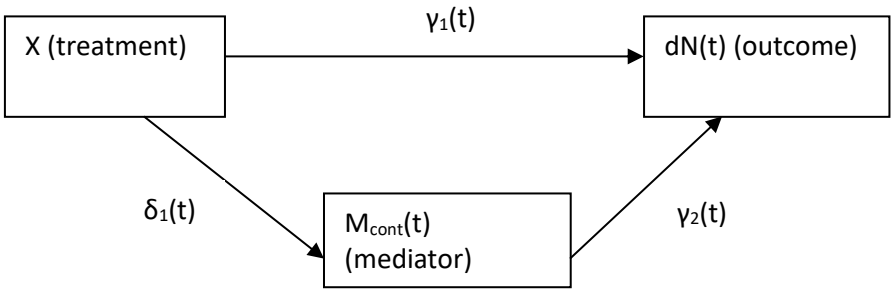
5.3.1 Characteristics of dynamic path analysis

The method of dynamic path analysis [20, 30, 31] can be thought of as a combination of path analysis and the additive hazards model [73]. It comprises a series of path analyses specific to each event time, which lead to estimating time-varying indirect effects by multiplying the relevant path coefficients at each event time [42]. This means that the values of the path coefficients, and the direct and indirect effects, can vary freely over time [20, 30, 31, 42]. This flexibility reflects that of the additive hazards model discussed in chapter 3 [39, 53, 72]. The multiplication of coefficients comprising the indirect effect is possible because in this approach the intensity process is modelled using an additive hazards model.

5.3.2 The dynamic path analysis model

In dynamic path analysis, a path diagram is defined at each event time t [20, 30, 31]. A simple example using X, $M_{cont}(t)$ and dN(t) is shown in Figure 5-4 below. Path coefficients specific to each time are shown in Figure 5-4 and refer to models 5-6 and 5-7 below.

Figure 5-4 Generalised path diagram for the time-specific relationships between X, $M_{cont}(t)$ and the event dN(t). The path coefficients specific to each time are shown in the diagram. From Aalen [20]



As shown in chapter 3, the relationship between the hazard of the event at time t and the covariates X and $M_{cont}(t)$ can be represented by an additive hazards model such as 5-6:

$$\alpha(t|X, M_{cont}(t)) = \gamma_0(t) + \gamma_1(t)X + \gamma_2(t)M_{cont}(t) \quad 5\text{-}6$$

The baseline hazard of the event dN(t) at time t is given by $\gamma_0(t)$, while $\gamma_1(t)$ and $\gamma_2(t)$ represent the mutually adjusted additional hazard associated with a 1-unit increase in X and $M_{cont}(t)$ respectively at time t.

The linear model for $M_{cont}(t)$ is given as model 5-7:

$$E(M_{cont}(t)|X) = \delta_0(t) + \delta_1(t)X \quad 5\text{-}7$$

where $\delta_0(t)$ represents the expected value of $M_{cont}(t)$ at time t when x=0, and $\delta_1(t)$ is the increase in the mean value of $M_{cont}(t)$ at time t when x=1 versus x=0. This model is similar to Model 5-3 but is specific to time t. Using path analysis at each event time as shown in Figure 5-4, the direct effect of X is $\gamma_1(t)$. The indirect effect of X is given by combining the effect of X on $M_{cont}(t)$ and the effect of $M_{cont}(t)$ on dN(t), that is by $\gamma_2(t)\delta_1(t)$, explained by Gamborg [73] in the following way:

> "As a 1-unit difference [in X] causes a [δ_1] … difference in [$M_{cont}(t)$], and a [δ_1] difference in [$M_{cont}(t)$] causes a [δ_1] times [γ_2] excess rate of [dN(t)], the indirect effect … at [time] t is estimated by the following: $\gamma_2(t)\delta_1(t)$".

Dynamic path analysis allows path coefficients to be multiplied together to estimate the indirect effect of X on dN(t) via $M_{cont}(t)$, because the models for the effect of X on $M_{cont}(t)$ at time t, and the effect of $M_{cont}(t)$ on dN(t) at time t, are taken to be linear [20, 30, 38, 42, 74]. The linearity of the model for the outcome dN(t) arises through the use of a counting process to denote the occurrence of the event of interest (see chapter 3 and [20, 53]).

To aid interpretability the direct and indirect effects obtained at each event time are usually reported cumulatively. Following Strohmaier [42], in this thesis the cumulative direct effect

corresponding to Figure 5-4 is given by $\int_0^t \gamma_1(u)du$ and the cumulative indirect effect by $\int_0^t \gamma_2(u)\,\delta_1(u)du$.

5.3.3 Estimating the indirect effect of X on dN(t) using dynamic path analysis

The indirect effect of X on dN(t) can be estimated at each event time t_D using models 5-6 and 5-7 (or their generalisations that include confounders) subject to the assumptions described in section 5.2.1. In particular, these are no unmeasured confounding of the X-$M_{cont}(t)$, X-dN(t) and $M_{cont}(t)$-dN(t) relationships, no intermediate confounding of the $M_{cont}(t)$-dN(t) relationship and no interaction between X and $M_{cont}(t)$ or other non-linearities in X or $M_{cont}(t)$, for every value of t [42, 75].

The estimation process described by Aalen [20] and Fosen [31] is given in the following steps:

1. The first step is to estimate $\delta_1(t)$ by fitting a linear regression model for the effect of X on $M_{cont}(t)$ at each event time t_D corresponding to model 5-7. This produces parameter estimates $\hat{\delta}_0(t_D)$ and $\hat{\delta}_1(t_D)$ for each t_D. Individuals who, just before time t_D, have not yet experienced the event represented by $dN(t_D)$ are included in these regression models.
2. The effect of $M_{cont}(t)$ on dN(t) is estimated by fitting an additive hazards model corresponding to 5-6. At each time t_D, the outcome $dN(t_D)$ comprises a vector of 0s and one 1 indicating the individual who experiences the event at time t_D. This outcome is regressed jointly on X and $M_{cont}(t)$ at each t_D to produce estimates $\hat{\gamma}_0(t_D)$, $\hat{\gamma}_1(t_D)$ and $\hat{\gamma}_2(t_D)$ (see chapter 3 for more information on estimating the additive hazards model). As in step 1, the risk set includes only those individuals who have not yet experienced the event represented by dN(t) just before time t_D.
3. The estimated indirect effect of X on dN(t) via $M_{cont}(t)$ at time t_D is given by $\hat{\gamma}_2(t_D)\hat{\delta}_1(t_D)$.
4. Estimates are often presented graphically as cumulative effects over time. This stabilises them, and makes it easy to identify changes of effect over time by a change in the slope of the graph [20, 30, 31, 53]. The cumulative estimate of the indirect effect of X on dN(t) from time t_0 up to and including time t_D is given by $\sum_{t_j \le t_D} \widehat{\gamma_2}(t_j)\,\widehat{\delta_1}(t_j)$.
5. Similarly, the direct effect is estimated as $\sum_{t_j \le t_D} \widehat{\gamma_1}(t_j)$.

Note that because the models in steps 1 and 2 include those individuals who have not yet experienced the event dN(t) by time t, the parameter estimates are conditional on not having experienced the event by time t. However, as shown by Strohmaier [42], estimates of the indirect effect of X on dN(t) through $M_{cont}(t)$ are not biased by this conditioning on survival up to time t, because the relationship between variables is preserved over time under this conditioning [42] in linear regression models. Strohmaier [42] demonstrates that two independent covariates measured at baseline are still independent at time t conditional on survival. This result is generalised to covariates in a linear structural equation model, and from there to the setting described by Figure 5-4 and equations 5-6 and 5-7. The implication of this is that the estimation of direct and indirect treatment effects is not biased by this conditioning [42].

Dynamic path analysis offers a simple and flexible way of estimating indirect effects on a survival outcome when the mediator is a continuous variable and the event time can be modelled using a simple additive hazards model. It allows all coefficients to vary freely over time, reflecting the view of relationships as processes that develop over time [38]. It does however still bear the constraints that there should not be non-linearities (including interactions) in X and $M_{cont}(t)$.

5.4 Dynamic path analysis with a time-to-event mediator

Dynamic path analysis could be used to estimate the indirect effect of a treatment in the secondary analysis of clinical trials with a time-to-event composite outcome, if appropriately adapted to situations where both the mediator and the distal outcome are time-to-event variables. In this section an adaptation of dynamic path analysis to this setting is proposed.

The distal outcome, as before, is referenced using counting process notation as dN(t). The mediator variable is characterised in this section as a time-updated binary variable $M_{bin}(t)$ with the qualification that if $M_{bin}(t_j)=1$ then $M_{bin}(t_k)=1$ for all $k>j$. Henceforward, $M_{bin}(t)$ will be referred to as a time-updated binary variable, or event mediator.

The new variables which will be referred to in this section are therefore the following:

- $M_{bin}(t)$, a time-updated binary variable indicating whether the event mediator has occurred up to time t;
- T_{Mbin}, the random variable representing time to the mediator;
- $N_{Mbin}(t)$, the counting process associated with the event mediator [20] (in this context, the variable is the same as $M_{bin}(t)$);
- $dN_{Mbin}(t)$, the increment of $N_{Mbin}(t)$ [20].

5.4.1 Model specification in dynamic path analysis with a time-to-event mediator

Dynamic path analysis with a time-to-event mediator uses a similar strategy to dynamic path analysis with a continuous mediator. Assuming that this strategy is appropriate, path coefficients are multiplied together to estimate the indirect effect of X on dN(t) via $dN_{Mbin}(t)$. The models for the effect of X on $dN_{Mbin}(t)$ at time t, and the effect of the time-updated binary variable $M_{bin}(t)$ on dN(t), are taken to be linear. As noted below, this assumption has ramifications that are not present when the mediator variable is continuous.

The assumed model for the hazard of the distal event, $\alpha_D(t)$, expressed as a function of X and $M_{bin}(t)$ is shown below as 5-8, and differs from Model 5-6 only with respect to the nature of the mediator:

$$\alpha_D(t|X, M_{bin}(t)) = \gamma_0(t) + \gamma_1(t)X + \gamma_3(t)M_{bin}(t) \qquad 5\text{-}8$$

In this model, $M_{bin}(t)=1$ for individuals who have experienced the event mediator at or before time t. This model is defined for the set of individuals who have not experienced the distal event by time t and are still in the study.

A linear model for the expected value of $M_{bin}(t)$ is defined in terms of X. Such a model is justified considering that the cumulative incidence of $M_{bin}(t)$, $I(M_{bin}(t))$, is the proportion of individuals at time t who have experienced the intermediate event. The expected value is then modelled in terms of X,

$$E(M_{bin}(t)|X) = \beta_0(t) + \beta_1(t)X \qquad 5\text{-}9$$

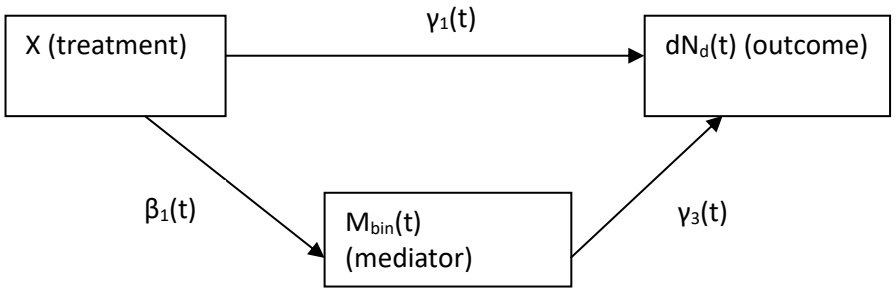
The set of individuals that contributes to the estimation of model 5-9 at time t (viewed from a survival analysis perspective as the risk set at time t) is the same as the risk set for model 5-8, that is, the individuals who have not yet experienced the distal event by time t and are still in

the study. Individuals who have experienced the event mediator some time before time t remain in the set for model 5-9 while they have not experienced the distal event and remain in the study. An additional consideration from fitting model 5-9 arises from the fact that a (potentially multivariable) linear model is fitted on a binary outcome. However, Hellevik [76] argues that this does not necessarily imply a poor model fit, and indeed that, because the interpretation of regression coefficients is straightforward in a linear regression with a binary outcome, such a model may in some cases be preferable to a logistic or other model [76].

The indirect effect of X is given in this setting by combining the effect of X on $M_{bin}(t)$ and the effect of $M_{bin}(t)$ on dN(t), in the same way as described in section 5.3.2 for traditional dynamic path analysis. Using the argument of Gamborg [73], at time t, a 1-unit change in the value of X causes a difference of $\beta_1(t)$ in the expected value of $M_{bin}(t)$, and this $\beta_1(t)$ change in the value of $M_{bin}(t)$ causes a change of $\beta_1(t)$ times $\gamma_3(t)$ in the hazard of dN(t). Therefore, the indirect effect of X at time t is estimated by $\gamma_3(t)\beta_1(t)$ (see Figure 5-5).

The relationships between X, $M_{bin}(t)$ and dN(t) can be shown using a path diagram such as Figure 5-5 below.

Figure 5-5 Generalised path diagram for the time-specific relationships between X, $M_{bint}(t)$ and the event dN(t). The path coefficients specific to each time are shown in the diagram.



As in traditional dynamic path analysis with a continuous mediator, the direct and indirect effects are usually given as cumulative functions. The cumulative direct effect is given by $\int_0^t \gamma_1(u)du$ and the cumulative indirect effect by $\int_0^t \gamma_3(u)\,\beta_1(u)du$.

5.4.2 Estimating the indirect effect of X for an event mediator

This section provides details on estimation based on the models outlined in the previous section. The estimation process for the situation with an event mediator is similar to that described in section 5.3.3 for traditional dynamic path analysis with a continuous mediator. The assumptions of no unmeasured confounders, no intermediate confounders, no interaction between X and $M_{bin}(t)$ and no non-linearities in X and $M_{bin}(t)$ [42, 75] are equivalent to the assumptions of traditional dynamic path analysis described in section 5.3.3. The steps in the estimation process are the following:

1. The first step is to estimate $\beta_1(t)$ by fitting a linear regression model using least-squares regression for the effect of X on $M_{bin}(t)$ corresponding to model 5-9 at each t_D. This produces parameter estimates $\hat{\beta}_0(t_D)$ and $\hat{\beta}_1(t_D)$. As noted above, individuals are censored from the risk set when they experience the distal event, not when they experience the event mediator. Thus, an individual i with any value of $M_{bin,i}(t)$ remains in the risk set at time t while $N_i(t)=0$.
2. The effect of $M_{bin}(t)$ on dN(t) is estimated by fitting an additive hazards model corresponding to model 5-8 at each t_D. The model produces estimates $\hat{\gamma}_0(t_D)$, $\hat{\gamma}_1(t_D)$ and $\hat{\gamma}_3(t_D)$.
3. The estimated direct effect of X on dN(t) at time t_D is given by $\hat{\gamma}_1(t_D)$. The estimated indirect effect of X on dN(t) at time t_D is given by $\hat{\gamma}_3(t_D)\hat{\beta}_1(t_D)$.
4. The cumulative estimate of the direct effect of X over the interval $(t_0, t_D]$ is given by $\sum_{t_j \le t_D} \widehat{\gamma_1}(t_j)$; the cumulative estimate of the indirect effect of X over the same interval is given by $\sum_{t_j \le t_D} \widehat{\gamma_3}(t_j)\,\widehat{\beta_1}(t_j)$.

In section 5.3.3, the work of Strohmaier [42] was cited to show that the dynamic path analysis estimate of the indirect effect of X on dN(t) through a continuous variable $M_{cont}(t)$ is unbiased by conditioning on survival to time t. This argument can also be applied to the current setting, meaning that the dynamic path analysis estimate of the indirect effect of X on dN(t) through $M_{bin}(t)$ should not be affected conditioning on survival to time t.

The performance of the estimator in dynamic path analysis with an event mediator is investigated using simulation studies in chapter 7.

5.5 Summary

This chapter has described some of the traditional approaches to mediation analysis in a clinical trials setting, focusing on traditional mediation analysis and in particular on path analysis. Under conditions of correct model specification, where the model includes no non-linearities in treatment or mediator, no interaction between treatment and mediator, no unmeasured confounding and no intermediate confounding, estimates of the direct and indirect effects of a treatment on an outcome using path analysis are unbiased.

Dynamic path analysis extends the path analysis approach to situations with a survival outcome. This is a flexible method for estimating direct and indirect effects which can readily allow for time-varying covariate effects under similar assumptions to those required by path analysis, where the survival outcome is modelled in terms of an additive hazards model.

Dynamic path analysis as described in the literature to date requires that the mediator be a continuous variable modelled using a linear regression. The extension to dynamic path analysis proposed in this chapter allows the mediator itself to be a time-to-event variable, which is here characterised as a time-updated binary variable in order to implement the dynamic path analysis approach. This setting may arise frequently in the secondary analysis of clinical trials with a composite time-to-event outcome, implying that the extension of dynamic path analysis may be widely applicable in a practical setting.

In chapter 7, the behaviour of estimates obtained by implementing this extended dynamic path analysis will be examined with respect to the effect of losses from the risk set through the censoring event (death).

6 The performance of dynamic path analysis

6.1 Introduction

The method of dynamic path analysis has been implemented in both cohort studies and clinical trials [20, 42, 73, 77] to estimate the indirect effect of an exposure on an outcome through a continuous mediator. This chapter considers the method in the setting of clinical trials.

Subject to the assumptions of no interaction between treatment and the mediator, no unmeasured confounding and no intermediate confounding for all the relevant relationships [17, 20, 21, 24, 30, 32, 64, 78-80] (see chapter 5), it has been shown analytically that dynamic path analysis provides an unbiased estimate of the indirect effect of a treatment [20, 30, 31]. Figure 6-1 shows the relationships between the main variables in a simple setting (confounders are not included for simplicity).

Figure 6-1 Path diagram for the time-specific relationships between X, $M_{cont}(t)$ and the event dN(t) (using notation introduced in chapter 5)

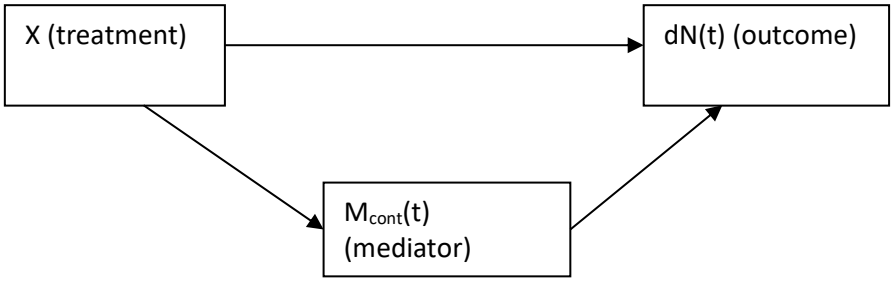


Figure 6-1 is similar to Figure 5-4 but does not contain path coefficients.

This chapter reports the results of simulation studies conducted to verify that application of dynamic path analysis leads to unbiased estimates of the indirect effect of a treatment on an outcome via a continuous mediator. These simulation studies will inform the investigations into the extension of dynamic path analysis to the setting with an event mediator which will follow in chapter 7.

6.1.1 Aims

The simulations reported in chapter 3 investigated the performance of the additive hazards model with a time-fixed binary as well as a time-fixed continuous explanatory variable. The simulation studies presented in this chapter first explore the performance of the additive hazards model with a time-varying continuous explanatory variable, before going on to consider the use of this model in dynamic path analysis.

Since the focus of this thesis is on the indirect effect of treatment on survival via an intermediate variable, the performance of the estimator for the direct effect of the treatment on the outcome (which can be estimated by fitting an additive hazards model for the effect of X on dN(t) controlling for the mediator) is not investigated here.

The aims of the chapter are therefore:

1) To use simulation studies to verify that fitting the additive hazards model described by Aalen [38] produces unbiased estimates with good coverage of the effect of a time-varying explanatory variable on a survival outcome in two situations: a) when there is a single continuous time-varying explanatory variable; b) when there are two explanatory variables: a time-varying continuous variable; and an independent time-fixed binary variable (such as randomised treatment) which is independent of the time-varying continuous variable. The simulation studies conducted to address this aim reflect parts of Figure 6-1. Scenario a) considers a setting without X, and scenario b) omits the arrow between X and $M_{cont}(t)$, so there is no mediator of the X-dN(t) relationship;
2) To use simulation studies to investigate the behaviour of the dynamic path analysis estimator of the indirect effect of a binary treatment variable on the outcome through a time-varying continuous mediator (see [20, 30, 31, 74]). This scenario is shown in Figure 6-1.

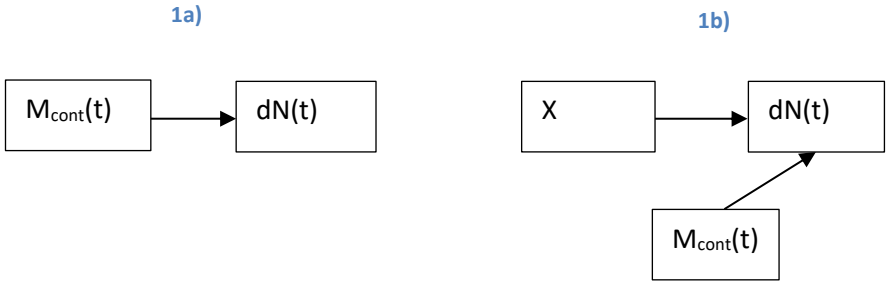
6.2 Dynamic path analysis using the additive hazards model

The variables under consideration in this chapter are the following:

- N(t), the counting process associated with the event of interest (taken here to be death) [20];
- dN(t), the increment of N(t) [20] ;
- T_D, the random variable representing time to death;
- $M_{cont}(t)$, a continuous time-varying explanatory variable. At event time t, $M_{cont}(t)$ refers to the value of M_{cont} just before time t, in line with the usage of Aalen [20];
- X, a binary explanatory variable taken in this chapter to indicate treatment group.

First, the chapter investigates the performance of the additive hazards model in scenarios (a) and (b) set out in Aim 1. Using the above notation, the two scenarios are illustrated using path diagrams in Figure 6-2 below.

Figure 6-2 Path diagram showing relationships between 1a) $M_{cont}(t)$ and dN(t), and 1b) X, $M_{cont}(t)$ and dN(t)



Sections 3.3 and 5.3.3 described time-to-event analysis using the additive hazards model and dynamic path analysis respectively. The methods are summarised below for ease of reference.

The estimation models, estimands and estimators for the settings shown in Figure 6-2 1a) and 1b) are shown in Table 6-1. The primary focus is on the association between $M_{cont}(t)$ and survival. The coefficient of $M_{cont}(t)$ is estimated at each event time t_D, and these estimates are summed over event times to give the cumulative coefficients. The data generating models are described in the next section.

Table 6-1 Models, estimands and estimators used for aim: 1a) with explanatory variable $M_{cont}(t)$; 1b) with explanatory variables X and $M_{cont}(t)$

Setting	**Estimation model**	**Estimand** (Cumulative coefficient at time t)	**Estimator** (Estimator for cumulative coefficient at death time t_D)
Additive hazards model, aim 1a), explanatory variable $M_{cont}(t)$ only	$\alpha(t\|M_{cont}(t)) = \gamma_0'(t) + \gamma_2'(t)M_{cont}(t)$	$\Gamma_2'(t) = \int_0^t \gamma_2'(u)du$	$\widehat{\Gamma_2'}(t_D) = \sum_{t_j \le t_D} \widehat{\gamma_2'}(t_j)$
Additive hazards model, aim 1b), explanatory variables $M_{cont}(t)$ and X	$\alpha(t\|X, M_{cont}(t)) = \gamma_0(t) + \gamma_1(t)X + \gamma_2(t)M_{cont}(t)$	$\Gamma_2(t) = \int_0^t \gamma_2(u)\,du$	$\widehat{\Gamma_2}(t_D) = \sum_{t_j \le t_D} \widehat{\gamma_2}(t_j)$

After investigating the component parts shown in Figure 6-2, the chapter investigates the full dynamic path scenario illustrated in Figure 6-1. In the setting used to investigate the performance of dynamic path analysis, X affects $M_{cont}(t)$, and both X and $M_{cont}(t)$ affect the distal outcome dN(t). Dynamic path analysis for the estimation of the indirect effect of X on dN(t) involves two models: one for the effect of X on $M_{cont}(t)$, and one for the effects of X and $M_{cont}(t)$ on the hazard. Table 6-2 below shows the models, estimand and estimator used in the dynamic path analysis. The model for the direct effect of X on dN(t) is also shown for completeness, although the simulation studies presented in this chapter do not examine the performance of the estimator of the direct effect.

Table 6-2 Models, estimands and estimators used for aim 2

Setting	**Estimation Models**	**Estimand** (Cumulative coefficient at time t)	**Estimator** (Estimator for cumulative coefficient at death time t_D)
Dynamic path analysis (indirect effect of X on dN(t))	$E(M_{cont}(t)\|X) = \delta_0(t) + \delta_1(t)X$ $\alpha(t\|X, M_{cont}(t)) = \gamma_0(t) + \gamma_1(t)X + \gamma_2(t)M_{cont}(t)$	$\int_0^t \delta_1(u)\gamma_2(u)\,du$	$\sum_{t_j \le t_D} \widehat{\delta_1}(t_j)\widehat{\gamma_2}(t_j)$
Additive hazards model (direct effect of X on dN(t))	$\alpha(t\|X, M_{cont}(t)) = \gamma_0(t) + \gamma_1(t)X + \gamma_2(t)M_{cont}(t)$	$\int_0^t \gamma_1(u)\,du$	$\sum_{t_j \le t_D} \widehat{\gamma_1}(t_j)$

The estimation process for the dynamic path analysis model has been described by several authors [20, 30, 31, 53] and in section 5.3.3. In brief, at each event time t_D the coefficient for

the effect of X on $M_{cont}(t)$ ($\delta_1(t)$ in Table 6-2) is estimated, and the coefficient for the effect of $M_{cont}(t)$ on dN(t), adjusted for X ($\gamma_2(t)$ in Table 6-2), is estimated. The two estimates are multiplied together to give an estimate of the indirect effect of X on dN(t) through the mediator $M_{cont}(t)$ at t_D. The indirect effect is presented as a plot of the cumulative estimate, given by $\sum_{t_j \le t_D} \widehat{\delta_1}(t_j)\widehat{\gamma_2}(t_j)$ where the sum is over all death times up to and including time t_D.

6.3 Data generation in the simulation studies

As in chapter 3, the simulation studies were carried out by generating the datasets, obtaining the parameter estimates for the additive hazards models or dynamic path analysis, and comparing the parameter estimates to the true value of the estimands. This section describes the data generation process.

Models used to generate the data for the simulation studies are shown in Table 6-3 below. Throughout the rest of this chapter, the parameter values chosen as part of data generation are marked with an asterisk to emphasise that they are known.

Table 6-3 Data generation models for assessment of the additive hazards model with explanatory variable(s) $M_{cont}(t)$ or X and $M_{cont}(t)$ (aim 1), and dynamic path analysis with mediator $M_{cont}(t)$ and explanatory variable X (aim 2).

Setting	Data generation models	True value of the estimand
Additive hazards model aim 1a), explanatory variable $M_{cont}(t)$ only	$\alpha(t\|M_{cont}(t)) = \gamma_0^*(t) + \gamma_2^* M_{cont}(t)$ $\gamma_0(t) = \gamma_0^*$ $E(M_{cont}(t)\|t) = \delta_0^* + \delta_2^* t$	$\Gamma_2(t) = \int_0^t \gamma_2^* \, du = \gamma_2^* t$
Additive hazards model aim 1b), explanatory variables $M_{cont}(t)$ and X	$\alpha(t\|X, M_{cont}(t)) = \gamma_0^*(t) + \gamma_1^* X + \gamma_2^* M_{cont}(t)$ $\gamma_0(t) = \gamma_0^*$ $P(X = 1) = p^*$ $E(M_{cont}(t)\|t) = \delta_0^* + \delta_2^* t$	$\Gamma_2(t) = \int_0^t \gamma_2^* \, du = \gamma_2^* t$
Dynamic path analysis with mediator $M_{cont}(t)$ and explanatory variable X	$\alpha(t\|X, M_{cont}(t)) = \gamma_0^*(t) + \gamma_1^* X + \gamma_2^* M_{cont}(t)$ $\gamma_0(t) = \gamma_0^*$ $P(X = 1) = p^*$ $E(M_{cont}(t)\|X, t) = \delta_0^* + \delta_1^* X + \delta_2^* t$	$\int_0^t \delta_1^*(u)\gamma_2^* \, du = \delta_1^* \gamma_2^* t$

The following characteristics apply to all the data generation processes described in this chapter:

- T_D was assumed to follow an exponential distribution in the baseline group, with constant hazard defined by γ_0^*. This portrays death as an outcome occurring monotonically throughout follow-up. In the Zactima trials, for example, time to death was approximately exponentially distributed over the first 18 months (the approximate 75th percentile of survival time) of the trial;
- The treatment indicator X was generated using a uniformly distributed random variable U_1 defined over the interval (0,1) with a cutoff $0<p^*<1$ such that X=0 if $U_1<p^*$, X=1 if $U_1 \geq p^*$.

Event times T_D were generated using the Stata command `survsim` (see [59]) according to the models for $\alpha(t|M_{cont}(t))$ or $\alpha(t|X, M_{cont}(t))$ shown in Table 6-3. The command allows complex survival time data to be generated with a user-defined hazard function. As shown in Table 6-3, the user-defined hazard functions comprise a baseline hazard $\gamma_0(t)$ (set in this chapter to constant γ_0^*) and effects representing the additive contribution to the hazard of $M_{cont}(t)$ alone, given by γ_2^* in the simulations addressing aim 1a), and of X and $M_{cont}(t)$, given by γ_1^* and γ_2^* respectively in the settings addressing aims 1b) and 2). An administrative censoring time was chosen so that very few individuals were censored from the risk set.

For the models used to generate data for the evaluation of the additive hazards model (aim 1), the intercept and slope of the data generating model for $M_{cont}(t)$ were set to vary between individuals. The following random effects data generation model was used:

$$M_{cont\,i}(t) = \delta_0^* + u_{0i} + (\delta_2^* + u_{2i})t + \epsilon_i$$

where $\delta_0^*$and δ_2^* are the fixed intercept and slope respectively, and u_{0i} and u_{2i} are the random intercept and slope terms for individual i. Values of u_{0i} and u_{2i} were generated from a bivariate normal distribution with zero means 0, variances 0.04 and 0.0025 respectively, and correlation as shown in Table 6-4. The values of the variances were chosen to give a reasonable spread of values around the respective means so that, for example, the 95% range for values of $\delta_{0i} = \delta_0^* + u_{0i}$ in simulation setting 1 was [0.11, 0.89] with a mean of 0.5, and the 95% range for values of $\delta_{2i} = \delta_2^* + u_{2i}$ in simulation setting 1 was [0.10, 0.30] with a mean of 0.2. Multiple observation times (up to 300) for each individual were created to record the observed values of $M_{cont}(t)$ over time at evenly spaced points between 0 and the fourth evaluation time, corresponding to roughly the 75th percentile of the observed survival time (see below).

The models used to generate $M_{cont}(t)$ when evaluating the performance of dynamic path analysis (aim 2, shown in the third row of Table 6-3) were similar to those used for the evaluation of the additive hazards model (the first and second rows of Table 6-3), with the addition that in the dynamic path analysis setting X affects $M_{cont}(t)$. This dependence is expressed through the parameter δ_1^*. To achieve this, the data generation for $M_{cont}(t)$ followed the procedure described above, but with an additional contribution to $E(M_{cont}(t))$ of δ_1^* for individuals in whom X=1 (ie $E(M_{cont}(t)|X,t) = \delta_0^* + \delta_1^* X + \delta_2^* t$). The δ_1^* did not vary across individuals. Under the data generation models for dynamic path analysis shown in the third row of Table 6-3, which set $\delta_1^*(t) = \delta_1^*$ and $\gamma_2^*(t) = \gamma_2^*$, the value of the true cumulative indirect effect of X, $\int_0^t \delta_1^*(u)\gamma_2^* \, du$, simplifies to $\delta_1^*\gamma_2^* t$.

For the simulations investigating the additive hazards model (aim 1), specific values for parameters γ_1^*, γ_2^*, δ_1^* and δ_2^* were chosen as shown in Table 6-4 below (note the numbering used to identify each simulation setting). For the simulations addressing aim 1a), negative values for δ_2^* were considered such that $M_{cont}(t)$ was either increasing or decreasing over time.

Values of the baseline parameters γ_0^*, δ_0^*, γ_0^* and δ_0^* were chosen next, so that:

c) the 75th percentile of survival time would fall at a time point such that results of the simulations could be reported at evenly spaced intervals between 0 and the 75th percentile of survival time (see below and [56]);
d) plausible hazard ratios would be implied, because hazard ratios are more familiar than differences in hazard. For example, in simulation setting 1 the coefficient for the explanatory variable $M_{cont}(t)$, γ_2^*, was set at 0.5. The baseline hazard γ_0^* was set to 0.5 so that the hazard ratio at t=0 comparing $M_{cont}(0)=1$ with $M_{cont}(0)=0$ was (0.5+(0.5*1))/0.5=2.

The parameter values for simulation settings investigating aim 1 are shown in Table 6-4.

Table 6-4 Parameters for simulations investigating the additive hazards model, aim 1

	Aim 1 a) Explanatory variable $M_{cont}(t)$ only			
Simulation setting number	1	2	3	4
Parameter				
$\boldsymbol{\gamma_0^*(t)}$	0.5 for all settings 1-4			
$\boldsymbol{\gamma_2^*}$	0.5	1	0.5	1
$\boldsymbol{\delta_0^*}$	0.5	0.5	1	1
$\boldsymbol{\delta_2^*}$	0.2	0.2	-0.2	-0.2
Corr($\boldsymbol{\delta_{0i}^*}$, $\boldsymbol{\delta_{2i}^*}$)	0.5	0.5	-0.5	-0.5

	Aim 1 b) Explanatory variables X and $M_{cont}(t)$					
Simulation setting number	5	6	7	8	9	10
Parameter						
$\boldsymbol{\gamma_0^*(t)}$	1	0.5	0.5	0.5	0.5	0.5
$\boldsymbol{\gamma_1^*}$	0	0.2	0.5	0	0.2	0.5
$\boldsymbol{\gamma_2^*}$	0.2	0.2	0.2	0.5	0.5	0.5
$\boldsymbol{\delta_0^*}$	0.5 for all settings 5-10					
$\boldsymbol{\delta_2^*}$	0.2 for all settings 5-10					
p*	0.5 for all settings 5-10					
Corr($\boldsymbol{\delta_{0i}^*}$, $\boldsymbol{\delta_{2i}^*}$)	0.5 for all settings 5-10					

The simulations investigating dynamic path analysis (aim 2) set values for parameters γ_1^*, γ_2^*, δ_1^* and δ_2^* in the range [0, 0.5]. Values of the baseline parameters γ_0^* and δ_0^* were chosen so that:

a) the 75th percentile of survival time would fall at t=2; results of the simulations are reported at t=0.5,1,1.5 and 2 in accordance with Hosmer and Royston [56];
b) Hazard ratios for the effect of X and $M_{cont}(t)$ on dN(t) would be plausible, as before. For example, in simulation setting 12 the parameter values $\gamma_0^* = 0.4$, $\gamma_1^* = 0.2$ and $\gamma_2^* = 0.2$ imply that the hazard ratio at time t=0 for the effect of X=1 compared to X=0 on death, if $M_{cont}(t)=0$, is 1.5, and the hazard ratio associated with $M_{cont}(0)=1$ compared to $M_{cont}(0)=0$ if X=0 is 1.5.

The parameter values are shown in Table 6-5 below, with each setting identified by a simulation number.

Table 6-5 Simulation parameters for the setting investigating dynamic path analysis, aim 2

Simulation setting number	11	12	13	14	15	16
Parameter						
$\boldsymbol{\gamma_0^*(t)}$	0.5	0.4	0.4	0.3	0.2	0.3
$\boldsymbol{\gamma_1^*}$	0	0.2	0.5	0	0.2	0.5
$\boldsymbol{\gamma_2^*}$	0.2	0.2	0.2	0.5	0.5	0.5
$\boldsymbol{\delta_0^*}$	0.8	0.5	0.5	0.5	0.5	0.2
$\boldsymbol{\delta_1^*}$	0.1 for all settings 11-16					
$\boldsymbol{\delta_2^*}$	0.2 for all settings 11-16					
p*	0.5 for all settings 11-16					
Corr($\boldsymbol{\delta_{0i}^*}$, $\boldsymbol{\delta_{2i}^*}$)	0.5 for all settings 11-16					

As in chapter 3, administrative censoring time for the simulations presented in this chapter was chosen to be t=5 for all individuals. Given the choices of parameter values shown in Table 6-4 and Table 6-5, this means that death would be experienced by all but a handful of patients.

For both the additive hazards models and dynamic path analysis simulations, 1000 datasets with N=1000 individuals were generated. The dataset size of N=1000 in this chapter (compared to N=3000 in chapter 3) was chosen because with the large numbers of observations generated per individual to create the time-varying mediator (up to 300, as described above), simulations on a sample size of N=3000 would have been computationally intensive. For similar reasons, the simulations to obtain the 95% coverage of the estimates derived from dynamic path analysis were based on 200 datasets of N=400.

6.4 Evaluation of methods using the simulated datasets

6.4.1 Criteria

Fitting the additive hazard model on the simulated datasets led to estimates of $\Gamma_2(t)$ and performing dynamic path analysis led to estimates of $\int_0^t \delta_1(u)\gamma_2\,du$. The estimates were compared with the true values of the estimands using the metrics listed in Table 6-6 where the symbol τ refers to the true value of the target of estimation.

Table 6-6 Metrics used to assess the results of the simulations

Metric[1]	Interpretation
τ	True value of the parameter of interest set in the data generation process
$\bar{\tau} = \frac{\sum_P \widehat{\tau_p}}{P}$	Mean value of the estimates of τ across P simulation runs
$\frac{\bar{\tau} - \tau}{\tau} \times 100$	Percentage bias
Percentage of times the 95% confidence interval for $\hat{\tau}_p$ includes τ	95% coverage
$\frac{\sum_P SE(\widehat{\tau_p})}{P}$	Mean model-based standard error (for the additive hazards model simulations only)
$SE(\hat{\tau}) = \sqrt{\frac{1}{P-1}\sum_P (\widehat{\tau_p} - \bar{\tau})^2}$	Empirical standard error

[1]Note that $\hat{\tau}_p$ denotes the estimate from simulated data set p, p=1, … P; P=1000.

The fifth metric, the mean model-based standard error, is presented for the simulations investigating the additive hazards model (aim 1), but not for simulations investigating dynamic path analysis (aim 2). This is because there is no expression available for the standard error of the cumulative indirect effect [30, 31].

In the literature, the results of simulation studies investigating dynamic path analysis have been presented graphically, allowing a comparison of the true parameter value with the mean of the estimated parameter values over time (see for example [42]). This allows any time-varying effects to be clearly shown. Results are also presented numerically at several timepoints. This allows the performance of the additive hazards model and dynamic path analysis to be assessed quantitatively, in a way that is not usual in this field.

In addition to this quantitative evaluation, a graphical comparison of the true parameter values and mean values of their estimates over time is provided as an illustrative example for one simulation setting addressing each aim. For the dynamic path analysis, following Strohmaier [42], the example graphs include the true and mean estimated values over time of the following: $\int_0^t \delta_1\gamma_2\,du + \int_0^t \gamma_1 du$ (the total effect); $\int_0^t \gamma_1 du$ (the direct effect of X on N(t)); $\int_0^t \delta_1\gamma_2\,du$ (the indirect effect of X); δ_1 (the effect of X on $M_{cont}(t)$); and $\int_0^t \gamma_2\,du$ (the effect of $M_{cont}(t)$ on N(t)).

An additional metric was used in the investigation of dynamic path analysis, not reported in Table 6-6. It consists of the average difference between the estimated total effect and the indirect effect, reported only for the simulation settings in which the direct effect was set to be 0. When the direct effect is 0 the indirect effect equals the total effect, under the property of

additivity (see expression 5-4). This is explained in the context of the models given in the last row of Table 6-3. From Table 6-3, $\alpha(t|X, M_{cont}(t)) = \gamma_0^*(t) + \gamma_1^* X + \gamma_2^* M_{cont}(t)$. If $\gamma_1^* = 0$, there is no direct effect of X on death. The indirect effect of X on the hazard, estimated by dynamic path analysis, is equivalent to the total effect, given at time t by $\gamma_1^{\times}(t)$ in:

$$\alpha(t|X) = \gamma_0^{\times}(t) + \gamma_1^{\times}(t)X \qquad 6\text{-}1$$

To check this equivalency, the true value of the indirect effect $\int_0^t \delta_1 \gamma_2 \, du$ is compared to the mean value of the estimate $\widehat{\Gamma_1^{\times}}(t)$ for simulations where $\gamma_1^* = 0$ (simulation settings 11 and 14 in Table 6-5).

6.4.2 Interpretation

Following Burton's recommendations on coverage [60], for the simulations investigating the performance of the additive hazards model, the acceptable level of coverage for a 95% confidence interval based on 1000 repetitions is between 93.6% and 96.4%. For the simulations investigating dynamic path analysis, coverage was calculated from 200 datasets using a bootstrapped estimate of the 95% confidence intervals. Each of the 200 datasets had N=400, and the confidence intervals used a normal bootstrap based on 100 bootstrap samples. The acceptable level of coverage for a 95% confidence interval based on 200 simulated datasets is between 91.9% and 98.1% [60].

If the methods under investigation perform well, percentage bias at each time point should be low, and coverage fall within the limits given above.

6.5 Results

Results of the evaluation of the additive hazards model and dynamic path analysis are presented as tables reporting the metrics listed in Table 6-6 at four different timepoints. The result tables are followed by plots representing one set of results per group of simulations as illustrative examples.

6.5.1 Results for the evaluation of the additive hazards model (aim 1)

The results from simulations evaluating the performance of the additive hazards model with a single time-varying continuous variable $M_{cont}(t)$ (aim 1a) are presented in Table 6-7. The results in Table 6-7 indicate agreement between $\Gamma_2(t)$ and $\widehat{\Gamma_2}(t)$ over time, with percentage bias low at all time points for simulation settings 1-4. Simulation settings 3 and 4 appear to have slightly greater percentage biases earlier in time (respectively -2.46% and -1.55% at the first evaluation timepoint), which decrease over time. This slightly larger bias at early timepoints may be a result of uncertainty in the estimates arising from the value of $M_{cont}(t)$ decreasing over time, while the association between $M_{cont}(t)$ and death was still positive (see Table 6-4). However, the magnitude of these percentage biases is small in absolute terms at all timepoints. For simulation settings 1-4, at all evaluation timepoints the 95% coverage falls within the acceptable limits of [93.6%, 96.4%]. For all simulations at all evaluation timepoints, the values of empirical and model-based standard errors are close. From Burton [60], when these two measures of variability are close, there is an implication of negligible bias.

Table 6-7 Evaluation of the performance of the additive hazards model specified for aim 1a (single continuous time-varying explanatory variable $M_{cont}(t)$). The values of the baseline parameters are given as footnotes. Results are based on 1000 simulated data sets of N=1000 individuals.

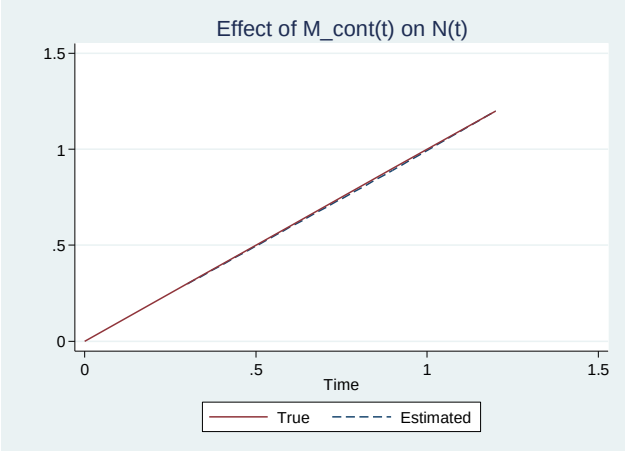
	Simulation setting number	Time				Simulation setting number	Time			
		0.4	0.8	1.2	1.6		0.4	0.8	1.2	1.6
	1	$\gamma_2^* = 0.5, \mathrm{E}(\delta_2^*) = 0.2$[1]				3	$\gamma_2^* = 0.5, \mathrm{E}(\delta_2^*) = -0.2$[3]			
True value $\Gamma_2(t)$		0.2	0.4	0.6	0.8		0.2	0.4	0.6	0.8
Mean of estimates $\hat{\Gamma}_2(t)$		0.197	0.397	0.594	0.802		0.195	0.390	0.595	0.808
Mean percentage bias		-1.11	-0.74	-1.00	0.27		-2.46	-2.50	-0.85	0.99
Mean % of deaths in sample		26.5	46.7	61.9	73.1		32.4	53.5	67.5	76.8
95% coverage		94.8	95.4	94.9	95.0		94.6	95.0	94.6	95.2
Empirical / Model-based SE		0.092 /0.092	0.138 /0.139	0.184 /0.183	0.233 /0.228		0.113 /0.112	0.178 /0.178	0.250 /0.245	0.316 /0.316
		Time					Time			
		0.3	0.6	0.9	1.2		0.25	0.50	0.75	1.0
	2	$\gamma_2^* = 1, \mathrm{E}(\delta_2^*) = 0.2$[2]				4	$\gamma_2^* = 1, \mathrm{E}(\delta_2^*) = -0.2$[4]			
True value $\Gamma_2(t)$		0.3	0.6	0.9	1.2		0.25	0.5	0.75	1
Mean of estimates $\hat{\Gamma}_2(t)$		0.298	0.594	0.891	1.199		0.246	0.492	0.742	1.005
Mean percentage bias		-0.65	-0.95	-1.03	-0.12		-1.55	-1.50	-1.12	0.53
Mean % of deaths in sample		26.4	46.7	61.9	73.1		30.8	51.4	65.4	74.9
95% coverage		94.7	95.2	95.2	95.2		94.9	95.3	95.4	95.8
Empirical/ Model-based SE		0.093 /0.093	0.141 /0.141	0.189 /0.188	0.238 /0.236		0.108 /0.107	0.167 /0.167	0.233 /0.228	0.292 /0.292

[1] $\gamma_0^* = 0.5, \mathrm{E}(\delta_0^*) = 0.5$ [2] $\gamma_0^* = 0.5, \mathrm{E}(\delta_0^*) = 0.5$ [3] $\gamma_0^* = 0.5, \mathrm{E}(\delta_0^*) = 1$ [4] $\gamma_0^* = 0.5, \mathrm{E}(\delta_0^*) = 1$ [1,2,3,4] p = 0.5 throughout

Illustrative example 6-1

Figure 6-3 below compares the true cumulative regression coefficient for $M_{cont}(t)$, $\Gamma_2(t)$, with the mean value of its estimate, $\widehat{\Gamma_2}(t)$ plotted over time for simulation setting 2. This provides an illustrative example of the performance of $\widehat{\Gamma_2}(t)$ under the circumstances set out in Table 6-4. Simulation setting 2 was chosen as an example, because the value of the parameter is easy to read off the y-axis.

Figure 6-3 Example graph showing the values of $\Gamma_2(t)$ and the mean of $\widehat{\Gamma_2}(t)$ over time in simulation setting 2



From Table 6-3, the expected cumulative change in α(t) at time t associated with a 1-unit increase in $M_{cont}(t)$ is given by $\int_0^t \gamma_2 \, du = \gamma_2 t$. The graph of $\Gamma_2(t)$ against time is therefore a straight line passing through the origin. Figure 6-3 demonstrates good agreement between the true parameter values and the mean of their estimates.

The results presented indicate together that the performance of the additive hazards model with a single time-updated continuous predictor $M_{cont}(t)$ is good under the conditions studied, producing parameter estimates with little bias and good coverage.

Next, the performance of the additive hazards model was evaluated in the extended setting in which the hazard is affected by a time-fixed treatment variable X as well as $M_{cont}(t)$ (aim 1b). The results are presented in Table 6-8, corresponding to simulation settings 5-10 set out in Table 6-4.

Table 6-8 Evaluation of the performance of the additive hazards model specified for aim 1b (explanatory variables $M_{cont}(t)$ and X). Note that results for $\Gamma_2(t)$ only are presented here. The values of the baseline parameters are shown as footnotes. Results are based on 1000 simulated data sets of N=1000 individuals.

	Simulation setting number	Time				Simulation setting number	Time			
		0.3	0.6	0.9	1.2		0.4	0.8	1.2	1.6
	5	$\gamma_1^*=0,\gamma_2^*=0.2,\mathrm{E}(\delta_2^*)=0.2$[5]				8	$\gamma_1^*=0,\gamma_2^*=0.5,\mathrm{E}(\delta_2^*)=0.2$[8]			
True value $\Gamma_2(t)$		0.06	0.12	0.18	0.24		0.20	0.40	0.60	0.80
Mean of estimates $\hat{\Gamma}_2(t)$		0.061	0.126	0.181	0.239		0.201	0.404	0.603	0.807
Mean percentage bias		1.48	4.94	0.82	-0.30		0.37	0.93	0.50	0.91
Mean % of deaths in sample		28.2	48.6	63.4	74.0		26.4	46.6	61.7	73.0
95% coverage		95.1	94.4	93.6	94.6		95.0	94.8	94.4	93.8
Empirical / Model-based SE		0.096 /0.097	0.153 /0.148	0.204/ 0.196	0.251 /0.243		0.092 /0.092	0.143/ 0.140	0.192 /0.184	0.238 /0.229
		Time					Time			
		0.5	1.0	1.5	2.0		0.4	0.8	1.2	1.6
	6	$\gamma_1^*=0.2,\gamma_2^*=0.2,\mathrm{E}(\delta_2^*)=0.2$[6]				9	$\gamma_1^*=0.2,\gamma_2^*=0.5,\mathrm{E}(\delta_2^*)=0.2$[9]			
True value $\Gamma_2(t)$		0.1	0.2	0.3	0.4		0.2	0.4	0.6	0.8
Mean of estimates $\hat{\Gamma}_2(t)$		0.102	0.205	0.302	0.400		0.200	0.405	0.603	0.806
Mean percentage bias		2.36	2.36	0.69	-0.11		0.21	1.14	0.48	0.77
Mean % of deaths in sample		29.7	51.0	66.0	76.7		29.2	50.5	65.9	76.7
95% coverage		95.3	94.2	93.5	94.7		95.3	93.6	94.1	93.6
Empirical/ Model-based SE		0.099 /0.099	0.156 /0.150	0.204 /0.197	0.251 /0.244		0.097 /0.099	0.157 /0.151	0.210 /0.201	0.264 /0.252
		Time					Time			
		0.4	0.8	1.2	1.6		0.3	0.6	0.9	1.2
	7	$\gamma_1^*=0.5,\gamma_2^*=0.2,\mathrm{E}(\delta_2^*)=0.2$[7]				10	$\gamma_1^*=0.5,\gamma_2^*=0.5,\mathrm{E}(\delta_2^*)=0.2$[10]			
True value $\Gamma_2(t)$		0.08	0.16	0.24	0.32		0.15	0.30	0.45	0.60
Mean of estimates $\hat{\Gamma}_2(t)$		0.083	0.164	0.245	0.325		0.152	0.302	0.453	0.604
Mean percentage bias		3.93	2.30	2.21	1.60		1.43	0.75	0.74	0.68
Mean % of deaths in sample		28.6	48.9	63.3	73.6		25.9	45.3	59.7	70.4
95% coverage		95.7	94.2	93.4	94.5		95.7	93.7	94.0	92.9
Empirical/ Model-based SE		0.096 /0.097	0.151 /0.146	0.199 /0.190	0.237 /0.233		0.089 /0.092	0.142 /0.138	0.187 /0.180	0.232 /0.223

[5] $\gamma_0^*=1,\mathrm{E}(\delta_0^*)=0.5$ [6] $\gamma_0^*=0.5,\mathrm{E}(\delta_0^*)=0.5$ [7] $\gamma_0^*=0.5,\mathrm{E}(\delta_0^*)=0.5$ [8] $\gamma_0^*=0.5,\mathrm{E}(\delta_0^*)=0.5$ [9] $\gamma_0^*=0.5,\mathrm{E}(\delta_0^*)=0.5$ [10] $\gamma_0^*=0.5,\mathrm{E}(\delta_0^*)=0.5$ [5-10]p=0.5

Table 6-8 shows agreement between $\Gamma_2(t)$ and the mean values of $\widehat{\Gamma_2}(t)$ over time, with percentage bias low in absolute terms. However, the percentage bias is higher at some evaluation timepoints than for simulation settings 1-4. For example, percentage bias at the second evaluation timepoint for simulation setting 5 is 4.94%, which is higher than any of the percentage biases reported in Table 6-7. This higher bias is attenuated over time; for simulation settings 5, 6 and 8-10, the percentage bias drops to less than 1% at the final evaluation timepoint. In general, 95% coverage falls within the acceptable limits of [93.6%, 96.4%], with the exception of simulation setting 5 at the third evaluation timepoint when coverage is 93.5%, and simulation setting 10 at the fourth evaluation timepoint when coverage is 92.9%. It is unclear why coverage falls outside the acceptable range in these cases. Coverage is a function of bias and model-based SE, and neither of these appears to take an outlying value in these two situations. These may be chance findings, given the relatively small number of simulations performed. However, the values of empirical and model-based standard errors reported in Table 6-8 are very similar, suggesting good performance of the model standard errors.

Illustrative example 6-2

Figure 6-4 below compares the cumulative regression coefficient for $M_{cont}(t)$, $\Gamma_2(t)$, with the mean value of the estimates $\widehat{\Gamma_2}(t)$ plotted over time for simulation setting 8. This illustrates the performance of $\widehat{\Gamma_2}(t)$ in the additive hazards model with two independent explanatory variables, $M_{cont}(t)$ and X. Simulation setting 8 was chosen for the larger value of $\Gamma_2(t)$, so that values of the parameter are easy to read from the plot.

Figure 6-4 Example graph showing the values of $\Gamma_2(t)$ and the mean of $\widehat{\Gamma_2}(t)$ over time in simulation setting 8

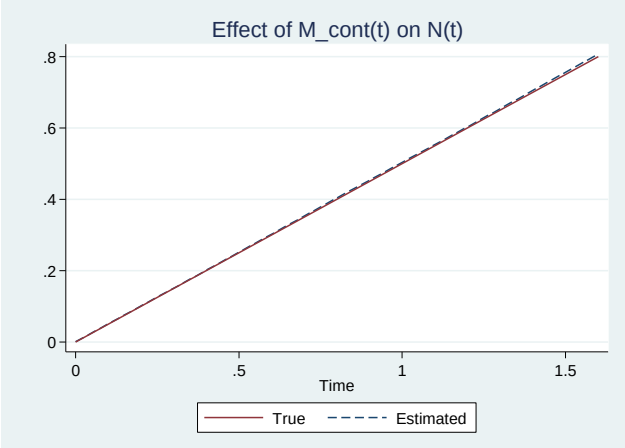


Figure 6-4 indicates agreement between the true and mean estimated parameter values.

In the settings investigated, the additive hazards model has performed well with two explanatory variables $M_{cont}(t)$ and X, with generally low percentage bias in estimates of $\Gamma_2(t)$ and coverage that usually falls within acceptable limits.

6.5.2 Results for the evaluation of dynamic path analysis with a time-varying continuous mediator $M_{cont}(t)$ (aim 2)

It was anticipated that the good performance of the additive hazards model reported in section 6.5.1 would feed through to dynamic path analysis with a continuous time-varying mediator variable $M_{cont}(t)$.

Table 6-9 shows results of the simulation studies for the dynamic path analysis (simulation settings 11-16). These show close agreement between the true values of the indirect effect of X that involves $M_{cont}(t)$ and the mean of the estimates for all the evaluation timepoints, with the largest percentage bias observed as 1.99% in simulation setting 11 at the second evaluation timepoint. Percentage bias is very low at the final evaluation timepoint for all six simulations. Coverage falls within the acceptable range of [91.9%, 98.1%] for all results except for simulation setting 14 at the third timepoint, where coverage is 91.0%, and simulation setting 15 at the fourth timepoint, where coverage is 91.5%. In simulation settings 11-13, the empirical standard errors of the estimates are large compared to the values of the estimates at the first two timepoints; for example, in simulation setting 11 the empirical standard error at the first timepoint is 0.010, and the mean of the estimates is 0.010. This implies that the estimated effects are very variable at early timepoints. At later timepoints, the magnitudes of the parameter estimates increase relative to the empirical standard errors (in simulation setting 11 at the final evaluation timepoint the empirical standard error is 0.026 while the mean of the estimates is 0.040), so the estimates show relatively less variability at later timepoints. In simulation settings 11 and 14, where $\gamma_1^* = 0$ (meaning that there is no direct effect of X on the hazard), the average of the estimates of the total effect of X, $\widehat{\Gamma_1^X}(t)$, should equal the indirect effect $\int_0^t \delta_1 \gamma_2 \, du$. The results reported in Table 6-9 show some initial disagreement between the indirect effect and the estimated total effect (respectively 9.6% and 4.8% at t=0.5), but this disagreement is attenuated over time.

Table 6-9 Evaluation of dynamic path analysis with a continuous time-varying mediator $M_{cont}(t)$ (aim 2). The values of the baseline parameters are given as footnotes. Results are based on 1000 simulated datasets of N=1000, with the exception of coverage, which is based on 200 repetitions of N=400. The column heading "Simulation setting no." is shortened to "No."

	No.	With no direct effect of baseline treatment, $\gamma_1^* = 0$				No.	With no direct effect of baseline treatment, $\gamma_1^* = 0$			
Time		0.5	1.0	1.5	2.0		0.5	1.0	1.5	2.0
	11	$\gamma_1^* = 0, \gamma_2^* = 0.2, \mathrm{E}(\delta_1^*) = 0.1, \mathrm{E}(\delta_2^*) = 0.2$[11]				14	$\gamma_1^* = 0, \gamma_2^* = 0.5, \mathrm{E}(\delta_1^*) = 0.1, \mathrm{E}(\delta_2^*) = 0.2$[14]			
True value $\int_0^t \delta_1 \gamma_2 \, du$		0.01	0.02	0.03	0.04		0.025	0.05	0.075	0.1
Mean of estimates $\sum_0^{t_D} \widehat{\delta_1}(t_D)\widehat{\gamma_2}(t_D)$		0.010	0.020	0.030	0.040		0.025	0.050	0.075	0.100
Mean percentage bias		1.15	1.99	-0.06	-0.51		0.01	-0.04	0.10	0.06
Mean % of deaths in sample		28.8	49.7	64.9	75.7		25.8	46.1	61.7	73.3
95% coverage		94.5	94.5	96.0	97.0		94.0	95.0	91.0	93.5
Empirical SE		0.010	0.016	0.021	0.026		0.098	0.016	0.022	0.029
Mean % difference between $\int_0^t \delta_1^*(u)\gamma_2^* \, du$ and $\widehat{\Gamma_1^{\times}}(t)$		-9.6	-4.2	-0.1	-3.7		-4.8	-2.8	-0.3	-2.1
		With direct effect of baseline treatment, $\gamma_1^* \neq 0$					With direct effect of baseline treatment, $\gamma_1^* \neq 0$			
Time		0.5	1.0	1.5	2.0		0.5	1.0	1.5	2.0
	12	$\gamma_1^* = 0.2, \gamma_2^* = 0.2, \mathrm{E}(\delta_1^*) = 0.1, \mathrm{E}(\delta_2^*) = 0.2$[12]				15	$\gamma_1^* = 0.2, \gamma_2^* = 0.5, \mathrm{E}(\delta_1^*) = 0.1, \mathrm{E}(\delta_2^*) = 0.2$[15]			
True value $\int_0^t \delta_1 \gamma_2 \, du$		0.01	0.02	0.03	0.04		0.025	0.05	0.075	0.10
Mean of estimates $\sum_0^{t_D} \widehat{\delta_1}(t_D)\widehat{\gamma_2}(t_D)$		0.010	0.020	0.030	0.040		0.025	0.050	0.075	0.010
Mean percentage bias		1.77	0.88	0.48	0.33		-0.04	-0.39	-0.09	-0.43
Mean % of deaths in sample		26.5	46.3	61.0	71.9		25.6	45.7	61.0	72.5
95% coverage		94.5	94.5	95.5	93.5		95.5	96.5	93.0	91.5
Empirical SE		0.009	0.014	0.019	0.023		0.009	0.015	0.029	0.028
Time		0.5	1.0	1.5	2.0		0.5	1.0	1.5	2.0
	13	$\gamma_1^* = 0.5, \gamma_2^* = 0.2, \mathrm{E}(\delta_1^*) = 0.1, \mathrm{E}(\delta_2^*) = 0.2$[13]				16	$\gamma_1^* = 0.5, \gamma_2^* = 0.5, \mathrm{E}(\delta_1^*) = 0.1, \mathrm{E}(\delta_2^*) = 0.2$[16]			
True value $\int_0^t \delta_1 \gamma_2 \, du$		0.01	0.02	0.03	0.04		0.025	0.05	0.075	0.10
Mean of estimates $\sum_0^{t_D} \widehat{\delta_1}(t_D)\widehat{\gamma_2}(t_D)$		0.010	0.020	0.030	0.040		0.025	0.050	0.075	0.099
Mean percentage bias		1.87	-0.36	0.33	-0.42		0.33	-0.54	0.07	-0.61
Mean % of deaths in sample		31.3	52.5	67.0	76.9		28.7	49.4	64.2	74.8
95% coverage		94.5	93.5	97.0	96.5		95.5	97.0	96.0	97.5
Empirical SE		0.010	0.016	0.021	0.025		0.010	0.016	0.022	0.028

[11] $\gamma_0^* = 0.5, \mathrm{E}(\delta_0^*) = 0.8$ [12] $\gamma_0^* = 0.4, \mathrm{E}(\delta_0^*) = 0.5$ [13] $\gamma_0^* = 0.4, \mathrm{E}(\delta_0^*) = 0.5$ [14] $\gamma_0^* = 0.3, \mathrm{E}(\delta_0^*) = 0.5$ [15] $\gamma_0^* = 0.2, \mathrm{E}(\delta_0^*) = 0.5$ [16] $\gamma_0^* = 0.3, \mathrm{E}(\delta_0^*) = 0.2$ [11-16] p=0.5

Note that the mean percentage difference between $\int_0^t \delta_1 \gamma_2 \, du$ and $\widehat{\Gamma_1^{\times}}(t)$ is reported only when there is no direct effect of treatment, $\gamma_1^* = 0$.

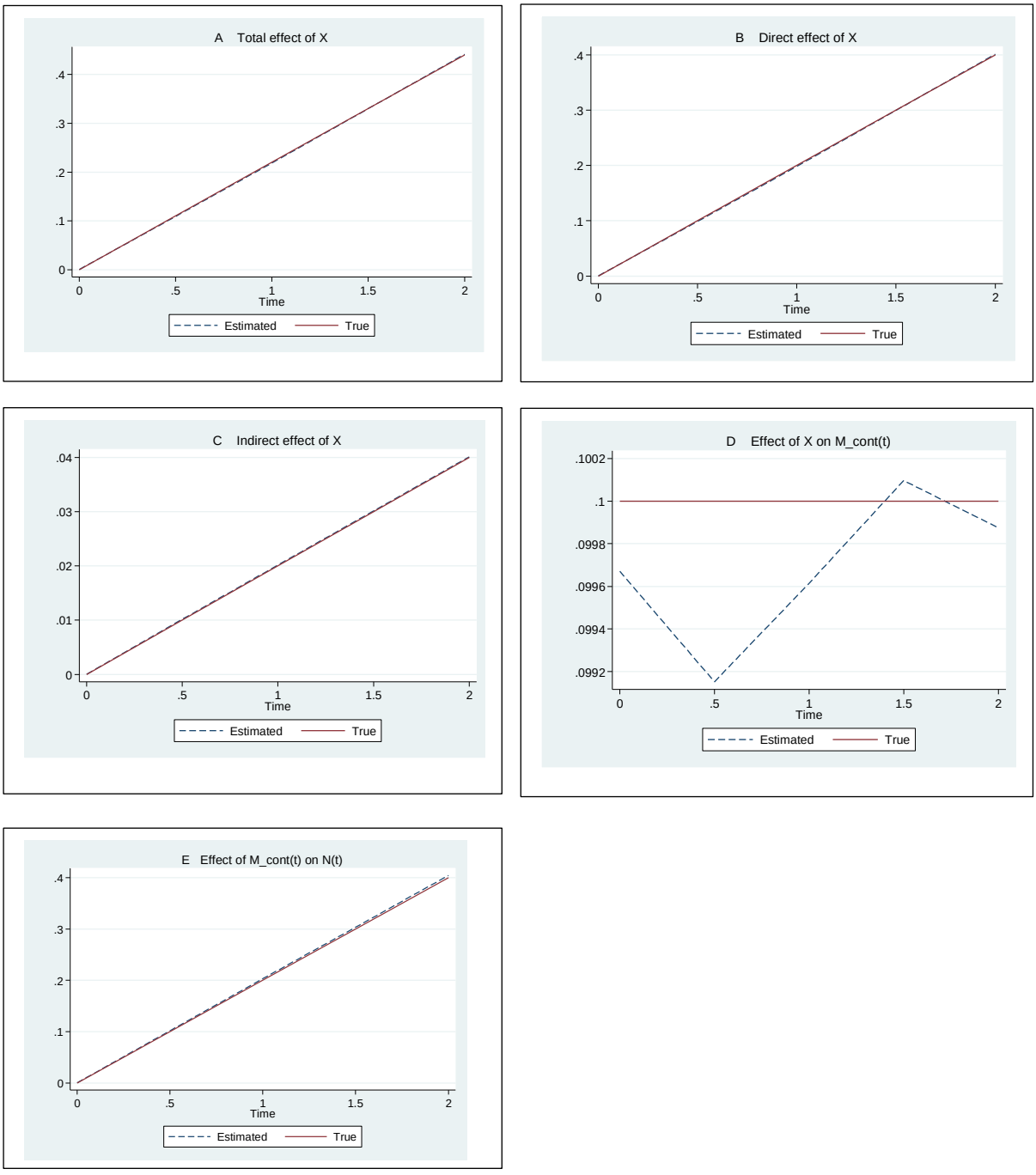
Illustrative example 6-3 (a)

Figure 6-5 shows illustrative graphs for the outcomes obtained from simulation setting 12. Setting 12 was chosen as an illustrative example because the direct effect of treatment was not set to 0, ie $\gamma_1^* \neq 0$. As in section 6.5.1, the graphs include the true and mean estimated values over time of the covariate effects calculated at the four evaluation timepoints shown in Table 6-9. The covariate effects shown in the separate graphs are the following: the true total effect $\int_0^t \delta_1\gamma_2\,du + \Gamma_1(t)$ and the mean of its estimates $\sum_{t_j \le t_D} \widehat{\delta_1}(t_j)\widehat{\gamma_2}(t_j) + \widehat{\Gamma_1}(t)$ (graph A); the true direct effect of X on N(t) $\Gamma_1(t)$ and the mean of its estimates $\widehat{\Gamma_1}(t)$ (graph B); the true indirect effect of X on N(t) $\int_0^t \delta_1\gamma_2\,du$ and the mean of its estimates $\sum_{t_j \le t_D} \widehat{\delta_1}(t_j)\widehat{\gamma_2}(t_j)$ (graph C); the true effect of X on M_{cont}(t) $\delta_1(t)$ and the mean of its estimates $\widehat{\delta_1}(t)$ (graph D); and the true effect of M_{cont}(t) on N(t) $\Gamma_2(t)$ and the mean of its estimates $\widehat{\Gamma_2}(t)$ (graph E).

Figure 6-5 indicates good agreement between the true parameter values and the mean values of the parameter estimated in simulation setting 12. Of particular interest in this context are the mean values of the estimates of the indirect effect of X, which as shown in graph C agree closely with the true values of the estimands over time. Graph D, showing the true effect of X on M_{cont}(t), $\delta_1(t)$, and the mean of the estimated effect over the 1000 simulation runs, appears to show an estimate that varies widely about the true parameter value. In fact, the variation about the estimate is very small as shown by the scale of the y-axis of the graph. The zigzag appearance reflects the comparison of the means of the estimates with the true values of the estimand at four evaluation timepoints.

Illustrative example 6-3 (b)

Figure 6-5 Example graphs showing true parameter values and mean values of the corresponding parameter estimates over time time for explanatory variables X and $M_{cont}(t)$ in simulation setting 12



The results indicate that the dynamic path analysis appears to be performing satisfactorily under the circumstances investigated, with very low bias, and reasonable coverage, bearing in mind however that coverage is calculated on the basis of a smaller sample size and fewer simulation runs compared with the results for bias.

6.6 Summary

This chapter has summarised the estimation process for an additive hazards model with a time-varying continuous explanatory variable $M_{cont}(t)$, an additive hazards model with a time-varying continuous explanatory variable $M_{cont}(t)$ and a treatment variable X, and for dynamic path analysis with explanatory variable X and time-varying continuous mediator $M_{cont}(t)$. Simulation studies have been designed and carried out to investigate the performance of both the additive hazards models and dynamic path analysis with a variety of parameter values. The reporting of the results of the simulation studies as a series of metrics, rather than as graphical output showing bias alone, is a new development in the assessment of dynamic path analysis.

Results of the simulation studies reported in section 6.5.1 have confirmed that, under the conditions investigated, the procedure used to fit the additive hazards model gives rise to unbiased estimates of the effect of a time-varying continuous explanatory variable $M_{cont}(t)$ on hazard. The model also performs well in the presence of an independent additional explanatory variable X, producing accurate results and generally good coverage.

Under the conditions described in section 6.3, with realistic but not exhaustive simulations using sample sizes of N=1000, "traditional" dynamic path analysis as described by Fosen, Aalen and colleagues [20, 30, 31] performs well. Bias is minimal and there is good coverage for most time points. This confirms the expected finding that the dynamic path estimator is unbiased. Estimates obtained using dynamic path analysis are subject to assumptions of linearity, no interaction between treatment and mediator in their effect on the outcome, no unmeasured confounding for the treatment-mediator, treatment-outcome and mediator-outcome relationships, and no intermediate confounding (see chapter 5). Interpretation of the estimates obtained using dynamic path analysis is therefore also subject to these constraints.

The primary context for dynamic path analysis is to supplement investigators' understanding of the biological mechanisms of treatment action [20]. Because dynamic path analysis

estimates are not constrained to be constant over time, the time-changing effects of treatment can also be explored [20].

The confirmation provided in this chapter that the dynamic path analysis estimator is unbiased will be used in the next chapter, along with the insight gained into the process of fitting the dynamic path analysis model, to inform the simulations in chapter 7 which examine the performance of dynamic path analysis in situations with a time-to-event mediator, as described in section 5.4.

7 The performance of dynamic path analysis with a time-to-event mediator

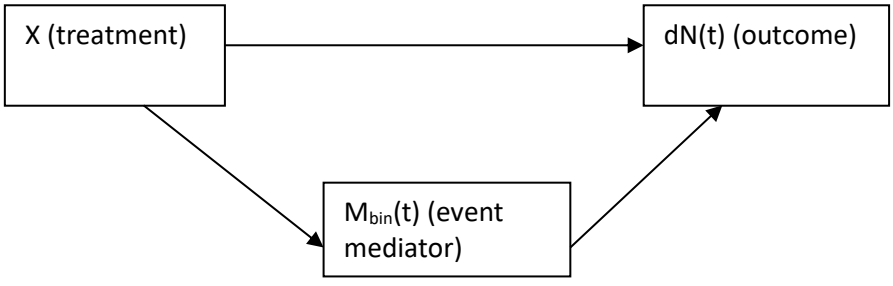
7.1 Introduction

Chapter 6 examined the performance of dynamic path analysis as a means of estimating the indirect effect of an explanatory variable on a time-to-event outcome through a time-varying continuous mediator variable. The results of the simulation studies indicated that, as expected, dynamic path analysis provides a generally unbiased estimate of the indirect effect of the explanatory variable in the settings that were considered, with good coverage when the assumptions of dynamic path analysis are met ([17, 20, 21, 24, 30, 32, 64, 78-80], and see chapter 5).

Chapter 5 described how dynamic path analysis could be adapted to settings with a time-to-event mediator (characterised, as in chapter 5, as a time-updated binary variable). This approach may be of interest in the secondary analysis of clinical trials with a composite time-to-event outcome, as discussed in chapter 1. The Zactima trials provide an example of such a setting.

The relationships between treatment, the time-to-event mediator and the survival outcome in a simple setting are shown in Figure 7-1 below. In line with notation introduced in chapter 5, X is a binary explanatory variable indicating treatment group, $M_{bin}(t)$ is a time-updated binary (survival) variable indicating the occurrence of the mediator, and dN(t) is the increment of the counting process for the distal outcome. The value of $M_{bin}(t)$ is observed just before the value of dN(t).

Figure 7-1 Path diagram showing the time-specific relationships between treatment X, outcome dN(t) and event mediator $M_{bin}(t)$, for $0 \leq t < T$



The indirect effect of treatment in the setting represented by Figure 7-1 is the X-$M_{bin}(t)$-dN(t) pathway.

7.1.1 Aims

Section 5.4 described the reasoning behind the proposed extension of dynamic path analysis to settings where the mediator is a time-to-event variable, and presented the steps involved in the estimation, which involve estimating both the effect of the treatment on the mediator, and of the mediator on the distal outcome. This chapter uses simulation studies to investigate the performance of these steps separately (because of the complexities introduced by a time-to-event mediator) and the performance of the dynamic path analysis estimation of the indirect effect.

There are three aspects that will be considered in this chapter which arise from adapting dynamic path analysis to a time-to-event mediator. These relate to:

a) Dealing with a time-to-event (time-updated binary) mediator;
b) Using linear regression to model the relationship between treatment and the time-to-event mediator;
c) Studying the impact that mortality has on the performance of the linear regression models for the binary mediator $M_{bin}(t)$.

These aspects will be addressed in this chapter via:

1) Simulation studies to verify the performance of the additive hazards model described by Aalen [20, 38, 39] when there is a time-updated binary explanatory variable $M_{bin}(t)$ (aim 1).
2) Simulation studies to assess the performance of fitting a linear regression model to estimate the effect of a binary explanatory variable X on a time-to-event outcome $M_{bin}(t)$, in the context of dynamic path analysis (aim 2).
3) Simulation studies to investigate dynamic path analysis when performed to estimate the indirect effect of treatment via a time-to-event mediator $M_{bin}(t)$ (aim 3).

To our knowledge, there are no published simulation-based investigations of the additive hazards model for a time-updated binary explanatory variable; this is the focus of the first set

of simulations (aim 1). Aim 2 assesses the performance of the first step of dynamic path analysis, where the effect of treatment on the time-to-event mediator is estimated. Because in dynamic path analysis this step is repeated at each time a distal event occurs, contributions to these regressions are potentially based on decreasing numbers of patients (the issue described in point c) above). Hence aim 3 assesses the performance of the dynamic path analysis in estimating the indirect effect of treatment in the setting where this censoring occurs. For aims 2 and 3, the estimation of respectively the time-varying regression coefficient and the indirect effect are compared to their true values in the scenario where no censoring occurs, and thus will quantify the impact of this censoring on the performance of the methods.

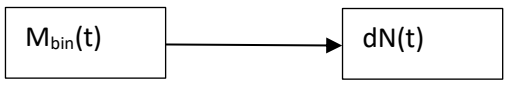
7.2 Dynamic path analysis with a time-to-event mediator

The variables under consideration in this chapter are the following:

- N(t), the counting process associated with the distal event (assumed to be death) [20];
- dN(t), the increment of N(t) [20];
- T_D, the random variable representing time to death;
- $M_{bin}(t)$, a time-updated binary variable indicating the occurrence of the mediator;
- T_{Mbin}, the random variable representing time to the mediator;
- $N_{Mbin}(t)$, the counting process associated with the mediator [20];
- $dN_{Mbin}(t)$, the increment of $N_{Mbin}(t)$ [20].
- X, a binary explanatory variable taken in this chapter to indicate treatment group.

Figure 7-2 shows the relationship between $M_{bin}(t)$ and dN(t) which forms the basis for the simulation studies addressing aim 1.

Figure 7-2 Path diagram showing relationships between $M_{bin}(t)$ and dN(t) for aim 1



In this setting, $M_{bin}(t)$ is the only explanatory variable. The effect of $M_{bin}(t)$ on dN(t) is estimated by fitting an additive hazards model with $M_{bin}(t)$ as the explanatory variable. The model is shown in Table 7-1 below. No simulation studies are performed to investigate the

additive hazards model when there are two explanatory variables because a similar setting (albeit with a time-varying continuous explanatory variable) has been considered in chapter 6.

The relationship between X and $M_{bin}(t)$ which underpins the simulation studies addressing aim 2 is shown in Figure 7-1. It can be seen that X is the only explanatory variable for $M_{bin}(t)$, and X also affects the distal outcome dN(t). The estimate of the effect of X on $M_{bin}(t)$ is obtained by ordinary least-squares estimation of the regression model shown in the second row of Table 7-1. These estimates are affected by loss of individuals from the risk set by censoring due to the distal event (see section 5.4.2).

For aim 3, the investigation into dynamic path analysis, the relationships between X, $M_{bin}(t)$ and dN(t) are shown in Figure 7-1. Estimation using dynamic path analysis with an event mediator $M_{bin}(t)$ was described in section 5.4.2. In brief, at each distal event time t_D the coefficient for the effect of X on $M_{bin}(t)$ is estimated, and the coefficient for the effect of $M_{bin}(t)$ on dN(t), adjusted for X, is estimated. The two estimates are multiplied together to give an estimate of the indirect effect of X on dN(t) through the mediator $M_{bin}(t)$ at time t_D. These time-specific estimates are summed over the interval $(0, t_D]$ to give an estimate of the cumulative indirect effect of X. The models, estimand and estimator used for the settings described are shown in Table 7-1.

Table 7-1 Models fitted to address the three aims. For clarity, the hazard of the distal outcome at time t is denoted $\alpha_D(t)$.

Setting	**Estimation model**	**Estimand** (Cumulative coefficient at time t)	**Estimator**[1] (Estimator for cumulative coefficient at death time t_D)
Additive hazards model with explanatory variable $M_{bin}(t)$	$\alpha_D(t\|M_{bin}(t)) = \gamma_0'(t) + \gamma_3'(t)M_{bin}(t)$	$\Gamma_3'(t) = \int_0^t \gamma_3'(u)du$	$\widehat{\Gamma_3'}(t_D) = \sum_{t_j \le t_D} \widehat{\gamma_3'}(t_j)$
Linear regression model with explanatory variable X and outcome $M_{bin}(t)$	$E(M_{bin}(t)\|X) = \beta_0(t) + \beta_1(t)X$	$\beta_1(t)$	$\widehat{\beta_1}(t_D)$
Dynamic path analysis with mediator $M_{bin}(t)$	$E(M_{bin}(t)\|X) = \beta_0(t) + \beta_1(t)X$ $\alpha_D(t\|X, M_{bin}(t)) = \gamma_0(t) + \gamma_1(t)X + \gamma_3(t)M_{bin}(t)$	$\int_0^t \beta_1(u)\gamma_3(u)\,du$	$\sum_{t_j \le t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$

[1] The estimated parameters within each summation are time-specific estimates.

7.3 Data generation in the simulation studies

The methods used to carry out the simulation studies described in this chapter are very similar to those described in chapter 6.

In general, the data were generated using the data generation models shown in Table 7-2, Table 7-3 and Table 7-4. The parameters were estimated by fitting additive hazards models (aim 1), linear regression models (aim 2), or dynamic path analysis (aim 3), and the estimates thus obtained were compared to their true value in the absence of censoring using the metrics shown in Table 7-7, which are the same as those used in chapter 6.

The core models used to generate the data for the simulation studies are shown in Table 7-2, Table 7-3 and Table 7-4 below. As in chapter 6, the parameter values set during data generation are marked with an asterisk.

Throughout the simulations presented in this chapter, T_D is set to follow an exponential distribution, with death taken to be an infrequent outcome. T_{Mbin} is set to follow either an exponential or a Weibull distribution (details are shown in Table 7-2, Table 7-3 and Table 7-4).

Table 7-2 Data generation models for aim 1. The hazard functions of the event mediator and distal outcome are written as $\alpha_{M_{bin}}(t)$ and $\alpha_D(t)$ respectively.

Settings for aim 1	Data generation models	True value of the estimand
Additive hazards model with binary time-updated explanatory variable $M_{bin}(t)$, T_{Mbin} is exponentially distributed	$\alpha_D(t\|M_{bin}(t)) = \gamma_0^*(t) + \gamma_3^* M_{bin}(t)$ $\gamma_0(t) = \gamma_0^*$ $\alpha_{M_{bin}}(t) = \theta_0^*$	$\Gamma_3(t) = \int_0^t \gamma_3^* \, du = \gamma_3^* t$
Additive hazards model with binary time-updated explanatory variable $M_{bin}(t)$, T_{Mbin} follows a Weibull distribution	$\alpha_D(t\|M_{bin}(t)) = \gamma_0^*(t) + \gamma_3^* M_{bin}(t)$ $\gamma_0(t) = \gamma_0^*$ $\alpha_{M_{bin}}(t) = \nu^* \kappa^* t^{\nu^*-1}$	$\Gamma_3(t) = \int_0^t \gamma_3^* \, du = \gamma_3^* t$

For the simulations addressing aim 1, event times T_D were generated using the Stata command `survsim` (see [59]) according to the model for $\alpha_D(t|M_{bin}(t))$ shown in Table 7-2. The procedure was similar to that described below Table 6-3. Event times for the time-updated binary explanatory variable, T_{Mbin}, were also generated using `survsim` according to the models shown in Table 7-2.

Data generation models for the simulations addressing aim 2, assessing the performance of a linear regression model to estimate the effect of a binary explanatory variable X on a time-to-event outcome $M_{bin}(t)$ at event times $t=t_D$, are shown in Table 7-3 below.

Table 7-3 Data generation models for aim 2

Setting for aim 2	**Data generation models**	**True value of the time-varying regression coefficient in the absence of censoring by the distal outcome[2]**
Regression modelling of the effect of X on $M_{bin}(t)$ at each death time	$\alpha_D(t\|X, M_{bin}(t)) = \gamma_0^*(t) + \gamma_1^* X + \gamma_3^* M_{bin}(t)$ $\gamma_0(t) = \gamma_0^*$ $P(X=1) = p^*$ $\alpha_{M_{bin}}(t\|X) = \theta_0^*(t) + \theta_1^* X$ $\theta_0(t) = \theta_0^*$	$\beta_1(t) = I(M_{bin}(t)\|X=1) - I(M_{bin}(t)\|X=0) = \exp(-\theta_0^* t) - \exp(-\theta_0^* t - \theta_1^* t)$

[2] See section 5.4.1

As described in section 7.2, the mediator $M_{bin}(t)$ is a time-to-event variable. However, for the purposes of dynamic path analysis as described in section 5.4.1, $M_{bin}(t)$ is treated as a time-updated binary variable. Hence, the data generating model shown in Table 7-3 is not expressed in the same terms as the estimation model which is the linear regression model shown in Table 7-1.

Data generation for event times T_D and T_{Mbin} used the `survsim` command and the models shown in Table 7-3. The procedure was similar to that described above and in chapter 6. As before, administrative censoring occurred for individuals who had not experienced death before a specified cutoff time.

Data generation of X was based on a uniformly distributed random variable U_1 defined over the interval (0,1) with a cutoff $0<p^*<1$ such that X=0 if $U_1<p^*$, X=1 if $U_1 \geq p^*$.

The estimation model for the effect of X on $M_{bin}(t)$ given in Table 7-1 is expressed as $E(M_{bin}(t)|X) = \beta_0(t) + \beta_1(t)X$. This model can be rewritten in terms of θ_0 and θ_1, using the well-known relationships between A(t), the cumulative hazard at time t of an event of interest, S(t), the corresponding survivor function, and I(t), the corresponding cumulative incidence function (the complement of the survivor function). These relationships are, where $\alpha(t)$ is the hazard function, $A(t) = \int_0^t \alpha(u)du$, $S(t) = \exp(-A(t))$ and $I(t) = P(T < t) = 1 - S(t)$ (see

for example [20, 47, 48]). Hence, for the data generating model for T_{Mbin} shown in Table 7-3 which assumes exponential time to the mediator event,

$$E(M_{bin}(t)|X) = I(M_{bin}(t)|X) = 1 - \exp\left(-\int_0^t(\theta_0 + \theta_1 X)du\right) \quad 7\text{-}1$$

$\beta_1(t)$, representing the expected increase in $M_{bin}(t)$ for a unit increase in X, can be rewritten in terms of θ_0 and θ_1:

$$\beta_1(t) = I(M_{bin}(t)|X = 1) \; - \; I(M_{bin}(t)|X = 0) = \; \exp(-\theta_0 t) - \exp(-\theta_0 t - \theta_1 t) \quad 7\text{-}2$$

As noted in section 5.4.1, expression 7-1 is true when individuals are not censored from the risk set when they experience the distal event. In fact, individuals are censored from the risk set when they experience the distal event, so the value of $\beta_1(t)$ obtained from expression 7-2 is not necessarily expected to reflect the results obtained by fitting the estimation model given in the second row of Table 7-1. Comparing the discrepancy between $\beta_1(t)$ and $\widehat{\beta_1}(t)$ will give insight into the effect of censoring on $\widehat{\beta_1}(t)$ as discussed in section 7.1.1.

The data generation models used for the simulations addressing aim 3, the performance of dynamic path analysis with event mediator $M_{bin}(t)$, are shown in Table 7-4 below. They are the same as the data generation models given in Table 7-3.

Table 7-4 Data generation models for aim 3. The indirect effect of X is given as Δ in the table and reproduced in full below the table for ease of reference. c refers to the constant of integration

Setting for aim 3	**Data generation models**	**True value of the indirect effect of X on T_D in the absence of censoring by the distal outcome[3]**
Dynamic path analysis with event mediator $M_{bin}(t)$	$\alpha_D(t\|X, M_{bin}(t)) = \gamma_0^*(t) + \gamma_1^* X + \gamma_3^* M_{bin}(t)$ $\gamma_0(t) = \gamma_0^*$ $P(X = 1) = p^*$ $\alpha_{M_{bin}}(t\|X) = \theta_0^*(t) + \theta_1^* X$ $\theta_0(t) = \theta_0^*$	$\int_0^t \beta_1(u)\,\gamma_3^* du = \Delta + c$

[3] The constant of integration c is given by $c = -\gamma_3^*\left(\frac{1}{\theta_0^*+\theta_1^*} - \frac{1}{\theta_0^*}\right)$ (equivalent to the estimand when t=0).

The term Δ is given by:

$$\Delta = \int_0^t \gamma_3^*\,(\exp(-\theta_0^* u) - \exp(-\theta_0^* u - \theta_1^* u))du \; = \gamma_3^* \exp(-\theta_0^* t - \theta_1^* t)\left(\frac{1}{\theta_0^* + \theta_1^*} - \frac{\exp(\theta_1^* t)}{\theta_0^*}\right) \quad 7\text{-}3$$

The indirect effect of X on T_D, $\int_0^t \beta_1(u)\,\gamma_3 du$, is defined as the product of $\beta_1(t)$ (shown in Table 7-3) and γ_3, integrated over the interval [0, t]. This follows the same steps as the definition of the indirect effect in dynamic path analysis with a time-varying continuous mediator $M_{cont}(t)$, shown in Table 6-3.

The process of data generation for the investigation of dynamic path analysis (aim 3) was the same as the process for the investigation of the regression model for the effect of X on $M_{bin}(t)$ (aim 2), and is therefore not further described here.

7.3.1 Setting the baseline parameter values

Values for the baseline parameters γ_0^*, $\nu^*, \kappa^*, \gamma_0^*$ and θ_0^* in the simulations investigating aims 1-3 were chosen in the following way:

a) for aim 1, the 75th percentile of T_D was set to fall at t=2, and results were reported at t=0.5, t=1.0, t=1.5 and t=2. For aims 2 and 3, six evaluation timepoints were used. This is because $M_{bin}(t)$ may happen much faster than death, so that, at some t, $M_{bin,i}(t) = 1\ \forall\ i$. This may mean that censoring due to the distal outcome (death) has a large effect on $\widehat{\beta_1(t)}$ (hence on $\sum_{t_j \le t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$) at some evaluation timepoints. The 85th percentile of T_{Mbin} was set at t=1, and three more evaluation timepoints were evenly spaced between 0 and 1. The other two evaluation timepoints were the 75th percentile of T_{Mbin} and the 75th percentile of T_D. Hosmer [56] notes that estimates may become unstable after the 75th percentile of T_D.
b) $M_{bin}(t)$ and death occurred at different rates. Three different relative event rates were considered, to determine whether the density of events relative to each other would affect the estimations:
    i. the 25th percentile of T_{Mbin} was set approximately equivalent to the 25th percentile of T_D, so that early on during the follow-up the two events would occur at roughly the same rate;
    ii. the 50th percentile of T_{Mbin} was set approximately equivalent to the 25th percentile of T_D, so that $M_{bin}(t)$ occurred faster than death;

iii. the 75th percentile of T_{Mbin} was set approximately equivalent to the 25th percentile of T_D, so that $M_{bin}(t)$ occurred much faster than death.

c) To give plausible hazard ratios, as noted in chapter 3 and chapter 6.

Parameter values chosen for the simulations investigating the additive hazards model (aim 1) are reported in Table 7-5 below.

Table 7-5 Parameters for simulations addressing aim 1. The nth percentile of $T_.$ is written as pn($T_.$)

	T_{Mbin} follows an exponential distribution					
Simulation setting number	1	2	3	4	5	6
Parameter						
$\boldsymbol{\gamma_0^*(t)}$	0.6	0.6	0.6	0.4	0.5	0.3
$\boldsymbol{\gamma_3^*}$	0.2	0.5	0.2	0.5	0.2	0.5
$\boldsymbol{\theta_0^*(t)}$	0.6	0.6	1.5	1.4	2.7	2.5
Relative event speed: p25(T_D) equal to	p25(T_{Mbin})	p25(T_{Mbin})	p50(T_{Mbin})	p50(T_{Mbin})	p75(T_{Mbin})	p75(T_{Mbin})
	T_{Mbin} follows a Weibull distribution					
Simulation setting number	7	8	9	10	11	12
Parameter						
$\boldsymbol{\gamma_0^*(t)}$	0.6	0.5	0.6	0.5	0.5	0.3
$\boldsymbol{\gamma_3^*}$	0.2	0.5	0.2	0.5	0.2	0.5
$\boldsymbol{\nu^*}$	1.0	0.9	1.7	1.7	3.3	2.7
$\boldsymbol{\kappa^*}$	1.8	1.9	1.1	1.1	1.5	1.5
Relative event speed: p25(T_D) equal to	p25(T_{Mbin})	p25(T_{Mbin})	p50(T_{Mbin})	p50(T_{Mbin})	p75(T_{Mbin})	p75(T_{Mbin})

Each simulation generated 1000 datasets with N=1000 individuals. The dataset size of N=1000 was chosen in line with the simulations described in section 6.3.

For the simulations addressing aim 2, the parameter values chosen were the same as for aim 3. These parameter values are shown in Table 7-6 below.

Table 7-6 Parameters for simulations addressing aims 2 and 3. The nth percentile of $T_{\cdot}$ is written as pn($T_{\cdot}$).

Simulation setting number	13	14	15	16	17	18
Parameter						
$\boldsymbol{\gamma_0^*(t)}$	1.8	1.9	1.8	1.9	0.8	0.8
$\boldsymbol{\gamma_1^*}$	0	0.1	0	0.1	0	0.1
$\boldsymbol{\gamma_3^*}$	0.2	0.2	0.5	0.5	0.2	0.2
$\boldsymbol{\theta_0^*(t)}$	1.8	1.8	1.8	1.8	1.7	1.8
$\boldsymbol{\theta_1^*}$			0.5 for all settings 13-18			
p*			0.5 for all settings 13-18			
Relative event speed: p25(T_D) equal to	p25(T_{Mbin})	p25(T_{Mbin})	p25(T_{Mbin})	p25(T_{Mbin})	p50(T_{Mbin})	p50(T_{Mbin})
Simulation setting number	19	20	21	22	23	24
Parameter						
$\boldsymbol{\gamma_0^*(t)}$	0.7	0.7	0.3	0.25	0.2	0.15
$\boldsymbol{\gamma_1^*}$	0	0.1	0	0.1	0	0.1
$\boldsymbol{\gamma_3^*}$	0.5	0.5	0.2	0.2	0.5	0.5
$\boldsymbol{\theta_0^*(t)}$	1.8	1.8	1.7	1.7	1.7	1.7
$\boldsymbol{\theta_1^*}$			0.5 for all settings 19-24			
p*			0.5 for all settings 19-24			
Relative event speed: p25(T_D) equal to	p50(T_{Mbin})	p50(T_{Mbin})	p75(T_{Mbin})	p75(T_{Mbin})	p75(T_{Mbin})	p75(T_{Mbin})

As in chapter 3 and chapter 6, administrative censoring time was chosen to be t=5 for all individuals. Each simulation generated 1000 datasets of N=3000 individuals, with the exception of simulations investigating 95% coverage in dynamic path analysis. The dataset size of N=3000 for simulation settings 13-24 was based on the size of the pooled Zactima trials dataset.

7.4 Evaluation of methods using the simulated datasets

7.4.1 Criteria

The simulation studies estimated the quantities of interest ($\sum_{t_j \le t_D} \widehat{\gamma_3}(t_j)$ for the investigation of the additive hazards model with explanatory variable $M_{bin}(t)$ (aim 1); $\widehat{\beta_1}(t_j)$ for the

investigation of the linear regression model (aim 2); $\sum_{t_j \le t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$ for the investigation of dynamic path analysis (aim 3)), and compared them with their target estimands (see Table 7-2, Table 7-3 and Table 7-4) using the metrics listed in Table 7-7 below. These metrics are the same as those listed in Table 6-6 and are reproduced here for convenience. The symbol τ refers to the true value of the target of the simulation for aim 1, and the value of the target of the simulation in the absence of censoring for aims 2 and 3.

Table 7-7 Metrics used to assess the results of the simulations addressing aims 1-3

Metric[1]	**Interpretation**
τ	True value of the parameter of interest set in the data generation process
$\bar{\tau} = \frac{\sum_P \widehat{\tau_p}}{P}$	Mean value of the estimate of τ across simulation runs
$\frac{\bar{\tau} - \tau}{\tau} \times 100$	Percentage bias for aim 1, and percentage difference between the mean value and the value of τ in the absence of censoring for aims 2 and 3
Percentage of times the 95% confidence interval for $\hat{\tau}_p$ includes τ	95% coverage
$\frac{\sum_P SE(\widehat{\tau_p})}{P}$	Mean model-based standard error, for the additive hazards model and linear regression model simulations (aims 1 and 2) only
$SE(\hat{\tau}) = \sqrt{\frac{1}{P-1}\sum_P (\widehat{\tau_p} - \bar{\tau})^2}$	Empirical standard error

[1]Note that $\hat{\tau}_p$ denotes the estimate from simulated dataset p, (p=1,…,P; P=1000)

There was no expression available for the standard error of the cumulative indirect effect [30, 31], so the fifth metric, the mean model-based standard error, is not presented for the simulations investigating dynamic path analysis (aim 3).

The 95% coverage for simulations addressing aim 3 was based on a bootstrapped estimate of the 95% confidence intervals using a normal bootstrap where N=3000, and 100 simulation runs. Within each simulation run 50 bootstrap samples were used, due to the computationally intensive character of the simulations.

A graphical comparison of the estimands and mean values of the estimates over time was generated for one simulation setting addressing each aim, as an illustrative example. As in chapter 6, example graphs for the dynamic path analysis graphs included the uncensored and mean estimated values over time of the following (after Strohmaier [42]): $\int_0^t \beta_1(u)\gamma_3\,du +$

$\int_0^t \gamma_1 \, du$ (the total effect); $\int_0^t \gamma_1 \, du$ (the direct effect of X on N(t)); $\int_0^t \beta_1(u)\gamma_3 \, du$ (the indirect effect of X); $\beta_1(t)$ (the effect of X on E(M_{bin}(t))); and $\int_0^t \gamma_3 \, du$ (the effect of M_{bin}(t) on N(t)).

For the investigation of dynamic path analysis (aim 3), one further metric reported the difference between the estimated indirect effect and the total effect, when the direct effect is set in the simulations to be 0. From Table 7-4, if $\gamma_1^* = 0$, there is no direct effect of X on the rate of death. The total effect of X on the hazard could be estimated by fitting the additive hazards model $\alpha_D(t|X) = \gamma_0^X(t) + \gamma_1^X(t)X$**.** The effect of X would be reported as the cumulative regression coefficient $\widehat{\Gamma_1^X}(t)$. If there is no direct effect of X, this cumulative regression coefficient would be equivalent to the value of the indirect effect expected in the absence of censoring. This equivalence is checked by comparing the indirect effect in the absence of censoring $\int_0^t \beta_1(u)\gamma_3 \, du$ with the mean value of the estimate $\widehat{\Gamma_1^X}(t)$ for simulations where $\gamma_1^* = 0$ (simulation settings 13, 15, 17, 19, 21 and 23 in Table 7-6).

7.4.2 Interpretation

For the simulations addressing aim 1, if the additive hazards model estimates are unbiased the 95% coverage should be close to 95% [60]. For the simulations addressing aims 2 and 3, the values reported under 95% coverage are affected by censoring and therefore should not be over-interpreted; 95% “coverage” in this context acts as a check on the performance of the dynamic path analysis estimator under different censoring scenarios.

For the simulations investigating the performance of the additive hazards model with explanatory variable M_{bin}(t), and the simulations investigating the performance of the linear regression estimation for the effect of X on M_{bin}(t) (aims 1 and 2), the acceptable level of coverage for a 95% confidence interval based on 1000 repetitions was between 93.6% and 96.4% [60]. For the simulations investigating dynamic path analysis, the level of coverage for a 95% confidence interval based on 100 simulations was between 90.7% and 99.3% [60].

7.5 Additional simulation studies

Additional simulation studies were carried out as described below to further investigate the behaviour of the dynamic path analysis estimator in settings with a non-constant baseline hazard or treatment effect.

7.5.1 Investigations of the dynamic path analysis estimator with varying treatment and mediator effects

As noted in section 7.3, the regression estimates for the effect of X on $M_{bin}(t)$ based on a linear regression model, $\widehat{\beta_1}(t_d)$, could diverge from the value of $\beta_1(t)$ obtained from expression 7-2 due to the loss of individuals from the risk set by the distal event. If this divergence occurs, estimates of the indirect effect of X on death $\sum_{t_j \leq t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$ would also diverge from their expected value given in expression 7-3. The simulation parameters γ_1^*, γ_3^* or θ_1^* (see Table 7-4), in affecting the rate of death, could influence the extent of this divergence. To check this, the dynamic path analysis simulation settings with the largest coefficients, settings 16, 20 and 24 ($\gamma_1^* = 0.1, \gamma_3^* = 0.5, \theta_1^* = 0.5$) were repeated with some modifications as shown below. The sizes of the simulation datasets were varied to limit the imprecision of the estimates when the estimands were small. The values of the coefficients were changed to the following:

- γ_1^* was changed from 0.1 to 0.01, keeping values of $\gamma_3^* = 0.5$ and $\theta_1^* = 0.5$, setting N=1500;
- γ_3^* was changed from 0.5 to 0.1, keeping values of $\gamma_1^* = 0.1$ and $\theta_1^* = 0.5$, setting N=5000;
- θ_1^* was changed from 0.5 to 0.1, keeping values of $\gamma_1^* = 0.1$ and $\gamma_3^* = 0.5$, setting N=5000.

The baseline values of γ_0^* and θ_0^* were modified to keep the 85th percentile of T_{Mbin} close to t=1, as in the original simulations. To allow these simulations to complete within a reasonable timeframe, 500 repetitions were used instead of 1000. The results were reported as graphs of $\int_0^t \beta_1(u)\gamma_3 \, du$ and the mean of $\sum_{t_j \leq t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$ over the 500 repetitions against time.

7.5.2 Investigations of non-constant baseline hazard or treatment effect

The planned dynamic path analysis simulations reported above have time-invariant parameters (see Table 7-4). This section briefly describes simulations for assessing the performance of dynamic path analysis when either the baseline hazard ($\gamma_0^*(t)$) or the treatment effect ($\gamma_1^*(t)$ and $\theta_1^*(t)$) is piecewise constant.

Data generation for simulations investigating dynamic path analysis when the baseline hazard is piecewise constant specified a cutoff time t_{bh} such that:

$$\alpha(t|X, M_{bin}(t)) = \gamma_0(t) + \gamma_1^* X + \gamma_3^* M_{bin}(t) \text{ where } \gamma_0(t) = \begin{cases} \gamma_{0,1}^* \text{ if } t < t_{bh} \\ \gamma_{0,2}^* \text{ otherwise} \end{cases}$$

Other than this modification, data generation was the same as described below Table 7-3. The expected value of the estimand for dynamic path analysis in the absence of censoring, $\int_0^t \beta_1(u)\gamma_3 \, du$, is unchanged and given below Table 7-4.

For the simulations with a piecewise constant baseline hazard, the value of the baseline hazards $\gamma_{0,1}^*$, $\gamma_{0,2}^*$ and θ_0^* were chosen so that:

a) the 85th percentile of T_{Mbin} occurred at around t=1 (as in simulation settings 13-24);
b) the 75th percentile of T_{Mbin} is approximately equal to the 25th percentile of T_D (as in simulation settings 21-24);
c) the value of $\gamma_{0,2}^*$ was set to either 90% or 50% of the value of $\gamma_{0,1}^*$.

Parameter values chosen for the investigation of dynamic path analysis with a piecewise constant baseline hazard are shown in Table 7-8 below.

Table 7-8 Simulation parameters for dynamic path analysis with a piecewise constant baseline hazard, N=3000

Simulation setting number	25	26	27	28
Parameter				
$\boldsymbol{\gamma^*_{0,1}}$	0.25	0.3	0.15	0.2
$\boldsymbol{\gamma^*_{0,2}}$	0.225	0.15	0.135	0.1
$\mathbf{t_{bh}}$	0.5 for all settings 25-28			
$\boldsymbol{\gamma^*_1}$	0.1 for all settings 25-28			
$\boldsymbol{\gamma^*_3}$	0.2	0.2	0.5	0.5
$\boldsymbol{\theta^*_0(t)}$	1.6	1.6	1.7	1.7
$\boldsymbol{\theta^*_1}$	0.5 for all settings 25-28			
p*	0.5 for all settings 25-28			
Relative event speed: p25(T_D) equal to	p75(T_{Mbin})	p75(T_{Mbin})	p75(T_{Mbin})	p75(T_{Mbin})

Administrative censoring was set as before to t=5. The simulations consisted of 1000 datasets with N=3000 individuals. As before, coverage was calculated based on 50 bootstrap samples and 100 repetitions and results for the simulations are presented at six timepoints. The metrics used to report on the performance of the dynamic path analysis are shown in Table 7-7.

Data generation for simulations with a piecewise constant treatment effect specified a cutoff time t_{trt} such that:

$$\alpha(t|X, M_{bin}(t)) = \gamma_0^*(t) + \gamma_1(t)X + \gamma_3^* M_{bin}(t) \text{ where } \gamma_1(t) = \begin{cases} \gamma_{1,1}^* \text{ if } t < t_{tr} \\ \gamma_{1,2}^* \text{ otherwise} \end{cases}, \text{ and:}$$

$$\alpha_{M_{bin}}(t|X) = \theta_0^*(t) + \theta_1(t)X \text{ where } \theta_1(t) = \begin{cases} \theta_{1,1}^* \text{ if } t < t_{tr} \\ \theta_{1,2}^* \text{ otherwise} \end{cases}.$$

Other than these modifications, data generation was the same as described above.

However, a simple expression for the uncensored value of the estimand $\int_0^t \beta_1(u)\gamma_3\, du$ in terms of $\theta_0^*(t)$, $\theta_{1,1}^*$ and $\theta_{1,2}^*$ is not available.

If $t<t_{tr}$, the uncensored value of the estimand is given by:

$$\int_0^t \beta_1(u)\gamma_3\, du = \int_0^t \gamma_3 \left(\exp(-\theta_0^* u) - \exp\left(-\theta_0^* u - \theta_{1,1}^* u\right)\right) du \qquad \text{7-4},$$

the same as the uncensored value of the estimand given in Table 7-4. If $t \geq t_{tr}$, the stratum-specific cumulative hazards for $M_{bin}(t)$ can be written as follows:

$$A(t_{Mbin}|X = 0) = \int_0^t \theta_0^* du = \theta_0^* t \qquad \text{7-5}$$

$$A(t_{Mbin}|X = 1) = \int_0^{t_{tr}} (\theta_0^* + \theta_{1,1}^*) du + \int_{t_{tr}}^t (\theta_0^* + \theta_{1,2}^*) du = \theta_0^* t + \theta_{1,1}^* t_{tr} + \theta_{1,2}^* t - \theta_{1,2}^* t_{tr}$$

7-6

Then, using expressions 7-1 and 7-2 and the relationships between A(t), S(t) and I(t) (see text above expression 7-1),

$$\beta_1(t) = I(M_{bin}(t)|X = 1) \; - \; I(M_{bin}(t)|X = 0)$$
$$= \; \exp(-\theta_0^* u) - \exp\left(-\theta_0^* u - \theta_{1,1}^* t_{tr} - \theta_{1,2}^* u + \theta_{1,2}^* t_{tr}\right)$$

7-7

Thence, the value of the estimand when the effect of treatment varies with time according to a piecewise constant function with no censoring due to the distal outcome (death) if $t \geq t_{tr}$ is given by:

$$\int_0^t \beta_1(u)\gamma_3 \, du = \int_0^t \gamma_3^* \left(\exp(-\theta_0^* u) - \exp\left(-\theta_0^* u - \theta_{1,1}^* t_{tr} - \theta_{1,2}^* u + \theta_{1,2}^* t_{tr}\right)\right) du$$

7-8

Expressions 7-4 and 7-8 were compared to the mean values of the indirect effect estimates at six timepoints, as before.

Values of the baseline hazards $\gamma_0^*(t)$ and $\theta_0^*(t)$ were set to constants γ_0^* and θ_0^* respectively. The values of these constants were chosen so that:

a) the 85th percentile of T_{Mbin} occurred at around t=1 (as in simulation settings 13-24);
b) the 25th percentile of T_{Mbin} was approximately equal to the 25th percentile of T_D (as in simulation settings 13-16); or, the 75th percentile of T_{Mbin} was approximately equal to the 25th percentile of T_D (as in simulation settings 21-24).

The values of the other parameters are given in Table 7-9 below.

Administrative censoring was set to t=5. The simulations consisted of 1000 datasets of N=3000, except for coverage which was calculated based on 200 repetitions of 50 bootstrap samples where n=3000. The acceptable range of coverage for a 95% confidence interval based on 200 simulations was [91.9, 98.0] [60].

Table 7-9 Simulation parameters for dynamic path analysis with a piecewise constant treatment effect, N=3000

Simulation setting number	29	30	31	32
Parameter				
$\boldsymbol{\gamma_0^*(t)}$	1.8	1.7	0.2	0.1
$\boldsymbol{t_{tr}}$	0.5 for all settings 29-32			
$\boldsymbol{\gamma_{1,1}^*}$	0.2 for all settings 29-32			
$\boldsymbol{\gamma_{1,2}^*}$	0.1 for all settings 29-32			
$\boldsymbol{\gamma_3^*}$	0.2	0.5	0.2	0.5
$\boldsymbol{\theta_0^*(t)}$	1.8	1.7	1.7	1.7
$\boldsymbol{\theta_{1,1}^*}$	0.5 for all settings 29-32			
$\boldsymbol{\theta_{1,2}^*}$	0.2 for all settings 29-32			
p*	0.5 for all settings 29-32			
Relative event speed: p25(T_D) equal to	p25(T_{Mbin})	p25(T_{Mbin})	p75(T_{Mbin})	p75(T_{Mbin})

7.6 Results

Results are first presented in tables, then an example graph is shown for one of each set of simulation settings.

7.6.1 Results for the evaluation of the additive hazards model with a time-updated binary explanatory variable $M_{bin}(t)$ (aim 1)

Table 7-10 reports results from simulation settings 1-6 investigating the performance of the additive hazards model with time-updated binary explanatory variable $M_{bin}(t)$ when T_{Mbin} is exponentially distributed. Results are presented at each of four evaluation timepoints, the final time point corresponding approximately to the 75th percentile of the distribution of T_D.

These results show low percentage bias at all time points for simulation settings 1-6. The highest percentage bias is reported as 3.23% at the first evaluation timepoint in simulation setting 3, however this is still small in absolute terms and decreases over time.

In simulation settings 1 and 2, coverage is below the lower acceptable limit of 93.6% at the first two evaluation timepoints. This is because $M_{bin}(t)$ happens relatively slowly throughout these simulations. This leads to estimates of $\widehat{\Gamma_3}(t)$ which are quite variable across the 1000 repetitions, giving rise to large empirical SEs. At the same time, within each repetition the $\widehat{\Gamma_3}(t)$ are estimated quite precisely at early timepoints, because the dataset is large, giving rise to smaller model-based SEs. The conjunction of higher empirical SE and lower model-based SE leads to low coverage at the first two evaluation timepoints. Increasing the sample size to N=3000 for simulation 1 decreases the variability of the estimates early in follow-up and leads to improved coverage (see Appendix IV).

Conversely, in simulation settings 5 and 6, when $M_{bin}(t)$ happens much faster than death, coverage is below acceptable at the last evaluation timepoint (corresponding to the 75th percentile of the distribution of T_D). This is because $M_{bin}(t)=1$ for most individuals as time increases, so that $\widehat{\Gamma_3}(t)$ levels off rather than increasing, and the confidence interval for $\widehat{\Gamma_3}(t)$ excludes the true value. If simulation 5 is repeated with estimation truncated at the 99th percentile of T_{Mbin}, coverage falls within acceptable limits (see Appendix IV).

Table 7-10 Evaluation of the additive hazards model specified for aim 1 (binary time-updated explanatory variable $M_{bin}(t)$ where T_{Mbin} is exponentially distributed). The values of the baseline parameters are given as footnotes. Results are based on 1000 simulated datasets of N=1000 individuals.

	Simulation	$p25(T_D)=p25(T_{Mbin})$, $M_{bin}(t)$ is slightly slower than death				Simulation				
Time	setting	0.5	1.0	1.5	2.0	setting	0.5	1.0	1.5	2.0
		$\gamma_3^* = 0.2$[1]					$\gamma_3^* = 0.5$[2]			
True value $\Gamma_3(t)$	1	0.1	0.2	0.3	0.4	2	0.25	0.5	0.75	1
Mean of estimates $\hat{\Gamma}_3(t)$		0.102	0.202	0.304	0.403		0.254	0.504	0.755	1.005
Mean percentage bias		1.87	1.18	1.41	0.78		1.82	0.85	0.64	0.55
Mean % of deaths /$M_{bin}(t)$		26.9 / 22.5	47.6 /34.9	63.0 /41.7	74.2 /45.4		28.2 /22.5	50.8 /34.9	67.4 /41.7	78.8 /45.4
95% coverage		90.6	92.5	94.0	95.3		90.8	93.0	94.4	95.4
Empirical / Model-based SE		0.106 /0.084	0.117 /0.100	0.130 /0.116	0.145 /0.136		0.132 /0.102	0.145 /0.121	0.159 /0.137	0.177 /0.162
		$p25(T_D)=p50(T_{Mbin})$, $M_{bin}(t)$ is slightly faster than death								
Time		0.5	1.0	1.5	2.0		0.5	1.0	1.5	2.0
		$\gamma_3^* = 0.2$[3]					$\gamma_3^* = 0.5$[4]			
True value $\Gamma_3(t)$	3	0.1	0.2	0.3	0.4	4	0.25	0.5	0.75	1
Mean of estimates $\hat{\Gamma}_3(t)$		0.103	0.204	0.307	0.407		0.253	0.504	0.758	1.007
Mean percentage bias		3.23	2.16	2.46	1.75		1.24	0.79	1.03	0.71
Mean % of deaths/ $M_{bin}(t)$		28.0 /46.4	50.0 /62.6	65.9 /68.3	76.9 /70.4		23.4 /46.2	45.9 /64.9	63.4 /72.5	75.7 /75.7
95% coverage		93.9	95.4	95.0	94.3		93.7	94.8	95.1	95.2
Empirical/ Model-based SE		0.081 /0.062	0.096 /0.082	0.123 /0.111	0.170 /0.163		0.084 /0.065	0.095 /0.080	0.110 /0.099	0.137 /0.129
		$p25(T_D)=p75(T_{Mbin})$, $M_{bin}(t)$ is much faster than death								
Time		0.5	1.0	1.5	2.0		0.5	1.0	1.5	2.0
		$\gamma_3^* = 0.2$[5]					$\gamma_3^* = 0.5$[6]			
True value $\Gamma_3(t)$	5	0.1	0.2	0.3	0.4	6	0.25	0.5	0.75	1
Mean of estimates $\hat{\Gamma}_3(t)$		0.099	0.203	0.308	0.406		0.250	0.503	0.753	1.008
Mean percentage bias		-0.08	1.49	2.56	1.56		-0.08	0.52	0.42	0.81
Mean % of deaths /$M_{bin}(t)$		25.6 /67.3	46.6 /80.9	62.3 /83.7	73.3 /84.2		22.4 /67.2	45.3 /83.8	62.7 /87.9	74.8 /89.0
95% coverage		93.8	95.5	93.5	84.7		94.0	94.7	94.7	89.5
Empirical/ Model-based SE		0.062 /0.049	0.087 /0.079	0.154 /0.146	0.322 /0.275		0.068 /0.050	0.083 /0.068	0.114 /0.105	0.195 /0.174

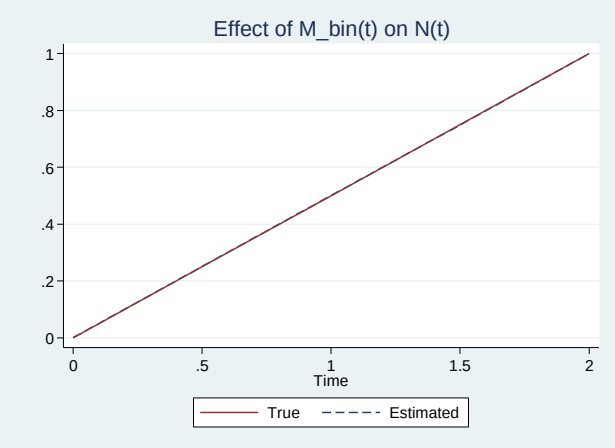
[1] $\gamma_0^* = 0.6, \theta_0^* = 0.6$ [2] $\gamma_0^* = 0.6, \theta_0^* = 0.6$ [3] $\gamma_0^* = 0.6, \theta_0^* = 1.5$ [4] $\gamma_0^* = 0.4, \theta_0^* = 1.4$ [5] $\gamma_0^* = 0.5, \theta_0^* = 2.7$ [6] $\gamma_0^* = 0.3, \theta_0^* = 2$

Overall, the results reported in Table 7-10 suggest that, although the additive hazards model with time-updated binary explanatory variable $M_{bin}(t)$ gives rise to unbiased estimates as expected, coverage may be low when $M_{bin}(t)$ events are slow to accumulate and the sample size is not large, or when $M_{bin}(t)=1$ for most of the population.

Illustrative example 7-1

Figure 7-3 below compares the true cumulative regression coefficient for $M_{bin}(t)$, $\Gamma_3(t)$, with the mean value of its estimate $\widehat{\Gamma_3}(t)$ plotted over time for simulation setting 4, as an example of the performance of the additive hazards model. Simulation setting 4 was chosen because $M_{bin}(t)$ is neither slower nor much faster than death, and the choice of $\gamma_3^* = 0.5$ means that the values of the estimands and mean values of estimates are easy to read off the y-axis.

Figure 7-3 Example graph showing the values of $\Gamma_3(t)$ and the mean of $\widehat{\Gamma_3}(t)$ over time in simulation setting 4



From Table 7-2, the expected cumulative change in the mortality hazard function at time t, α(t), associated with $M_{bin}(t)=1$ is $\Gamma_3(t) = \int_0^t \gamma_3 \, du = \gamma_3 t$. The graph of $\Gamma_3(t)$ against time is therefore a straight line passing through the origin with slope equal to γ_3. Figure 7-3 demonstrates good agreement between the true parameter values and the mean of their estimates.

Table 7-11 reports results from simulation settings 7-12 investigating the performance of the additive hazards model with binary time-updated explanatory variable $M_{bin}(t)$ when T_{Mbin} follows a Weibull distribution. There is little evidence of bias, with the greatest bias of -2.13% occurring at the first evaluation timepoint of simulation setting 8.

Table 7-11 Evaluation of the additive hazards model specified for aim 1 (binary time-updated explanatory variable $M_{bin}(t)$ where T_{Mbin} has a Weibull distribution). The values of the baseline parameters are given as footnotes. Results are based on 1000 simulated datasets of N=1000 individuals.

	Simulation	$p25(T_D)=p25(T_{Mbin})$, $M_{bin}(t)$ is slightly slower than death				Simulation				
Time	setting	0.5	1.0	1.5	2.0	settting	0.5	1.0	1.5	2.0
		$\gamma_3^* = 0.2$[7]					$\gamma_3^* = 0.5$[8]			
True value $\Gamma_3(t)$	7	0.1	0.2	0.3	0.4	8	0.25	0.5	0.75	1
Mean of estimates $\widehat{\Gamma_3}(t)$		0.101	0.201	0.305	0.405		0.247	0.495	0.746	0.998
Mean percentage bias		1.00	0.44	1.65	1.30		-2.13	-1.01	-0.49	-0.16
Mean % of deaths /$M_{bin}(t)$		26.6 /20.7	47.6 /45.3	64.2 /57.1	75.7 /60.5		23.5 /18.3	45.7 /44.4	64.4 /58.8	77.7 /63.4
95% coverage		84.7	89.1	92.9	95.2		82.6	86.4	89.8	94.7
Empirical/ Model-based SE		0.162 /0.117	0.170 /0.130	0.182 /0.149	0.227 /0.200		0.197 /0.146	0.205 /0.158	0.214 /0.172	0.241 /0.206
		$p25(T_D)=p50(T_{Mbin})$, $M_{bin}(t)$ is slightly faster than death								
Time		0.5	1.0	1.5	2.0		0.5	1.0	1.5	2.0
		$\gamma_3^* = 0.2$[9]					$\gamma_3^* = 0.5$[10]			
True value $\Gamma_3(t)$	9	0.1	0.2	0.3	0.4	10	0.25	0.5	0.75	1
Mean of estimates $\widehat{\Gamma_3}(t)$		0.102	0.203	0.306	0.408		0.253	0.503	0.758	1.006
Mean percentage bias		1.93	1.75	1.91	2.03		1.01	0.55	1.04	0.60
Mean % of deaths/ $M_{bin}(t)$		27.8 /45.3	50.0 /64.5	66.0 /70.4	77.1 /71.9		22.6 /41.4	44.8 /61.9	62.5 /70.5	75.1/74.1
95% coverage		93.5	95.3	95.5	92.4		92.3	95.2	95.0	94.2
Empirical/ Model-based SE		0.093 /0.070	0.107 /0.089	0.141 /0.125	0.217 /0.207		0.097 /0.073	0.105 /0.086	0.119 /0.104	0.146 /0.132
		$p25(T_D)=p75(T_{Mbin})$, $M_{bin}(t)$ is much faster than death								
Time		0.5	1.0	1.5	2.0		0.5	1.0	1.5	2.0
		$\gamma_3^* = 0.2$[11]					$\gamma_3^* = 0.5$[12]			
True value $\Gamma_3(t)$	11	0.1	0.2	0.3	0.4	12	0.25	0.5	0.75	1
Mean of estimates $\widehat{\Gamma_3}(t)$		0.100	0.204	0.304	0.406		0.250	0.501	0.754	1.006
Mean percentage bias		0.34	1.86	1.44	1.40		-0.20	0.30	0.50	0.62
Mean % of deaths / $M_{bin}(t)$		26.5 /71.2	47.1 /78.8	62.2 /81.5	73.1 /82.7		25.2 /72.7	46.8 /81.5	62.8 /85.0	74.1 /86.6
95% coverage		95.2	95.2	94.8	95.3		95.9	94.5	95.3	96.1
Empirical/ Model-based SE		0.040 /0.040	0.064 /0.065	0.097 /0.097	0.137 /0.137		0.037 /0.037	0.057 /0.057	0.078 /0.079	0.102 /0.106

[7] $\gamma_0^* = 0.6, \kappa^* = 1.0, \nu^* = 1.8$ [8] $\gamma_0^* = 0.5, \kappa^* = 0.9, \nu^* = 1.9$ [9] $\gamma_0^* = 0.6, \kappa^* = 1.7, \nu^* = 1.1$ [10] $\gamma_0^* = 0.5, \kappa^* = 1.7, \nu^* = 1.1$ [11] $\gamma_0^* = 0.5, \kappa^* = 3.3, \nu^* = 1.5$ [12] $\gamma_0^* = 0.3, \kappa^* = 2.7, \nu^* = 1.5$

The results of simulations 7 and 8 show unacceptably low coverage for three of the four evaluation timepoints. Setting the scale parameter v*=1.8 and v*=1.9 respectively for simulation settings 7 and 8 means that the hazard of $M_{bin}(t)$ is very low at early timepoints. As a result, $M_{bin}(t)$ events are even more sparse at the earlier timepoints than in the simulation settings where T_{Mbin} has an exponential distribution (Table 7-10). This leads to a greater mismatch between the empirical and the model-based SEs for simulation settings 7 and 8, which in turn causes low coverage. In contrast, the choice of v*=1.5 for simulation settings 11 and 12 when the rate of $M_{bin}(t)$ is much faster than that for death means that $M_{bin}(t)$ events continue to occur throughout follow-up, rather than reaching a point when $M_{bin}(t)=1$ for all individuals. This means that bias is minimal and coverage is satisfactory for all evaluation timepoints.

These findings confirm the observation made earlier that coverage may be poor when $M_{bin}(t)$ events are sparse at either early or late timepoints. However, the additive hazards model estimates, as expected, show minimal bias.

Illustrative example 7-2

Figure 7-4 below compares the true cumulative regression coefficient $\Gamma_3(t)$ with the mean of the estimates $\widehat{\Gamma_3}(t)$ over time for simulation setting 10. This simulation setting is similar to simulation setting 4, chosen for illustrative example 7-1, with respect to the magnitude of $\Gamma_3(t)$ and the relative timings of $M_{bin}(t)$ and death. In this setting T_{Mbin} follows a Weibull distribution.

Figure 7-4 Example graph showing the values of $\Gamma_3(t)$ and the mean of $\widehat{\Gamma_3}(t)$ over time in simulation setting 10

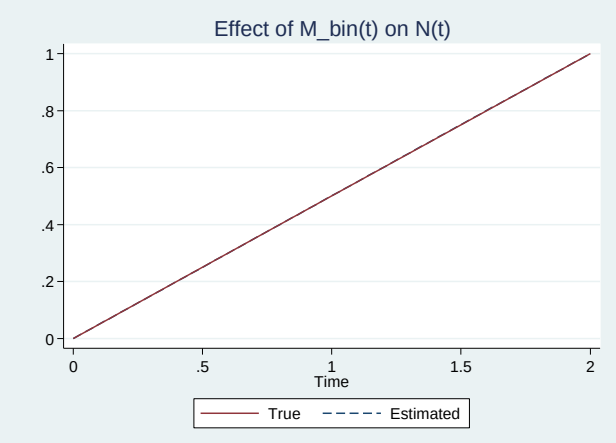


Figure 7-4 shows agreement between $\Gamma_3(t)$ and $\widehat{\Gamma_3}(t)$ over time.

7.6.2 Results for the evaluation of the regression models for the effect of X on time-to-event outcome $M_{bin}(t)$ (aim 2)

Table 7-12 and Table 7-13 show results for the performance of the estimation of the effect of X on $M_{bin}(t)$. As described in section 7.3.1, the regression models are assessed at six timepoints, with four of the timepoints evenly spaced between t=0 and t=1, with t=1 corresponding approximately to the 85th percentile of T_{Mbin}, and the other two timepoints representing approximately the 75th percentile of T_{Mbin} and the 75th percentile of T_D.

Table 7-12 Evaluation of the linear regression model specified for aim 2 (estimating the effect of X on $M_{bin}(t)$), part 1 of 2. The values of baseline parameters are given as footnotes. Results are based on 1000 simulated datasets of N=3000 individuals. "Uncensored value of $\beta_1(t)$" refers to the expected value of $\beta_1(t)$ if there were no distal events as discussed in section 7.3. The 95% coverage refers to the uncensored value.

	Simulation setting	p25(T_D)=p25(T_{Mbin}), $M_{bin}(t)$ is slightly slower than death $\gamma_1^*=0, \gamma_3^*=0.2, \theta_1^*=0.5$[13]						Simulation setting	$\gamma_1^*=0.1, \gamma_3^*=0.2, \theta_1^*=0.5$[14]					
Time	13	0.25	0.50	0.70 ($p75_D$)	0.71 ($p75_{Mbin}$)	0.75	1.0	14	0.25	0.50	0.68 ($p75_D$)	0.69 ($p75_{Mbin}$)	0.75	1.0
Uncensored value $\beta_1(t)$		0.075	0.090	0.084	0.083	0.081	0.065		0.075	0.090	0.085	0.084	0.081	0.065
Mean of estimates $\widehat{\beta_1}(t)$		0.074	0.091	0.087	0.087	0.085	0.072		0.074	0.091	0.088	0.088	0.085	0.071
Mean % difference		-1.36	0.96	4.03	4.21	4.80	10.13		-1.36	1.18	3.34	3.86	5.17	9.74
Mean % of deaths /$M_{bin}(t)$		36.9 /32.8	60.8 /45.3	73.4 /49.5	73.9 /49.6	75.9 /50.1	85.2 /51.9		39.2 /32.3	63.6 /44.1	75.0 /47.7	75.5 /47.8	78.4 /48.5	87.2 /50.1
95% coverage		96.2	94.8	94.7	94.8	94.9	94.7		95.1	94.7	95.3	94.9	95.3	95.2
Empirical / Model-based SE		0.022 /0.022	0.028 /0.028	0.030 /0.031	0.030 /0.031	0.031 /0.031	0.033 /0.034		0.023 /0.023	0.030 /0.029	0.032 /0.032	0.032 /0.032	0.032 /0.033	0.035 /0.037
	15	$\gamma_1^*=0, \gamma_3^*=0.5, \theta_1^*=0.5$[15]						16	$\gamma_1^*=0.1, \gamma_3^*=0.5, \theta_1^*=0.5$[16]					
Time		0.25	0.50	0.68 ($p75_D$)	0.69 ($p75_{Mbin}$)	0.75	1.0		0.25	0.50	0.64 ($p75_D$)	0.69 ($p75_{Mbin}$)	0.75	1.0
Uncensored value $\beta_1(t)$		0.075	0.090	0.085	0.084	0.081	0.065		0.075	0.090	0.087	0.084	0.081	0.065
Mean of estimates $\widehat{\beta_1}(t)$		0.073	0.092	0.092	0.092	0.090	0.080		0.073	0.092	0.093	0.092	0.090	0.080
Mean % difference		-2.41	2.03	8.38	9.09	11.10	23.33		-2.40	2.14	6.95	8.90	11.40	22.89
Mean % of deaths / $M_{bin}(t)$		37.9 /32.8	62.8 /45.3	74.6 /49.2	75.2 /49.3	78.2 /50.1	87.4 /51.9		40.2 /32.3	65.5 /44.1	74.9 /47.1	77.6 /47.8	80.5 /48.5	89.1 /50.1
95% coverage		95.8	94.5	94.5	94.8	94.1	93.7		95.5	94.4	95.1	94.6	95.2	93.9
Empirical / Model-based SE		0.022 /0.022	0.029 /0.029	0.032 /0.033	0.032 /0.033	0.033 /0.034	0.038 /0.039		0.023 /0.023	0.030 /0.030	0.033 /0.034	0.034 /0.035	0.035 /0.036	0.040 /0.042
		p25(T_D)=p50(T_{Mbin}), $M_{bin}(t)$ is slightly faster than death												
	17	$\gamma_1^*=0, \gamma_3^*=0.2, \theta_1^*=0.5$[17]						18	$\gamma_1^*=0.1, \gamma_3^*=0.2, \theta_1^*=0.5$[18]					
Time		0.25	0.50	0.70 ($p75_{Mbin}$)	0.75	1.0	1.50 ($p75_D$)		0.25	0.50	0.68 ($p75_{Mbin}$)	0.75	1.0	1.41 ($p75_D$)
Uncensored value $\beta_1(t)$		0.075	0.090	0.084	0.081	0.065	0.035		0.075	0.090	0.085	0.081	0.065	0.040
Mean of estimates $\widehat{\beta_1}(t)$		0.074	0.090	0.086	0.084	0.072	0.043		0.074	0.090	0.087	0.084	0.072	0.048
Mean % difference		-0.85	0.52	3.04	3.59	10.12	21.86		-0.62	0.61	2.63	3.59	10.34	19.34
Mean % of deaths / $M_{bin}(t)$		19.0 /36.5	35.4 /54.4	46.4 /61.9	48.9 /63.2	59.8 /67.5	75.4 /70.6		20.0 /36.3	36.9 /53.9	47.2 /60.6	50.7 /62.4	61.7 /66.5	74.8 /69.3
95% coverage		94.7	95.0	95.6	96.4	94.2	93.4		95.0	95.3	94.9	96.3	94.7	94.5
Empirical / Model-based SE		0.020 /0.020	0.022 /0.022	0.021 /0.022	0.020 /0.022	0.020 /0.020	0.018 /0.018		0.020 /0.020	0.022 /0.022	0.021 /0.022	0.021 /0.022	0.020 /0.021	0.019 /0.019

[13] $\gamma_0^*=1.8, \theta_0^*=1.8$ [14] $\gamma_0^*=1.9, \theta_0^*=1.8$ [15] $\gamma_0^*=1.8, \theta_0^*=1.8$ [16] $\gamma_0^*=1.9, \theta_0^*=1.8$ [17] $\gamma_0^*=0.8, \theta_0^*=1.8$ [18] $\gamma_0^*=0.8, \theta_0^*=1.8$

Table 7-13 Evaluation of the linear regression model specified for aim 2 (estimating the effect of X on $M_{bin}(t)$), part 2 of 2. The values of baseline parameters are given as footnotes. Results are based on 1000 simulated datasets of N=3000 individuals. "Uncensored value of $\beta_1(t)$" refers to the expected value of $\beta_1(t)$ if there were no distal events as discussed in section 7.3. The 95% coverage refers to the uncensored value.

	19	$\gamma_1^*=0, \gamma_3^*=0.5, \theta_1^*=0.5$[19]						20	$\gamma_1^*=0.1, \gamma_3^*=0.5, \theta_1^*=0.5$[20]					
Time		0.25	0.50	0.68 ($p75_{Mbin}$)	0.75	1.0	1.36 ($p75_D$)		0.25	0.50	0.68 ($p75_{Mbin}$)	0.75	1.0	1.30 ($p75_D$)
Uncensored value $\beta_1(t)$		0.075	0.090	0.085	0.081	0.065	0.043		0.075	0.090	0.085	0.081	0.065	0.046
Mean of estimates $\widehat{\beta_1}(t)$		0.073	0.091	0.091	0.089	0.080	0.061		0.073	0.092	0.091	0.089	0.080	0.064
Mean % difference		-1.98	1.74	7.15	9.62	22.33	43.74		-2.03	1.82	7.03	9.26	22.47	39.65
Mean % of deaths / $M_{bin}(t)$		18.2 /37.0	35.5 /55.5	46.4 /62.8	50.3 /64.8	62.1 /69.5	74.8 /72.5		19.2 /36.7	37.1 /54.9	48.2 /62.0	52.0 /64.0	63.9 / 68.5	74.6 /71.0
95% coverage		95.8	95.1	95.5	94.9	91.1	86.6		95.5	95.4	95.1	95.6	91.9	89.0
Empirical / Model-based SE		0.020 /0.020	0.022 /0.022	0.022 /0.023	0.021 /0.023	0.021 /0.022	0.022 /0.022		0.020 /0.020	0.022 /0.022	0.022 /0.023	0.022 /0.023	0.022 /0.023	0.022 /0.023
		$p25(T_D)=p75(T_{Mbin})$, $M_{bin}(t)$ is much faster than death												
	21	$\gamma_1^*=0, \gamma_3^*=0.2, \theta_1^*=0.5$[21]						22	$\gamma_1^*=0.1, \gamma_3^*=0.2, \theta_1^*=0.5$[22]					
Time		0.25	0.50	0.65 ($p75_{Mbin}$)	0.75	1.0	2.70 ($p75_D$)		0.25	0.50	0.72 ($p75_{Mbin}$)	0.75	1.0	3.0 ($p75_D$)
Uncensored value $\beta_1(t)$		0.077	0.095	0.092	0.087	0.072	0.008		0.077	0.095	0.089	0.087	0.072	0.005
Mean of estimates $\widehat{\beta_1}(t)$		0.076	0.095	0.094	0.091	0.078	0.011		0.076	0.095	0.092	0.091	0.078	0.007
Mean % difference		-1.27	0.14	2.32	3.63	8.38	50.03		-1.38	0.06	3.47	3.78	8.33	57.46
Mean % of deaths / $M_{bin}(t)$		8.2 /37.2	16.9 /68.3	22.1 /66.3	25.5 /70.3	33.6 /77.1	71.1 /86.3		8.2 /37.1	16.9 /58.2	24.4 /69.2	25.4 /70.3	33.5 /77.2	74.7 /86.6
95% coverage		94.8	95.7	95.4	95.8	95.0	93.0		94.6	95.4	95.5	95.3	95.0	97.2
Empirical /Model-based SE		0.018 /0.018	0.019 /0.019	0.018 /0.019	0.018 /0.018	0.016 /0.016	0.007 /0.007		0.018 /0.018	0.019 /0.019	0.018 /0.019	0.018 /0.018	0.016 /0.017	0.005 /0.006
	23	$\gamma_1^*=0, \gamma_3^*=0.5, \theta_1^*=0.5$[23]						24	$\gamma_1^*=0.1, \gamma_3^*=0.5, \theta_1^*=0.5$[24]					
Time		0.25	0.5	0.72 ($p75_{Mbin}$)	0.75	1.0	2.4 ($p75_D$)		0.25	0.5	0.72 ($p75_{Mbin}$)	0.75	1.0	2.4 ($p75_D$)
Uncensored value $\beta_1(t)$		0.077	0.095	0.089	0.087	0.072	0.012		0.077	0.095	0.089	0.087	0.072	0.012
Mean of estimates $\widehat{\beta_1}(t)$		0.075	0.095	0.096	0.095	0.086	0.027		0.075	0.095	0.096	0.095	0.086	0.027
Mean % difference		-2.56	0.97	7.65	8.85	20.06	128.82		-2.61	0.92	7.55	8.63	20.08	129.00
Mean % of deaths / $M_{bin}(t)$		7.2 /37.6	17.0 /59.5	26.0 /71.1	27.3 /72.2	37.1 /79.7	75.0 /90.0		7.2 /37.6	16.9 /59.4	25.9 /71.0	27.2 /72.2	37.0 /79.7	74.7 /90.2
95% coverage		94.9	95.9	94.1	93.0	87.8	78.3		94.4	95.9	94.3	94.0	89.3	80.5
Empirical / Model-based SE		0.018 /0.018	0.019 /0.020	0.019 /0.019	0.019 /0.019	0.017 /0.018	0.011 /0.012		0.018 /0.018	0.019 /0.020	0.019 /0.019	0.018 /0.019	0.017 /0.018	0.011 /0.012

[19] $\gamma_0^*=0.7, \theta_0^*=1.8$ [20] $\gamma_0^*=0.7, \theta_0^*=1.8$ [21] $\gamma_0^*=0.3, \theta_0^*=1.7$ [22] $\gamma_0^*=0.25, \theta_0^*=1.7$ [23] $\gamma_0^*=0.2, \theta_0^*=1.7$ [24] $\gamma_0^*=0.15, \theta_0^*=1.7$

The principal finding in Table 7-12 and Table 7-13 is that censoring by the distal event affects $\widehat{\beta_1}(t)$ in some settings. At the 75th percentile of T_D, the divergence between $\beta_1(t)$ and $\widehat{\beta_1}(t)$ is greatest when $M_{bin}(t)$ happens much more quickly than death (simulation settings 21-24) and smallest when $M_{bin}(t)$ happens slowly relative to death (simulation settings 13-16). Increased divergence is associated with a higher value of γ_3^*; for example, at the 75th percentile of T_D the mean percentage divergence in simulation setting 22 where $\gamma_3^* = 0.2$ was 57.5%, compared to the difference in simulation setting 24 where $\gamma_3^* = 0.5$ of 129%. These large divergences are however restricted to later timepoints. For simulation settings with γ_3^*=0.5, percentage difference at t=1 (the 85th percentile of T_{Mbin}) is around 20%.

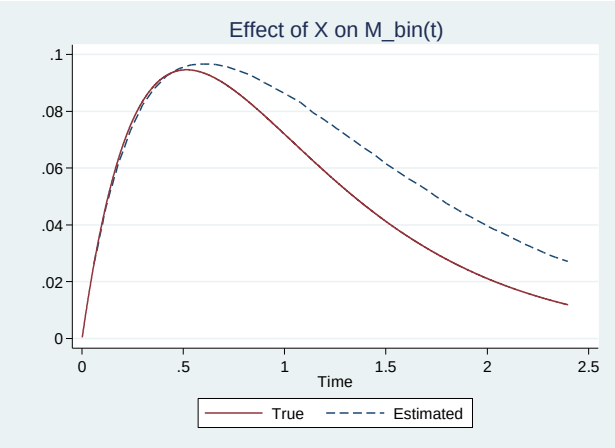
This divergence is caused by loss of individuals from the risk set by death. The divergence is marked in settings such as simulations 21-24 when deaths occur predominantly after the event mediator. This is why higher values of γ_3^*, which determines the rate of death after the time-to-event mediator (see Table 7-3) are associated with greater divergence.

This divergence between $\beta_1(t)$ and $\widehat{\beta_1}(t)$ may feed forward into divergence between $\int_0^t \beta_1(u)\gamma_3\,du$ and $\sum_{t_j \le t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$ in the dynamic path analysis estimates. However, as the divergence occurs at later timepoints and the indirect effect estimate is cumulative, divergence in estimates of the indirect effect of X are likely to be less influential.

Illustrative example 7-3

Figure 7-5 illustrates the divergence between $\beta_1(t)$ and the mean of $\widehat{\beta_1}(t)$ over time for simulation setting 24. This simulation setting was chosen because it demonstrated the greatest divergence at the 75th percentile of T_D of any of the simulation settings in this section (see Table 7-13).

Figure 7-5 Example graph showing the values of $\beta_1(t)$ and the mean of $\widehat{\beta_1}(t)$ against time from simulation setting 24 in the least-squares estimation of the regression model for the effect X on $M_{bin}(t)$. Parameter values are $\gamma_0^* = 0.15, \gamma_1^* = 0.1, \gamma_3^* = 0.5, \theta_0^* = 1.7, \theta_1^* = 0.5$.



From Figure 7-5, the divergence is apparent after about t=0.5, and is greatest after the 85th percentile of T_{Mbin} at t=1.

7.6.3 Results for the evaluation of the estimation of the indirect effect using dynamic path analysis with time-to-event mediator $M_{bin}(t)$ (aim 3)

Table 7-14 shows results for the evaluation of dynamic path analysis with a time-to-event mediator for simulation settings 13-17 and 19; Table 7-15 shows results for simulation settings 18 and 20-24. The evaluation timepoints and parameter values are the same as those used for the evaluation of least-squares estimation of the effect of X on $M_{bin}(t)$ in section 7.6.2, so the results can easily be compared.

Table 7-14 Evaluation of the indirect effect estimate in dynamic path analysis in aim 3, part 1 of 2. Baseline parameter values are given as footnotes. Results are based on 1000 simulated datasets of N=3000 individuals, except for coverage, which is based on 100 datasets of N=3000. Results are grouped according to the relative timings of $M_{bin}(t)$ and death. The 95% coverage refers to the uncensored value.

	Sim. setting	p25(T_D)=p25(T_{Mbin}), $M_{bin}(t)$ is slightly slower than death						Sim. setting						
		$\gamma_1^*=0, \gamma_3^*=0.2, \theta_1^*=0.5$[13]							$\gamma_1^*=0, \gamma_3^*=0.5, \theta_1^*=0.5$[15]					
Time		0.25	0.50	0.70 (p75$_D$)	0.71 (p75$_{Mbin}$)	0.75	1.0		0.25	0.50	0.68 (p75$_D$)	0.69 (p75$_{Mbin}$)	0.75	1.0
Uncensored value $\int_0^t \beta_1(u)\gamma_3 du$	13	0.0022	0.0065	0.010	0.010	0.011	0.015	15	0.0056	0.016	0.024	0.024	0.027	0.036
Mean of $\sum_{t_j \le t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$		0.0022	0.0063	0.010	0.010	0.011	0.015		0.0055	0.016	0.024	0.025	0.027	0.038
Mean % difference		0.32	-3.13	-1.80	-1.92	-1.37	0.15		-1.75	-2.39	-0.12	0.02	0.87	4.39
Mean % of deaths / $M_{bin}(t)$		36.9 /32.8	60.8 /45.3	73.3 /49.5	73.9 /49.6	75.9 /50.1	85.2 /51.9		37.9 /32.8	62.8 /45.3	74.6 /49.2	75.2 /49.3	78.2 /50.1	87.4 /51.9
95% coverage		97.0	98.0	96.0	97.0	97.0	97.0		95.0	97.0	94.0	92.0	93.0	94.0
Empirical SE		0.0018	0.0040	0.0059	0.0060	0.0064	0.0092		0.0024	0.0055	0.0080	0.0081	0.0091	0.013
Percentage difference between $\int_0^t \beta_1(u)\gamma_3 du$ and $\widehat{\Gamma_1^x}(t)$		28.1	-25.3	15.4	13.1	1.9	-2.4		7.4	-10.6	4.3	2.7	-2.5	-0.3
		$\gamma_1^*=0.1, \gamma_3^*=0.2, \theta_1^*=0.5$[14]							$\gamma_1^*=0.1, \gamma_3^*=0.5, \theta_1^*=0.5$[16]					
Time		0.25	0.50	0.68 (p75$_D$)	0.69 (p75$_{Mbin}$)	0.75	1.0		0.25	0.50	0.64 (p75$_D$)	0.69 (p75$_{Mbin}$)	0.75	1.0
Uncensored value $\int_0^t \beta_1(u)\gamma_3 du$	14	0.0022	0.0065	0.0097	0.0099	0.011	0.015	16	0.0056	0.016	0.022	0.024	0.027	0.036
Mean of $\sum_{t_j \le t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$		0.0022	0.0063	0.0096	0.0097	0.011	0.015		0.0055	0.016	0.022	0.024	0.027	0.038
Mean % difference		-0.88	-3.97	-1.00	-1.86	-0.82	3.22		-2.28	-2.83	-0.67	-0.01	1.06	5.65
Mean % of deaths / $M_{bin}(t)$		39.2 /32.3	63.6 /44.1	75.0 /47.7	75.5 /47.8	78.4 /48.5	87.2 /50.1		40.2 /32.3	65.5 /44.1	74.9 /47.1	77.6 /47.8	80.5 /48.5	89.1 /50.1
95% coverage		100	94.0	94.0	92.0	95.0	97.0		97.0	95.0	97.0	95.0	94.0	93.0
Empirical SE		0.0019	0.0043	0.0061	0.0063	0.0069	0.010		0.0024	0.0057	0.0077	0.0086	0.0097	0.014
		p25(T_D)=p50(T_{Mbin}), $M_{bin}(t)$ is slightly faster than death												
		$\gamma_1^*=0, \gamma_3^*=0.2, \theta_1^*=0.5$[17]							$\gamma_1^*=0, \gamma_3^*=0.5, \theta_1^*=0.5$[19]					
Time		0.25	0.50	0.70 (p75$_{Mbin}$)	0.75	1.0	1.50 (p75$_D$)		0.25	0.50	0.68 (p75$_{Mbin}$)	0.75	1.0	1.36 (p75$_D$)
Uncensored value $\int_0^t \beta_1(u)\gamma_3 du$	17	0.0022	0.0065	0.010	0.011	0.015	0.019	19	0.0056	0.016	0.024	0.027	0.036	0.046
Mean of $\sum_{t_j \le t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$		0.0022	0.0065	0.010	0.011	0.015	0.021		0.0055	0.016	0.024	0.028	0.038	0.051
Mean difference		-1.46	-0.61	0.25	1.05	2.70	5.80		-2.53	-0.79	0.61	1.45	5.32	10.78
Mean % of deaths / $M_{bin}(t)$		19.0 /36.5	35.4 /54.4	46.4 /61.9	48.9 /63.2	59.8 /67.5	75.4 /70.6		18.2 /37.0	35.5 /55.5	46.4 /62.8	50.3 /64.8	62.1 /69.5	74.8 /72.5
95% coverage		95.0	93.0	94.0	96.0	96.0	96.0		95.0	95.0	93.0	91.0	92.0	93.0
Empirical SE		0.0013	0.0026	0.0036	0.0038	0.0051	0.0074		0.0019	0.0042	0.0058	0.0064	0.0087	0.012
Percentage difference between $\int_0^t \beta_1(u)\gamma_3 du$ and $\widehat{\Gamma_1^x}(t)$		11.9	12.4	1.6	-1.0	-6.5	6.6		0.4	2.1	-0.1	1.8	1.8	10.7

[13] $\gamma_0^*=1.8, \theta_0^*=1.8$ [14] $\gamma_0^*=1.9, \theta_0^*=1.8$ [15] $\gamma_0^*=1.8, \theta_0^*=1.8$ [16] $\gamma_0^*=1.9, \theta_0^*=1.8$ [17] $\gamma_0^*=0.8, \theta_0^*=1.8$ [19] $\gamma_0^*=0.7, \theta_0^*=1.8$

Table 7-15 Evaluation of the indirect effect estimate in dynamic path analysis in aim 3, part 2 of 2. Baseline parameter values are given as footnotes. Results are based on 1000 simulated datasets of N=3000 individuals, except for coverage, which is based on 100 datasets of N=3000. Results are grouped according to the relative timings of $M_{bin}(t)$ and death. The 95% coverage refers to the uncensored value.

	Sim. setting	$\gamma_1^*=0.1, \gamma_3^*=0.2, \theta_1^*=0.5$[18]						Sim. setting	$\gamma_1^*=0.1, \gamma_3^*=0.5, \theta_1^*=0.5$[20]					
Time		0.25	0.50	0.68 ($p75_{Mbin}$)	0.75	1.0	1.41 ($p75_D$)		0.25	0.50	0.68 ($p75_{Mbin}$)	0.75	1.0	1.30 ($p75_D$)
Uncensored value $\int_0^t \beta_1(u)\gamma_3 du$	18	0.0022	0.0065	0.0097	0.011	0.015	0.019	20	0.0056	0.016	0.024	0.027	0.036	0.045
Mean $\sum_{t_j \le t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$of		0.0022	0.0065	0.0097	0.011	0.015	0.020		0.0055	0.016	0.024	0.028	0.038	0.049
Mean % difference		-2.55	-0.72	0.06	0.98	2.48	4.30		-2.06	-0.79	0.63	1.57	5.05	9.66
Mean % of deaths / $M_{bin}(t)$		20.0 /36.3	36.9 /53.9	47.2 /60.6	50.7 /62.4	61.7 /66.5	74.8 /69.3		19.2 /36.7	37.1 /54.9	48.2 /62.0	52.0 /64.0	63.9 /68.5	74.6 /71.0
95% coverage		95.0	95.0	95.0	96.0	96.0	98.0		95.0	95.0	95.0	97.0	94.0	96.0
Empirical SE		0.0013	0.0027	0.0036	0.0040	0.0054	0.0073		0.0019	0.0042	0.0058	0.0064	0.0085	0.011
		$p25(T_D)=p75(T_{Mbin})$, $M_{bin}(t)$ is much faster than death												
		$\gamma_1^*=0, \gamma_3^*=0.2, \theta_1^*=0.5$[21]							$\gamma_1^*=0, \gamma_3^*=0.5, \theta_1^*=0.5$[23]					
Time		0.25	0.50	0.65 ($p75_{Mbin}$)	0.75	1.0	2.70 ($p75_D$)		0.25	0.5	0.72 ($p75_{Mbin}$)	0.75	1.0	2.4 ($p75_D$)
Uncensored value $\int_0^t \beta_1(u)\gamma_3 du$	21	0.0023	0.0067	0.0095	0.011	0.015	0.025	23	0.0057	0.017	0.027	0.028	0.038	0.063
Mean of $\sum_{t_j \le t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$		0.0023	0.0067	0.0095	0.011	0.016	0.028		0.0056	0.017	0.027	0.029	0.040	0.078
Mean % difference		-0.96	-0.15	0.44	0.40	1.76	9.75		-1.70	-1.11	0.68	1.14	4.63	23.57
Mean % of deaths / $M_{bin}(t)$		8.2 /37.2	16.9 /58.3	22.1 /66.3	25.5 /70.3	33.6 /77.1	71.1 /86.3		7.2 /37.6	17.0 /59.5	26.0 /71.1	27.3 /72.2	37.1 /79.7	75.0 /90.0
95% coverage		93.0	92.0	93.0	93.0	96.0	96.0		95.0	96.0	94.0	93.0	94.0	82.0
Empirical SE		0.0009	0.0019	0.0025	0.0028	0.0036	0.0066		0.0016	0.0037	0.0053	0.0055	0.0071	0.014
Percentage difference between $\int_0^t \beta_1(u)\gamma_3 du$ and $\widehat{\Gamma_1^{\times}}(t)$		6.5	2.9	1.1	6.8	6.1	10.6		4.9	-1.6	2.7	3.1	6.0	21.6
		$\gamma_1^*=0.1, \gamma_3^*=0.2, \theta_1^*=0.5$[22]							$\gamma_1^*=0.1, \gamma_3^*=0.5, \theta_1^*=0.5$[24]					
Time		0.25	0.50	0.72 ($p75_{Mbin}$)	0.75	1.0	3.0 ($p75_D$)		0.25	0.5	0.72 ($p75_{Mbin}$)	0.75	1.0	2.4 ($p75_D$)
Uncensored value $\int_0^t \beta_1(u)\gamma_3 du$	22	0.0023	0.0067	0.011	0.011	0.015	0.026	24	0.0057	0.017	0.027	0.028	0.038	0.063
Mean of $\sum_{t_j \le t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$		0.0023	0.0067	0.011	0.011	0.016	0.029		0.0056	0.017	0.027	0.029	0.040	0.078
Mean % difference		-0.81	-0.72	0.39	0.64	2.07	10.50		-2.10	-1.13	0.73	1.11	4.40	23.31
Mean % of deaths / $M_{bin}(t)$		8.2 /37.1	16.9 /58.2	24.4 /69.2	25.4 /70.3	33.5 /77.2	74.7 /86.6		7.2 /37.6	16.9 /59.4	25.9 /71.0	27.2 /72.2	37.0 /79.7	74.7 /90.2
95% coverage		94.0	94.0	94.0	95.0	95.0	91.0		97.0	94.0	95.0	95.0	95.0	82.0
Empirical SE		0.00091	0.0019	0.0027	0.0028	0.0036	0.0064		0.0016	0.0037	0.0053	0.0055	0.0071	0.013

[18] $\gamma_0^*=0.8, \theta_0^*=1.8$ [20] $\gamma_0^*=0.7, \theta_0^*=1.8$ [21] $\gamma_0^*=0.3, \theta_0^*=1.7$ [22] $\gamma_0^*=0.25, \theta_0^*=1.7$ [23] $\gamma_0^*=0.2, \theta_0^*=1.7$ [24] $\gamma_0^*=0.15, \theta_0^*=1.7$

The expectation that the divergence between $\beta_1(t)$ and $\widehat{\beta_1}(t)$ may lead to divergence between $\int_0^t \beta_1(u)\gamma_3\,du$ and $\sum_{t_j \le t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$ is confirmed by the results reported in Table 7-14 and Table 7-15, although the magnitude of the divergence is smaller for dynamic path analysis estimates than for $\widehat{\beta_1}(t)$. In general, as in section 7.6.2, the greatest divergence is observed at later evaluation timepoints (t=1, corresponding to the 85th percentile of T_{Mbin}, or at the final evaluation timepoint when this is at t>1). Comparing the divergence at the final evaluation timepoint indicates that greater divergence is associated with $M_{bin}(t)$ occurring faster than death. For example, at the final evaluation timepoints (the 75th percentile of T_D) for simulation settings 23 and 24, percentage differences are 23.6% and 23.3% respectively. In contrast, for simulation settings 15 and 16 where $M_{bin}(t)$ is slow relative to death, percentage differences at the final evaluation timepoint are respectively 4.4% and 5.7%. As in section 7.6.2, greater divergence is also associated with higher values of γ_3^*. For example, simulation setting 22 with $\gamma_3^* = 0.2$ reported a percentage difference of 10.5% at the 75th percentile of T_D, compared to simulation setting 24 with $\gamma_3^* = 0.5$ where the percentage difference at the 75th percentile of T_D was 23.3%. As noted in section 7.6.2, this divergence is due to loss of individuals from the risk set by the occurrence of death, especially after the occurrence of the time-to-event mediator.

The simulations reported in Table 7-14 and Table 7-15 all have a fixed value of $\theta_1^* = 0.5$. To be confident that the divergence alluded to above is associated with a higher γ_3^* and not with θ_1^*, simulation settings 13 and 24 were repeated with alternative values of $\theta_1^* = 0.1$ and $\theta_1^* = 0.8$. There were no notable changes in the percentage difference when the value of θ_1^* was changed (see Appendix IV).

In general, "coverage" for the dynamic path analysis estimates of the indirect effect is satisfactory, falling within the acceptable limits, except for simulations 23 and 24 where "coverage" at the final evaluation timepoints falls to 82%, accompanying high percentage differences between $\int_0^t \beta_1(u)\gamma_3\,du$ and $\sum_{t_j \le t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$. Note that here, coverage refers to the uncensored value of the indirect effect (see section 7.4.2).

For settings with no direct effect of X, in general the cumulative regression coefficient for the overall effect of X, $\widehat{\Gamma_1^X}(t)$, agrees with the value of the indirect effect in the absence of censoring, $\int_0^t \beta_1(u)\gamma_3\,du$, in the middle of follow-up when neither $M_{bin}(t)$ events nor deaths are sparse. At early and late evaluation timepoints, there is much less agreement. This is partly related to sample size. When the $\widehat{\Gamma_1^X}(t)$ was compared to the indirect effect estimates $\sum_{t_j \le t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$ in a single simulation of setting 15 with a sample size of either N=20000 or

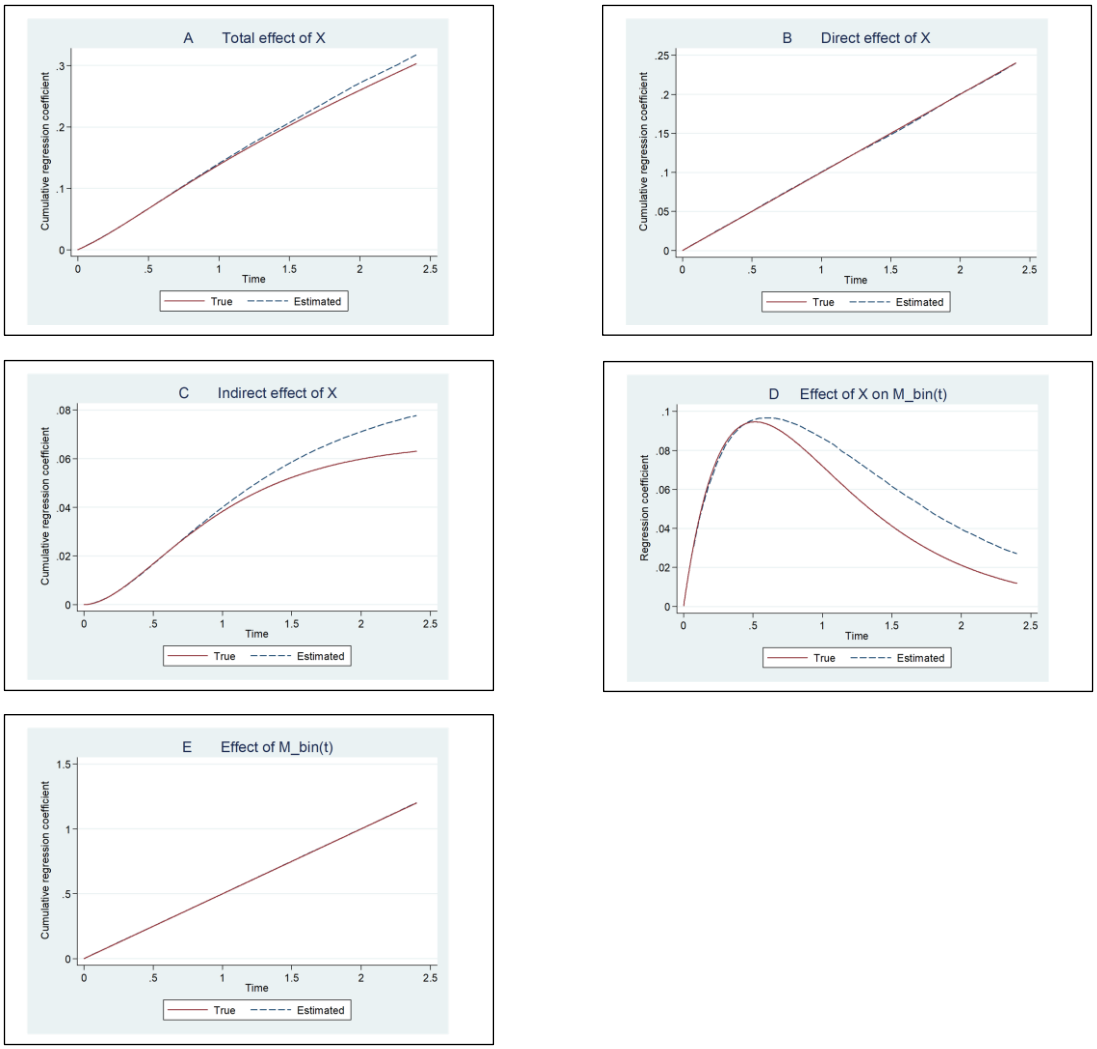
N=100000, it was clear that larger sample sizes were related to much less variability in the indirect effect estimates (see Appendix IV). Another reason for the differences between $\widehat{\Gamma_1^{\times}}(t)$ and $\int_0^t \beta_1(u)\gamma_3$ at early timepoints for simulation settings 13 and 15 is a relative scarcity of intermediate events, and consequent uncertainty around the estimates, as discussed in section 7.6.1. There are also large percentage differences between $\widehat{\Gamma_1^{\times}}(t)$ and $\int_0^t \beta_1(u)\gamma_3$ reported at later timepoints for simulation settings 17, 19, 21 and 23. These percentage differences however correspond to the large percentage differences between $\sum_{t_j \le t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$ and $\int_0^t \beta_1(u)\gamma_3 \, du$ and therefore reflect the role of censoring due to death as discussed above. Agreement between $\widehat{\Gamma_1^{\times}}(t)$ and $\sum_{t_j \le t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$ is shown for large sample sizes for simulation setting 23 in Appendix IV.

For simulation settings 13-16, where death occurs relatively more frequently, a suitable cut-off point for considering the estimated indirect effect of X would be the 75th percentile of T_D, as suggested by Hosmer [56]. For simulations 17-24, death occurs less frequently relative to $M_{bin}(t)$, so the 75th percentile of T_D falls well after the 85th percentile of T_{Mbin}, meaning that at the 75th percentile of T_D (the final evaluation timepoint) most mediator events $M_{bin}(t)$ have occurred, so the remaining death events occur after the mediator events, and the $\widehat{\beta_1}(t)$ diverge noticeably from $\beta_1(t)$. In these cases, the effect of censoring is minimised if the results are considered up until the 85th percentile of T_{Mbin} (corresponding to t=1 in these simulations). If the results shown in Table 7-14 and Table 7-15 are considered up until the cut-off point min(p75(T_D), p85(T_{Mbin})), the dynamic path analysis estimates show little effect from the censoring event, with percentage difference less than 6% in the simulations presented above.

Illustrative example 7-4 (a)

Figure 7-6 is a set of example graphs for simulation setting 24 showing the uncensored parameter values and the mean of their estimates over 1000 repetitions. This simulation setting was chosen because the results of the linear regression model for the effect of X on $M_{bin}(t)$ were graphed for simulation setting 24 in section 7.6.2 above.

Figure 7-6 Example graphs showing the true parameter values and mean values of the corresponding parameter estimates over time for simulation setting 24 investigating the performance of dynamic path analysis with event mediator $M_{bin}(t)$



Illustrative example 7-4 (b)

From Figure 7-6, it appears that the divergence between $\beta_1(t)$ and $\widehat{\beta_1}(t)$ observed in section 7.6.2 (also shown in Figure 7-6-D) feeds forward into dynamic path estimates of the indirect effect of X (Figure 7-6-C). There is also a small knock-on effect on estimates of the total effect of X on death (Figure 7-6-A) (which is estimated by adding the direct and indirect effect estimates as given in section 7.4.1). However, the divergence in the dynamic path analysis estimates appears smaller than divergence in $\widehat{\beta_1}(t)$, because the estimate $\sum_{t_j \le t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$ is the product of $\widehat{\beta_1}(t)$ which demonstrates divergence and $\widehat{\gamma_3}(t)$ which does not. Further, the dynamic path analysis estimate is cumulative, so the larger divergence in $\widehat{\beta_1}(t)$ at higher values of t has less effect on the indirect effect estimate.

Figure 7-6-B shows agreement between the cumulative regression coefficient for the direct effect of X on death $\Gamma_1(t)$ and the mean of its estimates $\widehat{\Gamma_1}(t)$. This agreement is expected, because estimates are obtained by fitting an additive hazards model for the hazard of death, containing explanatory variables X and $M_{bin}(t)$ (shown as the second model in the third row of Table 7-1). Estimates obtained by fitting an appropriately specified additive hazards model are expected to be unbiased, as shown in sections 7.6.1, 7.6.2 and 3.4.3, and reported by Aalen [39, 53].

7.6.3.1 Behaviour of the dynamic path analysis estimator with varying treatment and mediator effects

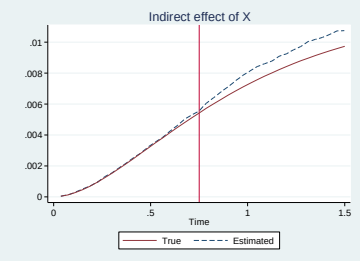
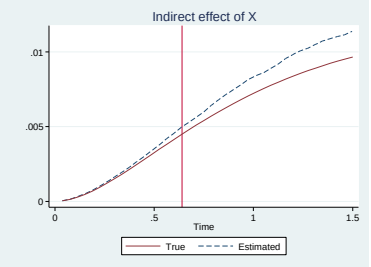
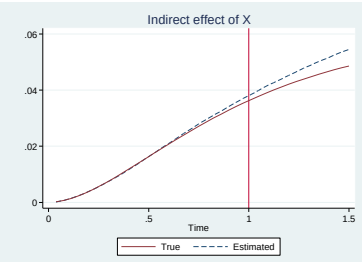
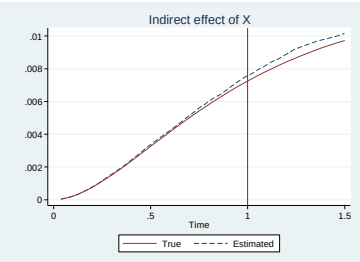
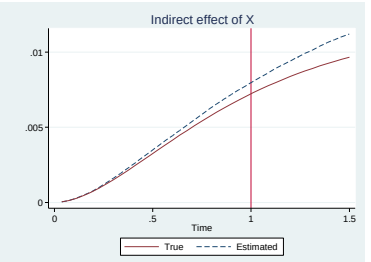
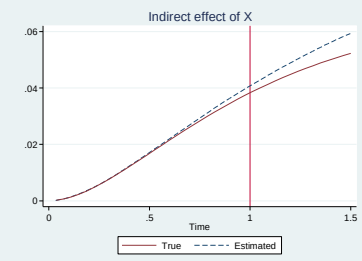
Table 7-16 shows graphs of $\int_0^t \beta_1(u)\gamma_3\,du$ and the mean of $\sum_{t_j \le t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$ for simulations based on settings 16, 20 and 24 as described in section 7.5.1. These simulations performed 500 repetitions rather than the 1000 repetitions reported in the main body of section 7.6.3 above, because the simulations were computationally intensive. Simulation settings 16, 20 and 24 were chosen because they had the highest values of the coefficients ($\gamma_1^* = 0.1, \gamma_3^* = 0.5, \theta_1^* = 0.5$) and had different relative timings of $M_{bin}(t)$ and death. The investigation into the divergence between $\int_0^t \beta_1(u)\gamma_3\,du$ and $\sum_{t_j \le t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$ involved making successive changes to the values of γ_1^*, γ_3^* and θ_1^* and observing whether the divergence changed. To make comparison across simulations easier, the x-axis of all graphs was truncated at t=1.5. The

vertical line represents the 85th percentile of T_{Mbin} or the 75th percentile of T_D, whichever came first. Note that changes in the values of γ_3^* and θ_1^* lead to changes in the y-scale of the graphs in the third and fourth columns of Table 7-16.

The clearest finding from examining the graphs in Table 7-16 is that, in the second and third rows of the table (when $M_{bin}(t)$ is much faster than death), a reduction in γ_3^* is accompanied by a reduced divergence from $\int_0^t \beta_1(u)\gamma_3\,du$, meaning that the effect of the censoring event is stronger when γ_3^* is larger (especially in the third row). This confirms the finding in section 7.6.3 that the main driver of the censoring event in the settings investigated in this chapter is γ_3^*.

A general consideration of pattern of divergence over time for the graphs shown in Table 7-16 confirms that the use of min(p75(T_D), p85(T_{Mbin})) as a cutoff point for reporting the estimated indirect effect of X via $M_{bin}(t)$ would be less affected by selective censoring and thus easier to interpret.

Table 7-16 Changes in bias in estimates of the indirect effect of X on death $\sum_{t_j \le t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$ when γ_1^*, γ_3^* and θ_1^* are changed. Results are based on 500 repetitions, sample sizes are shown in each column

Simulation setting description	Original simulation (1000 repetitions of N=3000)	Setting repeated with $\gamma_1^* = 0.01$ (N=1500)	Setting repeated with $\gamma_3^* = 0.1$ (N=5000)	Setting repeated with $\theta_1^* = 0.1$ (N=5000)
Simulation setting 16 p25(T_D) = p25(T_{Mbin}), M_{bin}(t) is slightly slower than death $\gamma_1^* = 0.1, \gamma_3^* = 0.5, \theta_1^* = 0.5$				
Simulation setting 20 p25(T_D) = p50(T_{Mbin}), M_{bin}(t) is slightly faster than death $\gamma_1^* = 0.1, \gamma_3^* = 0.5, \theta_1^* = 0.5$				
Simulation setting 24 p25(T_D)= p75(T_{Mbin}), M_{bin}(t) is much faster than D $\gamma_1^* = 0.1, \gamma_3^* = 0.5, \theta_1^* = 0.5$				

7.6.3.2 Behaviour of the dynamic path analysis estimator with non-constant baseline hazard or treatment effect

Table 7-17 shows results of the investigation of dynamic path analysis when the baseline hazard of death is piecewise constant. Note that all the simulations presented in Table 7-17 have p25(T_d)=p75(T_{Mbin}) (ie $M_{bin}(t)$ is much faster than death).

The results of simulation settings 25-28 follow a pattern similar to the results of simulation settings 22 and 24 (Table 7-15), which have the same values of γ_1^*, γ_3^* and θ_1^* but a constant baseline hazard. The percentage difference between $\int_0^t \beta_1(u)\gamma_3\,du$ and $\sum_{t_j \le t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$ is low up to the 85th percentile of T_{Mbin} (ie at t=1). The highest percentage difference observed at t=1 is 4.5% for simulation setting 28. As in simulation settings 22 and 24, the divergence increases after t=1, with the highest percentage difference of 24.2% occurring at the 75th percentile of T_D for both simulation settings 27 and 28. Estimates in simulation settings 25 and 26 also show high percentage differences, respectively 11.1% and 11.6%, at the 75th percentile of T_D. These percentages are similar in magnitude to the percentage differences observed for simulation settings 22 and 24 (see Table 7-15).

"Coverage" for simulations 25-28 generally falls within acceptable boundaries, except at the final evaluation timepoints of simulations 27 and 28 where low "coverage" (respectively 84% and 83%) is observed in conjunction with high percentage differences as noted above. "Coverage" is lower than acceptable at the first evaluation timepoint of simulation 26, for reasons similar to those described in section 7.6.1.

Table 7-17 Evaluation of the indirect effect estimate in dynamic path analysis with a time-to-event mediator $M_{bin}(t)$ and piecewise constant baseline hazard. Results are based on 1000 simulated datasets of N=3000 individuals, except for coverage, which is based on 200 datasets of N=3000. Results are grouped according to the relative timings of $M_{bin}(t)$ and death. The 95% coverage refers to the uncensored value.

	Sim. setting	$\gamma_1^* = 0.1, \gamma_3^* = 0.2, \theta_1^* = 0.5$[25]						Sim. setting	$\gamma_1^* = 0.1, \gamma_3^* = 0.5, \theta_1^* = 0.5$[27]					
Time	25	0.25	0.50	0.75	0.77 ($p75_{Mbin}$)	1.0	3.20 ($p75_D$)	27	0.25	0.50	0.73 ($p75_{Mbin}$)	0.75	1.0	2.50 ($p75_D$)
Uncensored value of $\int_0^t \beta_1(u)\gamma_3 du$		0.0023	0.0069	0.012	0.012	0.016	0.029		0.0057	0.017	0.027	0.028	0.038	0.064
Mean value of $\sum_{t_j \le t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$		0.0023	0.0069	0.012	0.012	0.016	0.032		0.0056	0.017	0.028	0.029	0.040	0.079
Mean % difference		-0.82	-0.82	0.35	0.47	1.78	11.07		-2.10	-1.13	0.84	1.07	4.36	24.24
Mean % of deaths / $M_{bin}(t)$		8.1 /35.6	16.8 /56.4	24.8 /68.5	25.4 /69.3	32.4 /75.7	75.3 /86.3		7.2 /37.6	16.9 /59.4	26.1 /71.5	26.9 /72.3	36.5 /79.8	75.6 /90.5
95% coverage		98.0	94.0	97.0	96.0	94.0	98.0		97.0	96.0	97.0	97.0	96.0	84.0
Empirical SE		0.0009	0.0019	0.0028	0.0029	0.0036	0.0067		0.0016	0.0037	0.0053	0.0055	0.0070	0.013
	26	$\gamma_1^* = 0.1, \gamma_3^* = 0.2, \theta_1^* = 0.5$[26]						28	$\gamma_1^* = 0.1, \gamma_3^* = 0.5, \theta_1^* = 0.5$[28]					
Time		0.25	0.5	0.75	0.77 ($p75_{Mbin}$)	1.0	3.60 ($p75_D$)		0.25	0.50	0.72 ($p75_{Mbin}$)	0.75	1.0	2.50 ($p75_D$)
Uncensored value of $\int_0^t \beta_1(u)\gamma_3 du$		0.0023	0.0069	0.012	0.012	0.016	0.029		0.0057	0.017	0.027	0.028	0.038	0.064
Mean value of $\sum_{t_j \le t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$		0.0023	0.0069	0.012	0.012	0.016	0.033		0.0056	0.017	0.027	0.029	0.040	0.079
Mean % difference		-0.62	-0.68	0.29	0.36	1.65	11.62		-1.95	-1.06	0.81	1.17	4.49	24.24
Mean % of deaths / $M_{bin}(t)$		9.3 /35.4	18.8 /55.8	25.3 /67.8	25.8 /68.5	31.6 /74.9	74.8 /86.2		8.4 /37.4	19.0 /58.8	27.0 /70.2	28.1 /71.4	37.0 /78.8	74.5 /89.6
95% coverage		90.0	93.5	95.5	95.0	95.0	91.0		96.0	97.0	98.0	98.0	98.0	83.0
Empirical SE		0.0010	0.0020	0.0028	0.0029	0.0035	0.0067		0.0017	0.0037	0.0053	0.0055	0.0071	0.013

[25] $\gamma_{0,1}^* = 0.25, \gamma_{0,2}^* = 0.225, \theta_0^* = 1.6$ [26] $\gamma_{0,1}^* = 0.3, \gamma_{0,2}^* = 0.15, \theta_0^* = 1.6$ [27] $\gamma_{0,1}^* = 0.15, \gamma_{0,2}^* = 0.135, \theta_0^* = 1.7$ [28] $\gamma_{0,1}^* = 0.2, \gamma_{0,2}^* = 0.1, \theta_0^* = 1.7$

Table 7-18 presents results for the estimation of the indirect effect from the dynamic path analysis with a piecewise constant treatment effect on both $M_{bin}(t)$ and death, as outlined in section 7.5.2. The method is investigated at two relative event speeds: $p25(T_D)=p25(T_{Mbin})$ (when the two events occur at roughly the same speed); and $p25(T_D)=p75(T_{Mbin})$ (when $M_{bin}(t)$ is much faster than death).

The results here are similar to the results reported in Table 7-14 and Table 7-15. For simulation settings 29 and 30, when the rate of $M_{bin}(t)$ is slower than death, the percentage difference between $\int_0^t \beta_1(u)\gamma_3\,du$ and $\sum_{t_j \le t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$ is low at all evaluation timepoints (the highest percentage difference of 2.7% is reported at t=1 for simulation setting 30). For settings 31 and 32, where the rate of $M_{bin}(t)$ is much higher than that of death, percentage difference is highest at the final evaluation timepoints (respectively 8.2% and 18.8%). These percentage differences are similar in magnitude to those reported in section 7.6.3 (settings 22 and 24 had percentage differences 10.5% and 23.3% respectively, see Table 7-15).

"Coverage" falls within acceptable boundaries at all evaluation timepoints for all simulation settings 29-32, with the exception of the final evaluation timepoint of setting 32, where it is 86%.

From these results, it can be inferred that dynamic path analysis with a piecewise constant treatment effect performs similarly to dynamic path analysis with a constant treatment effect, which is not surprising given that the additive hazards model does not rely on the assumption of constant baseline hazards, nor of proportional hazards.

Table 7-18 Evaluation of the indirect effect estimate in dynamic path analysis with a time-to-event mediator $M_{bin}(t)$ and piecewise constant treatment effect. Results are based on 1000 simulated datasets of N=3000 individuals, except for coverage, which is based on 200 datasets of N=3000. Results are grouped according to the relative timings of $M_{bin}(t)$ and death. The 95% coverage refers to the uncensored value.

		$p25(T_D)=p25(T_{Mbin})$, $M_{bin}(t)$ is slightly slower than death												
	Setting	$\gamma_{1,1}^*=0.2, \gamma_{1,2}^*=0.1, \gamma_3^*=0.2, \theta_{1,1}^*=0.5, \theta_{1,2}^*=0.2$[29]						Setting	$\gamma_{1,1}^*=0.2, \gamma_{1,2}^*=0.1, \gamma_3^*=0.5, \theta_{1,1}^*=0.5, \theta_{1,2}^*=0.2$[30]					
Time	29	0.25	0.50	0.70 ($p75_D$)	0.71 ($p75_{Mbin}$)	0.75	1.0	30	0.25	0.50	0.70 ($p75_D$)	0.74 ($p75_{Mbin}$)	0.75	1.0
Uncensored value of $\int_0^t \beta_1(u)\gamma_3 du$		0.0022	0.0065	0.0097	0.0099	0.010	0.013		0.0057	0.017	0.025	0.027	0.027	0.035
Mean value of $\sum_{t_j \le t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$		0.0022	0.0063	0.0096	0.0097	0.010	0.013		0.0056	0.016	0.025	0.027	0.027	0.036
Mean % difference		-0.94	-3.85	-1.73	-2.06	-1.46	0.14		-2.67	-2.47	-0.71	-0.39	-0.41	2.68
Mean % of deaths / $M_{bin}(t)$		38.4 /32.4	62.6 /44.5	74.9 /48.2	75.4 /48.4	77.2 /48.8	86.2 /50.5		37.8 /31.5	62.6 /43.8	75.3 /47.8	77.2 /48.3	77.7 /48.4	86.9 /50.3
95% coverage		96.0	95.0	94.0	94.0	94.0	95.0		97.0	95.0	94.0	97.0	97.0	94.0
Empirical SE		0.0018	0.0041	0.0058	0.0059	0.0063	0.0087		0.0024	0.0056	0.0081	0.0086	0.0088	0.013
		$p25(T_D)=p75(T_{Mbin})$, $M_{bin}(t)$ is much faster than death												
	31	$\gamma_{1,1}^*=0.2, \gamma_{1,2}^*=0.1, \gamma_3^*=0.2, \theta_{1,1}^*=0.5, \theta_{1,2}^*=0.2$[31]						32	$\gamma_{1,1}^*=0.2, \gamma_{1,2}^*=0.1, \gamma_3^*=0.5, \theta_{1,1}^*=0.5, \theta_{1,2}^*=0.2$[32]					
Time		0.25	0.50	0.74 ($p75_{Mbin}$)	0.75	1.0	3.30 ($p75_D$)		0.25	0.50	0.74 ($p75_{Mbin}$)	0.75	1.0	2.60 ($p75_D$)
Uncensored value of $\int_0^t \beta_1(u)\gamma_3 du$		0.0023	0.0067	0.011	0.011	0.014	0.021		0.0057	0.017	0.027	0.027	0.035	0.053
Mean value of $\sum_{t_j \le t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$		0.0023	0.0066	0.011	0.011	0.014	0.023		0.0056	0.017	0.027	0.027	0.036	0.063
Mean % difference		-0.87	-1.14	0.07	0.14	1.18	8.20		-1.91	-1.08	0.57	0.61	2.98	18.8
Mean % of deaths / $M_{bin}(t)$		8.1 /37.1	16.8 /58.2	24.1 /69.4	24.4 /69.7	31.6 /76.7	74.7 /87.2		7.2 /37.6	16.8 /59.4	25.7 /71.3	26.1 /71.7	35.2 /79.2	75.2 /91.0
95% coverage		93.0	95.0	95.0	97.0	98.0	97.0		94.0	95.0	93.0	93.0	93.0	86.0
Empirical SE		0.0009	0.0019	0.0026	0.0026	0.0033	0.0059		0.0016	0.0036	0.0053	0.0054	0.0069	0.013

[29] $\gamma_0^*=1.8, \theta_0^*=1.8$ [30] $\gamma_0^*=1.7, \theta_0^*=1.7$ [31] $\gamma_0^*=0.2, \theta_0^*=1.7$ [32] $\gamma_0^*=0.1, \theta_0^*=1.7$

7.7 Discussion

This chapter has presented results of investigations into the behaviour of the two components of the dynamic path analysis estimator when the intermediate event is a time-to-event variable. The behaviour of the dynamic path analysis estimator itself, when the mediator is a time-to-event variable, has also been examined.

Results of the investigations into the performance of the additive hazards model confirm that the estimation of this model gives rise to an unbiased estimate of the cumulative effect of a time-updated binary explanatory variable $M_{bin}(t)$ on a survival outcome when the model is properly specified.

The investigations of the consequences of fitting a linear regression model for the effect of a treatment X on a time-updated binary variable $M_{bin}(t)$ in the presence of loss of individuals from the risk set by death confirm that the estimates are affected by informative loss at the later time points when the mediator has a strong association with the distal outcome, meaning that there is a strong indirect effect. This effect carries forward into the dynamic path analysis estimate of the cumulative indirect effect of X on death via the time-to-event mediator $M_{bin}(t)$.

The effect of censoring on the estimates varies according to the timing of the intermediate and distal events relative to each other. This effect is larger when $M_{bin}(t)$ happens much more quickly and association between $M_{bin}(t)$ and death is strong, with individuals experiencing the event mediator $M_{bin}(t)$ being more likely to die (assuming γ_3 is positive), and hence not to contribute to later estimates of $\beta_1(t)$.

In the clinical setting of the secondary analysis of trials with a composite time-to-event outcome, it is likely that $M_{bin}(t)$ will occur more frequently than death, because the proximal component event of a composite outcome is usually chosen partly on this basis (see chapter 1 and [5]). The impact of censoring on the indirect effect estimates may therefore be notable in practice.

If there is interest in reporting an indirect effect estimate that is not greatly affected by censoring and thus easier to interpret, the choice of when to stop estimating the indirect effect of X should be informed in part by the relative event rates. In classical dynamic path analysis with a continuous mediator, estimation is usually stopped at around the 75^{th} percentile of T_D (see chapter 5 and [56]). This rule of thumb is not universally applicable to dynamic path analysis with a time-to-event mediator, because if $M_{bin}(t)$ is slow relative to death, using the 75^{th} percentile of T_D as a final time point may exclude large numbers of $M_{bin}(t)$

events. Conversely, if $M_{bin}(t)$ is much faster than death, the effect of censoring may be very large by the 75th percentile of T_D. In the scenarios investigated in this chapter, choosing a stopping point representing the minimum of the 85th percentile of T_{Mbin} or the 75th percentile of T_D appeared to be a good compromise. Clinical considerations may also influence the choice of stopping point for the estimation of an indirect treatment effect in this setting.

Possible additional sources of bias in the indirect effect estimate include violations of the assumptions of dynamic path analysis outlined in chapter 5. For this setting these would include no interaction between X and $M_{bin}(t)$, no intermediate confounding, and no unmeasured confounding. In addition, the simulation studies reported in this chapter had very little administrative censoring and no loss to follow-up. Caution should therefore be exercised when interpreting estimates obtained using the extension to dynamic path analysis introduced in this chapter.

With all these caveats, there is great potential to use the novel extension of dynamic path analysis proposed in this thesis for exploring treatment effects in clinical trials with composite time-to-event outcomes. By quantifying the pathways through which treatment works, dynamic path analysis with a time-to-event mediator can provide a context for understanding the biological mechanisms underlying complex disease processes [20, 42].

8 Estimating the indirect effect of treatment via progression in the Zactima trials

8.1 Introduction

In chapter 4, additive hazards models were fitted to assess the effect of treatment in the Zactima trials. The results led to the following inferences:

1) Treatment was found to have a statistically significantly protective effect on cancer progression;
2) Treatment was found to have an overall protective, though not statistically significant, effect on death;
3) Treatment was found to have virtually no effect when progression was included in the mortality model.

The estimated treatment effect in 2) corresponds to the total effect of treatment on death, while in 3) it refers to the direct effect of treatment on death, if the relevant assumptions are met (that is, there are no unmeasured confounders, no intermediate confounders, and the model is correctly specified). Under these assumptions, a difference in these estimated treatment effects implies that treatment may have some indirect protective effect on death, working through the intermediate event of progression. The magnitude of this indirect effect of treatment can be estimated using the extension to dynamic path analysis proposed in chapter 5.

8.1.1 Aims

The aims of this chapter are:

1. To obtain the dynamic path analysis estimate of the indirect effect of treatment on death via progression in the pooled Zactima trials dataset;

2. To use simulation studies to investigate the impact of the timing of death, especially after progression, on estimates of the indirect effect of treatment.

Section 8.2 describes the implementation of dynamic path analysis in the Zactima trials and presents the results (aim 1). Section 8.3 describes and reports the simulation studies aimed at quantifying the potential distortion due to the timing of death on the estimates of the indirect effect of treatment on death (aim 2).

8.2 Dynamic path analysis estimate of the indirect effect of treatment in the Zactima trials

8.2.1 Methods

Dynamic path analysis estimation in the Zactima trials dataset is summarised below using the Zactima trials variables introduced in section 4.2.

As a first step, the effect of *treat* on *prog(t)* (the binary time-updated explanatory variable indicating progression) at each death time t= t_{dth} is estimated by fitting the following regression model:

$$\mathrm{E}\big(\mathrm{prog}(\mathrm{t})\big) = \beta_0(\mathrm{t}) + \beta_1(\mathrm{t})\mathrm{treat} + \boldsymbol{\beta_2^{\mathrm{T}}}(\mathrm{t})\mathbf{trial} + \boldsymbol{\beta_4^{\mathrm{T}}}(\mathrm{t})\mathbf{w} \qquad \text{8-1}$$

This produces parameter estimates $\hat{\beta}_0(\mathrm{t_{dth}})$ and $\hat{\beta}_1(\mathrm{t_{dth}})$ adjusted for the additive effects of ***trial*** and the baseline covariate vector ***W***.

In the second step, the effects of *prog(t)* and *treat* on the hazard of death are estimated by fitting the following additive hazards model at each death time t=t_{dth}:

$$\alpha_{\mathrm{dth}}(\mathrm{t}) = \gamma_0(\mathrm{t}) + \gamma_1(\mathrm{t})\mathrm{treat} + \boldsymbol{\gamma_2^{\mathrm{T}}}(\mathrm{t})\mathbf{trial} + \gamma_3(\mathrm{t})\mathrm{prog}(\mathrm{t}) + \boldsymbol{\gamma_4^{\mathrm{T}}}(\mathrm{t})\mathbf{w} \qquad \text{8-2}$$

The model produces estimates $\hat{\gamma}_0(\mathrm{t_{dth}})$, $\hat{\gamma}_1(\mathrm{t_{dth}})$ and $\hat{\gamma}_3(\mathrm{t_{dth}})$ specific to time t_{dth} for, respectively, the baseline hazard of death, the additive effect of *treat* adjusted for progression (that is, the time-specific direct effect of treatment on death), and the additive effect of *prog(t)* on death at time t_{dth}, adjusted for the effects of ***trial*** and the baseline covariate vector ***W***. This

model is identical to model 4-3, where the $\hat{\gamma}_1(t_{dth})$ were summed over time to estimate the cumulative direct effect of treatment on death $\widehat{\Gamma_1}(t) = \sum_{t_{dth} \le t} \widehat{\gamma_1}(t_{dth})$. In the current context, the estimates of interest are the $\hat{\gamma}_3(t_{dth})$ for all death times.

1. The estimated indirect effect of *treat* on the hazard of death at each death time t_{dth} is obtained by multiplying the relevant coefficients giving $\hat{\gamma}_3(t_{dth})\hat{\beta}_1(t_{dth})$.
2. The estimated cumulative effect of the indirect effect of *treat* up to time t is given by $\sum_{t_{dth} \le t} \widehat{\gamma_3}(t_{dth})\, \widehat{\beta_1}(t_{dth})$.

Following the recommendation made in chapter 7, the cumulative estimate of the indirect effect is reported until the 75th percentile of T_{dth} or the 85th percentile of T_{prog}, whichever came first. In the case of the Zactima trials, the 85th percentile of T_{prog} occurred at 8 months, while the 75th percentile of T_{dth} occurred at 18 months. The cutoff for reporting the cumulative estimate is therefore chosen to be 8 months after randomisation.

Following Fosen [30], the 95% confidence interval for the estimates $\sum_{t_{dth} \le t} \widehat{\gamma_3}\,(t_{dth})\widehat{\beta_1}(t_{dth})$ is obtained using a bootstrap with 1000 bootstrap samples (see for example [81]) at 10 evenly spaced timepoints between t=0 and t=8 months.

8.2.2 Results

Figure 8-1 shows a plot of the estimated effect of treatment on progression $\hat{\beta}_1(t)$ (estimated by fitting Model 8-1) against time, with the pointwise 95% confidence limits. The graph is truncated at the 85th percentile of T_{prog}, 8 months after randomisation.

Figure 8-1 Estimated effect of treatment on progression obtained by fitting Model 8-1 at each death time, and pointwise 95% confidence limits

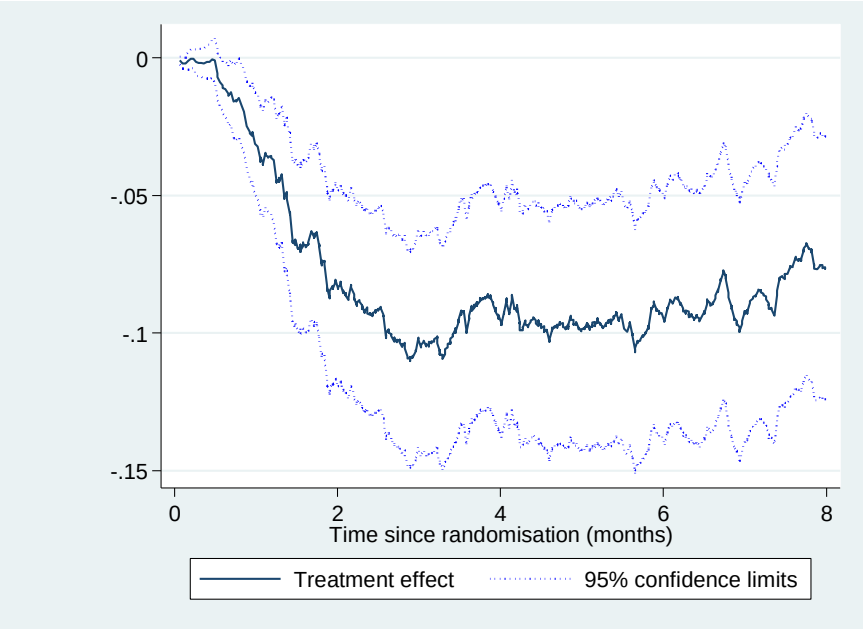


Figure 8-1 indicates that for the first 0.5 months, treatment has no effect on progression. After this time, treatment has a rapidly increasing protective effect on progression which reaches -0.1 at 2.5 months. After 2.5 months, the protective effect stays fairly constant around -0.1. At 2.5 months after randomisation, the 95% confidence bands indicate that the protective effect of treatment could plausibly be between -0.05 and -0.13. At 8 months, the protective effect is -0.08 with a 95% CI of [-0.03, -0.13].

Figure 8-2 shows a plot of the estimated cumulative effect of progression on death $\widehat{\Gamma_3}(t)$ (estimated by fitting Model 8-2) against time, with the pointwise 95% confidence limits, truncated at 8 months.

Figure 8-2 Estimated cumulative effect of progression on death obtained by fitting Model 8-2, and pointwise 95% confidence limits

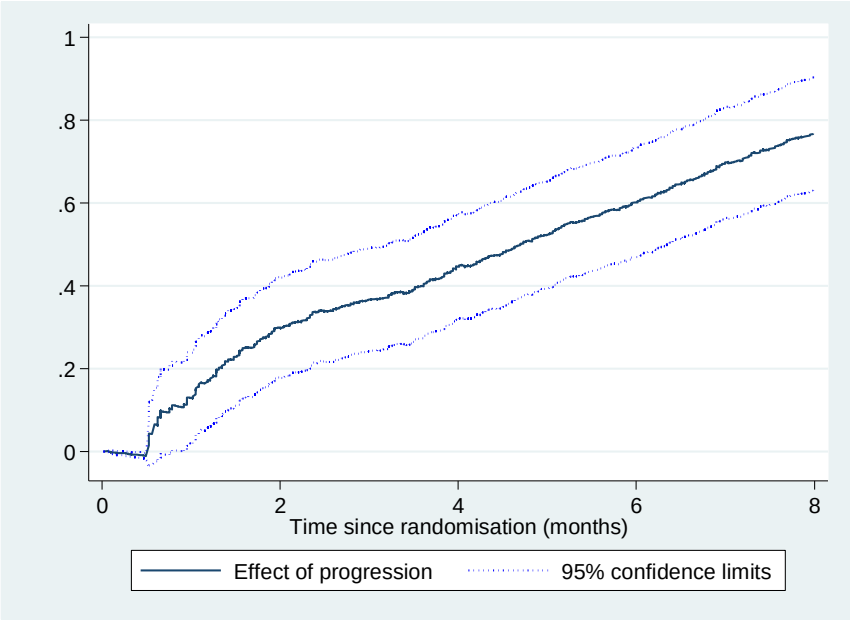


Figure 8-2 indicates that after 0.5 months, the cumulative effect of progression on death is positive. At 1 month post-randomisation, the cumulative change in the hazard of death is 0.13 with the confidence bands indicating a plausible range of effect of [0.02, 0.24]. After 1.5 months, the slope of the plot is nearly constant at 0.07 per month, meaning that the effect of progression on death is nearly constant. At 4 months, the cumulative effect is 0.45 [0.32, 0.58] and at 8 months the cumulative effect is 0.77 [0.64, 0.91].

Figure 8-3 shows a plot of the dynamic path analysis estimate of the cumulative indirect effect of treatment on death via progression $\sum_{t_j \le t} \widehat{\gamma_3}(t_j)\, \widehat{\beta_1}(t_j)$ against time, with the bootstrapped pointwise 95% confidence limits, truncated at 8 months.

Figure 8-3 Dynamic path analysis estimate of the cumulative indirect effect of treatment on death via progression in the pooled dataset. The 95% confidence interval is calculated at 10 evenly spaced timepoints 0.8, 1.6,…, 8.0 and is based on 1000 bootstrap samples

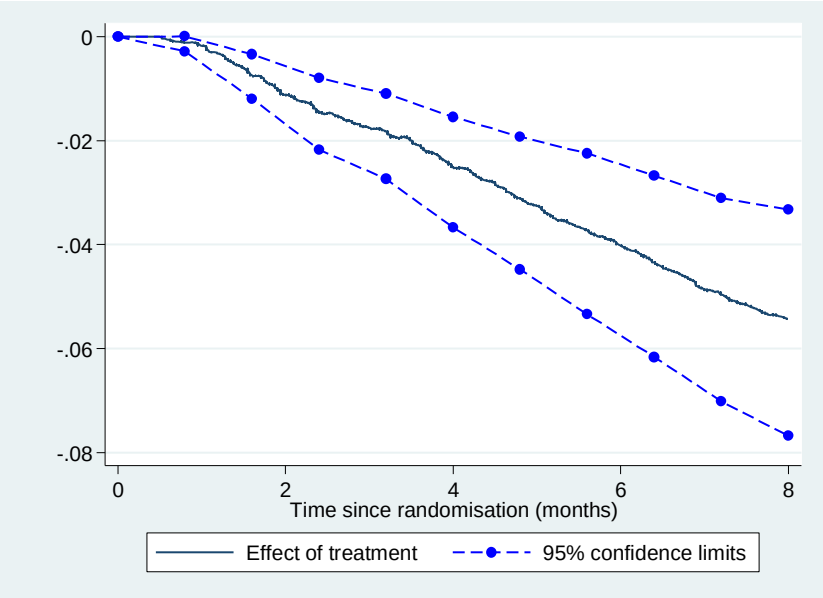


Figure 8-3 shows a protective cumulative indirect effect of treatment on death via progression. During the first month, the effect appears close to null. At 1.6 months (the time of the second pointwise 95% confidence interval), the cumulative indirect effect is estimated as -0.008 with a bootstrapped 95% confidence interval of [-0.005, -0.010]. At 4 months, a total of 1365 progressions (64%) have occurred, and a total of 626 deaths (35%) have occurred. The cumulative indirect effect and its 95% confidence interval are -0.025 [-0.020, -0.031]. At 8 months, 1970 (92%) progressions and 1182 (66%) deaths have occurred, and the cumulative indirect effect and 95% confidence interval are -0.055 [-0.046, -0.066]. The rate of change of the cumulative effect (given by the slope of the plot) is close to constant; at 4 months, it is -0.009 per month [-0.008, -0.009] and at 8 months it is -0.007 per month [-0.007, -0.007]. The slopes are estimated using the change in the cumulative effect over the preceding month.

The estimated cumulative overall effect of treatment on the hazard of death is shown in Figure 4-3. The estimated cumulative direct effect of treatment on death is shown in Figure 4-5. Comparing these figures with Figure 8-3 confirms that the overall effect of treatment on death comprises the sum of the direct and indirect effects. For example, at 8 months the cumulative indirect effect read from Figure 8-3 is -0.055 (and statistically significant). Reading from Figure 4-5, the cumulative direct effect is 0, and reading from in Figure 4-3, the cumulative overall effect is -0.055 (but not statistically significant). However, to interpret this partitioning of the total effect into direct and indirect components requires the assumptions that there are no unmeasured confounders, no intermediate confounders, and that the mediator and outcome models are correctly specified. In summary, a comparison of results from the additive hazards

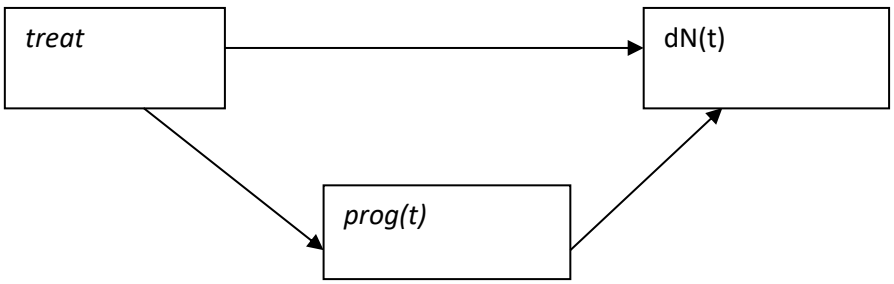
models fitted in chapter 4 and the dynamic path analysis performed in this section suggests that there is a non-statistically significant overall effect of treatment, while the indirect effect of treatment is statistically significant.

8.3 Simulation study to investigate bias due to deaths in the dynamic path analysis estimates of the Zactima trials

An association between progression and death, such as that shown in Figure 8-2, leads to individuals who have experienced progression being more likely to experience death, and hence leave the risk set contributing to the estimation of the mediator model. This affects the relationship between treatment and progression over time, as patients who have progressed are excluded from the analyses because of death. This section conducts a simulation study to investigate the possible effect of this censoring by death on the estimates of the effect of treatment on progression and hence of the indirect effect of treatment on death. They are examined in this chapter because in the Zactima trials most of the death events followed a progression event, with progressions occurring faster than deaths (see section 2.4.3.1).

These simulations have the same structure as those presented in chapter 7 and apply to the simple setting shown in Figure 8-4 below, which omits the ***trial*** and ***W*** covariates. The simulation parameters are set at values corresponding to estimates obtained from the Zactima trials data (details are given below).

Figure 8-4 Path diagram showing the time-specific relationships between treat, prog(t) and death (dN(t)) in the simulation study motivated by the Zactima trials. This diagram is similar to the general path diagram shown in Figure 7-1



Here, *treat* is a binary variable indicating treatment group, *prog(t)* is a binary time-updated variable indicating the occurrence of progression, and dN(t) is the increment of the counting

process associated with death. At event time t, the value of *prog(t)* refers to a time just before time t.

8.3.1 Methods

The parameter values used in data generation for this simulation study are guided by the Zactima trials data. The values for the regression parameters used in the data generation models (see Table 7-4) γ_1^*, γ_3^* and θ_1^* were based on their estimates obtained by fitting Models 8-2 and 8-3 shown in Table 8-1 below. Because these models allow for their parameters to be time-varying, plots of their cumulative sums, $\widehat{\Gamma_1(t)}, \widehat{\Gamma_3(t)}$ and $\widehat{\Theta_1(t)}$ against time up to the 75th percentile of event time (after Hosmer [56]) were superimposed with Lowess smoothers. The slope in the last month of time before the 75th percentile (that is, between 7 and 8 months for the progression outcome and between 17 and 18 months for the death outcome) was used to select the value of the simulation parameters above. These time periods were chosen because the slopes of the plots of cumulative regression coefficients were constant after a short initial period, and the estimates were based on large numbers of events. In addition, two additional values for γ_3^* were chosen corresponding to the slopes for the upper and lower limits of the 95% confidence bands for $\widehat{\Gamma_3(t)}$ between 17 and 18 months (see Table 8-2). Meanwhile, the value of the simulation parameter representing the hazard of progression in the placebo group, $\theta_0^*(t)$, was chosen by examining the slope of a Nelson-Aalen plot of the estimated cumulative hazard of progression in the placebo group, $\widehat{\Theta_0^{\times}(t)}$, between 7 and 8 months and assumed to be constant for simplicity. The value of the simulation parameter representing the hazard of death in the placebo group for patients who had not experienced progression, $\gamma_0^*(t)$, was chosen similarly, by examining the slope of a Nelson-Aalen plot of the estimated cumulative hazard of death in this group, $\widehat{\Gamma_0^{\times}(t)}$, between 17 and 18 months, also assumed to be constant.

Table 8-1 Additive hazards models fitted to the Zactima trials data to estimate parameters for the simulation study

Outcome	Estimation model	Model number
Progression	$\alpha_{\text{prog}}(t) = \theta_0(t) + \theta_1(t)\text{treat} + \boldsymbol{\theta_2^T}(t)\mathbf{trial} + \boldsymbol{\theta_4^T}(t)\mathbf{w}$	8-3
Death	$\alpha_{\text{dth}}(t) = \gamma_0(t) + \gamma_1(t)\text{treat} + \boldsymbol{\gamma_2^T}(t)\mathbf{trial} + \gamma_3(t)\text{prog}(t) + \boldsymbol{\gamma_4^T}(t)\mathbf{w}$	8-2

The simulation parameters are shown in Table 8-2 below. Due to the randomisation ratio of 2:1 in the Zephyr trial, P(*treat*=1) was set at 0.55.

Table 8-2 Simulation parameters derived from fitting additive hazards models for time to progression and time to death to the pooled Zactima trials dataset

Parameter	**Value**		
	Simulation setting number		
	1	2	3
$\boldsymbol{\gamma_0^*}$	0.03 for all settings 1-3		
$\boldsymbol{\gamma_1^*}$	-0.001 for all settings 1-3		
$\boldsymbol{\gamma_3^*}$	0.07	0.06	0.09
$\boldsymbol{\theta_0^*}$	0.25 for all settings 1-3		
$\boldsymbol{\theta_1^*}$	-0.06 for all settings 1-3		
p*	0.55 for all settings 1-3		

The simulation study generated 1000 datasets of N=3000 individuals (the full size of the Zactima pooled trials data was 2849, see chapter 2). Results were reported at t=2, 4, 6 ,8, 12, 18 months. The 85th percentile of the simulated progression time T_{prog} was found to be t_{prog}=8.0 months (as in section 8.2), while the 75th percentile of the simulated death time T_{dth} was found to be t_{dth}=18 months.

As in chapter 7, the results of the simulation were reported as a set of metrics assessed at the six timepoints given above. The metrics used to report the results are shown below in Table 8-3 for ease of reference (they are the same as those used in chapters 3, 6 and 7). The symbol τ refers to the value of the target of the simulation in the absence of censoring due to death. The value of this was calculated using the values of θ_0^*, θ_1^* and γ_3^* shown in Table 8-2, as described in Table 7-4 and the accompanying text.

Table 8-3 Metrics reported for the simulation study

Metric[1]	**Interpretation**
τ	Value of the parameter of interest in the absence of censoring (calculated as described in section 7.3)
$\bar{\tau} = \frac{\sum_P \widehat{\tau_p}}{P}$	Mean value of the estimate of τ
$\frac{\bar{\tau} - \tau}{\tau} \times 100$	Percentage difference between the mean value and the value of τ in the absence of censoring
$SE(\hat{\tau}) = \sqrt{\frac{1}{P-1}\sum_P (\widehat{\tau_p} - \bar{\tau})^2}$	Empirical standard error

[1]Note that $\hat{\tau}_p$ denotes the estimate from simulated dataset p, (p=1,…,P; P=1000).

In addition, at each timepoint the mean percentage of individuals who had experienced either progression or death across the 1000 simulations was reported.

8.3.2 Results

Table 8-4 below shows results for the evaluation of bias in the dynamic path analysis estimation of the indirect effect of treatment on death via progression using the simulation parameters derived from the Zactima dataset as described above.

Table 8-4 Evaluation of the indirect effect estimate in dynamic path analysis using parameters derived from the Zactima trials dataset (part 1 of 2). Results are based on 1000 simulated datasets of N=3000 individuals.

	Simulation setting 1 $\gamma_0^* = 0.03, \gamma_1^* = -0.001, \gamma_3^* = 0.07, \theta_0^* = 0.25, \theta_1^* = -0.06$					
Time	2	4	6	8 ($p85_{Tprog}$)	12	18 ($p75_{Tdth}$)
Uncensored value $\int_0^t \beta_1(u)\gamma_3 du$[1]	-0.006	-0.019	-0.033	-0.046	-0.065	-0.079
Mean of estimates $\sum_{t_j \le t_{dth}} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$	-0.006	-0.019	-0.033	-0.048	-0.072	-0.098
Mean % difference	-2.73	-2.08	0.70	3.87	11.65	23.23
Mean % of deaths / mean % progressions	8.1 /34.2	18.6 /55.0	29.5 /67.6	39.9 /75.4	57.5 /83.1	75.7 /86.7
Empirical SE	0.0018	0.0040	0.0060	0.0080	0.011	0.016
	Simulation setting 2 $\gamma_0^* = 0.03, \gamma_1^* = -0.001, \gamma_3^* = 0.06, \theta_0^* = 0.25, \theta_1^* = -0.06$					
Time	2	4	6	8 ($p85_{Tprog}$)	12	18 ($p75_{Tdth}$)
Uncensored value $\int_0^t \beta_1(u)\gamma_3 du$[1]	-0.005	-0.016	-0.028	-0.039	-0.055	-0.068
Mean of estimates $\sum_{t_j \le t_{dth}} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$	-0.005	-0.016	-0.029	-0.041	-0.061	-0.081
Mean % difference	-2.42	-1.64	0.66	3.39	10.09	19.59
Mean % of deaths / mean % progressions	7.8 /34.2	17.6 /55.0	27.8 /67.6	37.7/75.4	54.5 /83.1	72.6 /86.7
Empirical SE	0.0016	0.0035	0.0053	0.0069	0.0097	0.013
	Simulation setting 3 $\gamma_0^* = 0.03, \gamma_1^* = -0.001, \gamma_3^* = 0.09, \theta_0^* = 0.25, \theta_1^* = -0.06$					
Time	2	4	6	8 ($p85_{Tprog}$)	12	18 ($p75_{Tdth}$)
Uncensored value $\int_0^t \beta_1(u)\gamma_3 du$[1]	-0.008	-0.025	-0.043	-0.059	-0.083	-0.10
Mean of estimates $\sum_{t_j \le t_{dth}} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$	-0.008	-0.024	-0.043	-0.062	-0.095	-0.13
Mean % difference	-3.69	-2.52	0.62	4.66	14.70	30.6
Mean % of deaths / mean % progressions	8.7 34.2	20.4 /55.0	32.6 /67.6	44.0 /75.4	62.7 /83.1	80.7 /86.7
Empirical SE	0.0022	0.0050	0.0077	0.010	0.015	0.021

[1]As noted above, this measures the true indirect effect of treatment on death in the absence of the depletion of patients by death contribution to the treatment-progression model.

The uncensored value of the indirect effect is used as a comparator because depletion of patients by death has implications for the value of $\beta_1(t)$. As described in chapter 7, the expected values of $\beta_1(t)$ are calculated from $\theta_0^*(t)$ and $\theta_1^*(t)$, but there is no simple way of deducing the true value of $\beta_1(t)$ in the presence of censoring, apart from the direction of change of $\beta_1(t)$ over time.

If, as in these simulations, $\beta_1(t)$ is negative (treatment has a protective effect on progression) and $\gamma_3(t)$ is positive (progression has a harmful effect on death), more patients in the placebo

arm would suffer progression and those patients would be more likely to die, so that over time patients at risk of progression would be increasingly in the treatment group. This would lead to $\beta_1(t)$ becoming more negative with time as the placebo group becomes smaller relative to the treatment group, and the time-specific indirect effect would also be increasingly negative.

In the light of this, comparisons with the uncensored value of the indirect effect are interpreted accounting for this expected divergence. The difference is referred to as "bias", although this is not a study of bias in the usual sense.

In simulation setting 1, the indirect effect of treatment estimated using our extension of dynamic path analysis is on average fairly close to the expected value where there is no depletion of patients at most time points except for the penultimate and last evaluation timepoints (11.65% and 23.23% respectively). In simulation setting 2, where γ_3^* is smaller, the corresponding percentage differences are also smaller (10.09% and 19.59% respectively), and in simulation setting 3, where γ_3^* is larger, the percentage differences at these same time points are noticeably larger (14.70% and 30.6%).

The differences between the means of the estimates and the uncensored values of $\int_0^t \beta_1(u)\gamma_3 du$ are caused by loss of patients from the risk set by death after progression as discussed in chapter 7. If one wished to report results that were not greatly affected by early deaths and ended reporting at the 85th percentile of T_{prog} (at t=8 months) as discussed in chapter 7, the percentage difference at the final evaluation timepoint would be 3.87% for setting 1, 3.39% for setting 2 and 4.66% for setting 3 respectively. The empirical SE is small relative to the magnitude of the estimates for all simulations at all timepoints. This implies that the estimated indirect effects have low variability across simulations.

The simulation study is based on an exponential distribution of both T_{prog} and T_{dth}. This is quite realistic for an outcome such as death which occurs relatively slowly in the absence of progression, but may be less realistic for an outcome such as progression which occurs rapidly at the start of the trial. In addition, the simulations are based only on the relationship between the three variables shown in Figure 8-4, while in fact the models used for estimation in the Zactima trials contain the covariates ***trial*** and ***W***. As a result, the percentage differences between the estimated and uncensored indirect effects are only indicative of the difference that might exist in the estimated cumulative indirect treatment effect shown in Figure 8-3 because in a real-life setting the parametric model assumed for these additional variables might not be specified correctly.

8.4 Discussion

The analysis of the Zactima trials presented in this chapter represents a new and interesting use of dynamic path analysis for the estimation of a cumulative indirect treatment effect through a survival mediator. The estimated protective cumulative indirect effect of treatment on the hazard of death is small in magnitude but increases with time from -0.008 [-0.005, -0.010] at 1.6 months to -0.055 [-0.046, -0.066] at 8 months. As noted in section 8.3.2, the estimate may be affected by the occurrence of censoring due to death. However, as reporting of the indirect effect estimate was curtailed at the 85th percentile of progression time, the results presented in section 8.2.2 are unlikely to be greatly biased.

The estimated indirect effect represents the difference between the total effect of treatment on death and the direct effect of treatment on death. This analysis is an addition to the traditional cause-specific analyses of treatment effects on the components of a composite outcome, as it explicitly models the role played by progression as being both a result of treatment and a precursor of death. This approach could be extended to more complex settings with multiple possible indirect pathways of action, providing greater understanding of the mechanisms of action of treatment, subject to the assumptions described in chapter 5 of no unmeasured confounding, no intermediate confounding, and no non-linearities in the explanatory variables.

9 Discussion

9.1 Introduction

This thesis aimed to develop and demonstrate an approach to estimating the indirect effect of an exposure or treatment variable in a specific setting arising from the secondary analysis of treatment effects on a time-to-event composite outcome. The challenge was to disentangle treatment effects on the component events of this composite outcome, as these usually occur in sequence, and are therefore classified as proximal and distal events. The research was motivated by the Zactima trials, where the proximal event was cancer progression and the distal event was death. The indirect effect of interest was the effect of treatment on death, working through the mediator of cancer progression. Hence the main aim of this thesis was to extend dynamic path analysis, an approach to mediation analysis that can be used with a survival outcome, to the setting where both outcome and mediator are time-to-event variables. To achieve this aim, the following objectives were identified:

1) To introduce the dynamic path analysis method of Fosen, Aalen et al [20, 30, 31] as a means of estimating the indirect effect of a treatment on a time-to-event outcome via a continuous mediator, and to verify its properties;
2) To extend dynamic path analysis, and verify the properties of this extension, to the setting where the outcome and mediator are time-to-event variables;
3) To apply this extension to the Zactima trials dataset, estimating the indirect effect of treatment on death through its effect on cancer progression.

This chapter outlines how these objectives have been met within this thesis, describes how the extension to dynamic path analysis applies in the clinical trials setting, and identifies further areas of research.

9.2 Discussion of the motivation and objectives of this thesis

9.2.1 The Zactima trials

The three Zactima trials estimated the effect of treatment on the composite outcome of time to cancer progression or death. Published guidance for the estimation of treatment effects on composite outcomes suggests that treatment effects should be reported separately for each component event [1, 3, 6]. For each trial, treatment effects on the component events were estimated by fitting Cox proportional hazards models, revisiting earlier published results [8-10]. The datasets from the three trials were then pooled for the first time and a similar analysis carried out. The main findings were a statistically significant protective effect of treatment on progression, and a non-statistically significant protective effect of treatment on death, not controlling for progression. The former finding supplemented the original published analyses, which focused on the composite outcome of progression-free survival, and overall survival [8-10].

Further investigation requires a consideration of the ordering of the events, and how a proximal event may affect a distal event. The ideas of mediation analysis, especially the concepts of overall, direct and indirect effects can be used in this context.

The overall effect of treatment on death can be thought of as the effect of treatment on death along any pathway. The direct effect of treatment on death is the effect of treatment on death through a pathway that does not involve cancer progression. The indirect effect of treatment on death, where the mediator is progression, is that part of the effect of treatment which works specifically through cancer progression.

The overall effect of treatment on death was estimated by fitting a Cox proportional hazards model to the pooled dataset. The direct effect of treatment on death was derived by fitting a Cox proportional hazards model for the effect of treatment on death, controlling for cancer progression, under the assumptions of proportionality and correct model specification. This direct treatment effect estimate was very close to null. The findings of a protective overall effect of treatment on death, and no direct effect of treatment on death, suggested an indirect effect of treatment on death. However, such an indirect effect couldn't be estimated by

comparing the estimated hazard ratios of the overall and direct effects of treatment [14, 17, 19, 20], because the scale of the effects estimated by Cox regression is not additive.

Additive hazards models were then fitted to estimate the overall and direct effects of treatment on death in the pooled Zactima trials data. The results from these additive hazards models were substantively similar to the results obtained by fitting Cox proportional hazards models. The structure of the additive hazards model allows the overall and direct effects of treatment to be compared, given certain assumptions (no unmeasured confounding, no intermediate confounding, and correct model specification [14, 24, 33]). A comparison of these treatment effects suggested that an indirect treatment effect should be investigated.

9.2.1.1 The additive hazards model

The additive hazards model introduced by Aalen [20, 39, 53] uses counting process terminology to define a model where coefficients are expressed on the additive scale as potentially time-varying differences in hazards with respect to a time-to-event outcome. When the additive hazards model is correctly specified, it provides unbiased estimates of covariate effects over time [20, 39, 53].

This thesis carried out several simulation studies investigating the performance of the additive hazards model to justify its application to the Zactima trials data and its role in dynamic path analysis. The results of these simulations were reported using a range of metrics including percentage bias, coverage and empirical standard error. These metrics captured aspects of the model performance [60] not usually addressed in the literature. The simulations examined: a) the performance of the additive hazards model with a single time-fixed binary or a single time-fixed continuous explanatory variable; b) the performance of the model with a time-varying continuous explanatory variable, either as a single predictor or with a time-fixed binary covariate; c) the performance of the additive hazards model with a time-updated binary (survival) explanatory variable, that is, a time-to-event mediator in aim 2 above. The performance of the additive hazards model has not previously been investigated in this last setting. Results indicated that the additive hazards model gave estimates with low percentage bias and good coverage in settings a) and b), and that in setting c) the coverage of the estimates may be low when the time-updated binary explanatory variable occurs sparsely. This

could occur for example at early timepoints when explanatory variable events are slow to accumulate, or late in follow-up after most of the explanatory variable events have happened.

9.2.2 Introduction to and verification of dynamic path analysis

The structure of the additive hazards model allows it to be adapted into a path analysis framework. This framework forms the basis of much of the literature on mediation analysis, and methods used to estimate direct and indirect effects (see for example [14, 19, 32, 33, 36, 37, 40, 41]).

In terms of defining an indirect effect, the additive hazards model combined with path analysis forms the basis of dynamic path analysis [73], a method described by Fosen, Aalen and colleagues [20, 30, 31] for the estimation of indirect effects with a (possibly time-varying) continuous mediator and a time-to-event outcome. By allowing the continuous mediator to vary with time, the method allows covariate effects to be explored as processes that change with time, rather than being considered static [82]. In addition, the indirect effect itself is allowed to vary with time, which may reflect clinical realities in some settings.

Chapter 5 introduced and described dynamic path analysis [20, 30, 31]. Simulation studies conducted in chapter 6 verified the properties of dynamic path analysis, confirming that the estimator gives rise to low percentage biases and good coverage. There was some evidence that indirect effect estimates might be variable at early timepoints, while events were still accumulating.

9.2.3 The extension to dynamic path analysis proposed in this thesis

Dynamic path analysis is not directly applicable to settings with a time-to-event mediator exemplified by mediation analysis in the Zactima trials. In fact, Pratschke [28] notes that “the statistical theory and software tools for causal mediation analysis with survival outcomes are currently confined to continuous mediators”. The thesis proposed a novel extension to dynamic path analysis to settings where both mediator and outcome are time-to-event

variables. This extension shares the advantages of dynamic path analysis, in that the indirect effect is allowed to vary freely over time. The formulation of the indirect treatment effect is simple, and its estimation straightforward. At the time of writing, the extension to dynamic path analysis proposed in this thesis is original, as it specifically deals with mediation analysis where both the mediator and outcome are time-to-event variables.

The components of the dynamic path analysis estimator are unbiased (linear regression gives rise to unbiased estimates; estimates derived from fitting additive hazards model with a time-updated binary explanatory variable were found to be unbiased as noted in section 9.2.1.1). The dynamic path analysis estimator in the setting with a continuous mediator was found to be unbiased as noted in section 9.2.2. The extension to dynamic path analysis was not therefore expected to give rise to biased estimates.

In some cases, occurrence of the distal event was found to have some impact on estimates of the effect of treatment on the proximal event. This is an unusual setting in survival analysis, where follow-up was not ended at the occurrence of the (proximal) event of interest. The nature and magnitude of the effect of the distal event on the estimates is therefore highly relevant. Consequently, the performance of dynamic path analysis estimator was compared with the expected value if the distal event had not occurred, in order to gain insight to this effect. The performance of the estimator was found to depend on the relative speeds of the proximal and distal events, the direction of effect of treatment on the proximal event, and the strength of association between the two events. In settings when the two events occurred at similar rates, the occurrence of the distal event had very little effect on estimates obtained by dynamic path analysis. In settings when the proximal event occurred much more quickly than the distal event, and there was a strong association between proximal and distal events, occurrence of the distal event was found to affect the estimates late in follow-up.

9.2.4 Application of the proposed method to the Zactima trials dataset

The possibility of an indirect effect of treatment on death via progression in the Zactima trials dataset was raised by comparing the estimated overall and direct effects of treatment on death. This indirect effect was estimated by implementing the extension of dynamic path analysis proposed in this thesis. It was shown that treatment had a protective indirect effect on death. During the first month after randomisation, this effect was close to null. At 4

months, the cumulative indirect effect estimate and its 95% confidence interval were -0.025 [-0.020, -0.031]. At 8 months, the cumulative indirect effect estimate was -0.055 with a 95% confidence interval of [-0.046, -0.066]. These findings were in accord with previous estimates of the overall effect of treatment on death and the direct effect of treatment on death.

Simulation studies using parameters estimated from the Zactima trials were also carried out to determine whether the dynamic path analysis estimates were likely to be affected by selective depletion due to death, as noted in section 9.2.3. These parameters corresponded to progression occuring 8.3 times faster than death, and a hazard ratio of 3.3 representing the association between progression and death. It was expected from the findings of the simulation studies presented in chapter 7 that the dynamic path analysis estimator could be affected by substantial accumulation of death events late in follow-up, and this was found to be the case.

The application of the method to the Zactima trials data demonstrated how the method proposed in this thesis could be applied to give a quantitative estimate of a treatment effect on a time-to-event outcome via a time-to-event mediator.

9.3 General application of the proposed method in clinical trials

Time-to-event composite are commonly encountered in cardiovascular medicine. The Lim survey [6] found that among cardiovascular trials published between 2000 and 2007, 27% had a time-to-event composite outcome. Therefore, the extension to dynamic path analysis proposed in this thesis can be considered in the context of the secondary analysis of these trials. Consideration of the relative frequency of the component events, and the strength of the relationship between the component events is important when considering the applicability of the method, in view of the effect of the distal event on the estimator discussed above. Myocardial infarction (MI) and all-cause mortality are frequently chosen as component events of a composite outcome in cardiovascular clinical trials [6]. Examining a small group of cardiovascular trials which used MI and all-cause mortality as component events of a composite outcome (chosen from [83]) gives some insight into the relative frequency of these component events in the literature.

In the TIMI-IIIB trial [84], the one-year incidence of MI was 2.0 times that of mortality. In the CURE trial [85], the incidence of MI over one year of follow-up was almost the same as that of mortality (743 MIs compared to 749 deaths). In the PROVE-IT trial [86], over 30 months of follow-up MI was 2.6 times as likely to occur as death. Conversely, in the COMMIT trial [87], over the first three days following treatment, death was 3.5 times more likely to occur than MI. Finally, in the COURAGE trial [88], over 4.6 years of follow-up there were 1.9 times as many MIs as deaths from any cause. In the Zactima trials used in this thesis, cancer progression was 1.2 times more likely to occur than death over the course of follow-up (see Figure 2-2). This ratio is smaller in magnitude to those of the cardiovascular trials cited.

Cannon [5] stated that "[myocardial infarction] has been found to be associated with an approximately 2.5-fold increase in subsequent mortality in several trials […]" [5]. As another example, the TIMI-7 trial [89] found that over six weeks, mortality was 7.2 times more prevalent in patients who had experienced a non-fatal component events than in those who hadn't. In the Zactima trials, death was 3.2 times more likely to occur in patients who had experienced cancer progression than in those who had not.

The generally higher incidence of MIs than deaths, and the strong relationships between MI and death in the trials cited above suggests that the dynamic path estimator proposed in this thesis could be affected late in follow-up by the occurrence of death if applied widely to trials in this clinical area. This implies that some of the results obtained using dynamic path analysis would have to be interpreted acknowledging the effect of post-MI deaths on the dynamic path analysis estimator. Analysis could be truncated as suggested in chapter 7 to mitigate this issue.

The method could also be applied in other clinical areas. A survey of prospective randomised trials published in the Lancet Oncology in 2008 showed that of 20 trials, 6 had time-to-event composite outcomes. It therefore appears that there is scope to apply the extension to dynamic path analysis in different clinical fields. Application of this method would in general require some consideration at the design stage. Specifically, the main assumptions of the method described in section 5.4.2 (of no unmeasured confounding, no intermediate confounding and no treatment-medator interaction) would need to be considered. In a randomised trial, relationships between the treatment and mediator or distal outcome variables are unconfounded by design. However, attention may need to be given to potential confounders of the mediator-outcome relationship so that such confounders can be included in the analysis. In addition, intermediate confounding (see section 5.2.4), where treatment affects a variable which itself affects both the mediator and the outcome variable, could amount in this setting to the specification of an additional indirect effect of treatment. The

existence of such an effect would require changes to the structural models and path diagrams involved, and also lead to further complexities as discussed in the multiple mediators literature [90]. The assumption of no interaction between treatment and the mediator on the distal outcome would also need to be considered when planning to use dynamic path analysis. Finally, a trial planning to use dynamic path analysis as a secondary analysis would need to give some consideration to issues of sample size and power, especially as composite outcomes are often chosen in part to address sample size requirements [1].

There is potential for the extension to dynamic path analysis proposed in this thesis to be applied in other areas such as epidemiological research. This would require consideration of possible confounders of the effect of the exposure variable as outlined above. In some complex epidemiological settings, time-varying exposures may affect time-varying confounders, which in turn affect later values of the exposure variables (see for example [24]). This setting poses a set of complications similar to those of intermediate confounding. It would be interesting to investigate whether the extension to dynamic path analysis could be applied in this setting.

The extension to dynamic path analysis proposed in this thesis is easy to implement using standard software (see the Zactima trials example in Appendix II). It produces simple graphical output which can be compared with estimates of the overall and direct effects to shed light on the mechanisms of action of treatment. It is therefore likely that the method could be widely and successfully applied to the secondary analysis of clinical trials.

9.4 Areas for further research

There are several areas of interest for further research in the application of dynamic path analysis with a time-to-event mediator. It would be useful to investigate whether an expression for the expected value of the estimator could be developed, perhaps inspired by the use of inverse probability of censoring weighting (IPCW), which has been used to correct estimates for dependent censoring. Roysland [77] gave an example of the use of inverse probability of censoring weighting (IPCW) in analysis of the Swiss HIV Cohort Study. The setting was different from the setting used in this thesis, in that the authors constructed a series of "mimicked" randomised trials from the cohort data, based on treatment group during each of

a set of discrete time periods. Dependent censoring was introduced by assigning the treatment group on the basis of treatment during a given time period, and individuals who did not receive the treatment were the control group, censored at the later time they started treatment. This led to dependent censoring for individuals who started treatment when their CD4 count rose. Inverse probability of censoring weighting (IPCW) [91, 92] was used to correct for this dependent censoring, creating in effect a notional dataset where the censoring mechanism was independent. Traditional dynamic path analysis was then used to estimate the indirect effect of treatment on the composite outcome of AIDS or death through the time-varying continuous mediator of CD4 count. The dependent censoring in this case (caused by individuals in the control group starting treatment) occurred before the outcome of AIDS or death. However, it might be of interest to investigate whether a similar approach could be applied to developing an expression for the expected value of the estimator in the presence of the distal event.

Observation of the dates of cancer progression in the Zactima trials was subject to interval censoring, as described by Lindsey [93]. This occurs when an event of interest can only be observed at set follow-up times. Typically, such an event is identified by the results of investigations performed at scheduled follow-up visits. This contrasts with events requiring immediate medical intervention, or death, the precise dates of which are usually known. Interval-censored data are often analysed by attributing the date of the visit when the event is observed to have occurred to the event data, as in this thesis. This attribution can lead to results that are biased in either direction [93, 94], and to underestimated standard errors, leading in turn to type I error in the results of hypothesis tests [94]. However, Dorey [95] suggested that this bias is unlikely to be important in a randomised trial of a serious disease with a short interval between follow-up visits, as was the case with the Zactima trials.

The interval censoring of the progression outcome in the Zactima trials datasets can be seen by examining the Kaplan-Meier estimates of survivor function for progression shown in Figure 2-1. The plots appear stepped, with each vertical drop corresponding to the scheduled follow-up visits when progression was assessed. When the datasets were pooled this stepping became less apparent (see Figure 2-3), because the follow-ups were staggered at every 6 weeks in the Zodiac and Zeal trials, and every 8 weeks in the Zephyr trial. A closer examination suggests that in practice follow-up visits were spread out around the 6 and 8-week points. For example, of the 373 progressions recorded between 5 and 7 weeks, 58 (15.5%) were recorded at exactly 6 weeks. Of the 344 progressions recorded between 7 and 9 weeks, 87 (25.3%) were recorded at exactly 8 weeks.

Interval censoring may therefore not constitute a large source of bias in the analyses of the Zactima trials datasets presented in this thesis. However, it is likely that interval-censored events may commonly be component events of a composite outcome, and therefore it would be relevant to investigate the effects of interval censoring on the dynamic path analysis estimator.

Throughout this thesis, estimates from both the additive hazards model and dynamic path analysis have been truncated at the 75th percentile of follow-up time, in line with recommendations by Hosmer and Royston [56]. This strategy addresses the issues of extreme variability of estimates based on very small sample sizes late in follow-up, and hence lack of variability in the data leading to some time points where the regression coefficients for the mediator and outcome models are not estimable. Other strategies could be used to mitigate these effects. For example, a weighting approach could be used to reduce the effects of very variable point-specific estimates on the cumulative effect late in follow-up; or standard errors of the point-specific coefficients could be estimated using a bootstrap, with a pre-specified maximum used to define "extreme" estimates to be excluded. Smoothing techniques could be used to address "missing" regression coefficients later in follow-up. Alternatively, a cut-off could be specified such that reporting ends after a certain proportion of "missing" regression coefficients are observed. These strategies could increase the amount of information used in the estimation both of the additive hazards model and dynamic path analysis, and as such would constitute interesting areas of further work.

As noted in chapter 5 and in [20], direct and indirect effects are defined with respect to a specific mediator or mediators. The setting considered in this thesis has included one mediator variable. However, with more detailed data it could be possible to define a plurality of indirect pathways operating through one or more mediator variables, although no such examples currently exist in the literature. The application of dynamic path analysis in this context would be a useful area for further research.

9.5 Concluding remarks

This thesis was motivated by extending composite outcome analysis into cause-specific analysis of the effect of treatment on cancer progression and death in the Zactima trials. A

strong protective effect of treatment on progression was observed. A comparison of the overall effect of treatment on death and the direct (not via progression) effect of treatment on death suggested an indirect effect of treatment on death via progression, underscored by the strong protective effect of treatment on progression. The difficulty lay in estimating an indirect effect of treatment on a time-to-event outcome via a time-to-event mediator.

This thesis has extended dynamic path analysis to propose a simple method of estimating an indirect effect on a time-to-event outcome via a time-to-event mediator. This extension represents a novel means of conducting mediation analysis in this setting and gaining insight into the possible mechanisms of action of treatment. When applied to the Zactima trials dataset, a small but statistically significant indirect effect of treatment on death of -0.025 at 4 months and -0.055 at 8 months was estimated.

Further research is needed into the properties of this estimator. As it stands, however, the method represents a step forward in the secondary analysis of clinical trials with a time-to-event composite outcome, and the elucidation of pathways through which treatment might work.

10 References

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Appendix I: fitting an additive hazards model in Stata

Analysis in this thesis was performed using Stata version 12.1.

Additive hazards models were fitted using the `stlh` command, written by David W Hosmer and Patrick Royston and published on 8 March 2002.

The full text of the command is reproduced below. It can be used in any version of Stata from version 6 onwards.

```
*****************

*! version 1.0.0 DWH/PR 08Mar2002.    (SJ2-4: st0024)
program define stlh
version 6
st_is 2 analysis
syntax varlist(min=1) [if] [in], [ noDOTs GENerate(string) noGRAph
LEVel(string) /*
 */ noMORE SAVing(string) TCent(real 75) TESTwt(numlist >=1 <=4 integer sort)
* ]
if "`saving'"!="" {
       tokenize "`saving'", parse(" ,")
       local s `1'
       local replace `2'`3'
       if "`4'"!="" | ("`replace'"!="" & "`replace'"!=",replace") {
              di in red "invalid saving(`saving')"
              exit 198
       }
       local saving `s'
}
* key st chars
local id: char _dta[st_id]
local wt: char _dta[st_wt]      /* type of weight */
if "`wt'"!="" {
       di in red "weights not supported"
       exit 198
}
local time _t
local t0 _t0
local dead _d

if `tcent'>100 | `tcent'<10 {
       di in red "tcent() must be between 10 and 100 (default is 75)"
       exit 198
}
if "`level'"!="" {
       confirm num `level'
}
else local level $S_level
tempname zlevel
scalar `zlevel'=-invnorm((100-`level')/200)

if "`graph'"=="nograph" & "`saving'"!="" {
       di in red "no graphs to save"
       exit 198
}

quietly {
       marksample touse
```

```
markout `touse' `varlist'
	replace `touse'=0 if _st==0
	count if `touse'
	local nobs=r(N)
	if "`graph'"!="nograph" & `tcent'<100 {
		centile `time', centile(`tcent')
		local tp=r(c_1)
		local iftc "& `time'<=`tp'"
	}
	* Remove collinearities
	noi _rmcoll `varlist' if `touse'
	local varlist `r(varlist)'
	local nx: word count `varlist'
	local p 0
	while  `p'<=`nx' {
		local p=`p'+1
		if `p'>`nx' {
			local nm`p' "_cons"
		}
		else local nm`p': word `p' of `varlist'
		tempvar a`p'
		gen `a`p''=.
		if "`generat'"!="" {
			confirm new var `generat'A`p'
			confirm new var `generat'S`p'
		}
	}
	noi di in gr _n "Graphs and tests for Aalen's Additive Model" _n
_dup(43) "-"
	noi di in gr "Model:  " in ye "`varlist'"
	noi di in gr "Obs:    " in ye `nobs' _n
	local Np=`nobs'-`p'
	* Handle possible ties by sorting data in order of time, censoring,
covariates.
	* Covariates are ordered lexicographically, so results can never change
even
	* if covariates are ordered differently on input.
	listsort "`varlist'", lexicographic
	local vlsort `s(list)'
	* put obs with missing last then drop them
	gsort -`touse' `time' -`dead' `vlsort'
	local todrop=`nobs'<_N
	if `todrop' {
		preserve
		if "`generat'"!="" {
			tempfile orig
			save `orig'
		}
		drop if `touse'==0
	}
	tempvar dN
	gen byte `dN'=0
	local it 1
	while `it'<=`Np' {  /* begin it loop */
		if "`dots'"!="nodots" {
			if mod(`it',100)==0 { noi di in gr "." _continue }
		}
		if `dead'[`it']==1 {   /* begin dead==1 loop */
			replace `dN'=(_n==`it')
			* regress for any obs for which time>=current failure time
			* and entry time (t0) is earlier than current failure time
			capture regress `dN' `varlist' if _n>=`it' &
`t0'<`time'[`it']
			if e(df_m)==`nx' {  /* full rank; regression can continue
*/
				local k 1
				while `k'<=`p' {
					replace `a`k''=_b[`nm`k'''] in `it'
					local k=`k'+1
				}
			} /* end of rss>0 */
```

```
                } /* end of the dead==1 loop */
                local it=`it'+1
        } /* end it loop */
        noi di
        local k 1
        while `k'<=`p' {
                tempvar A`k' VA`k'
                gen `A`k''=sum(`a`k'')
                gen `VA`k''=sum(`a`k''^2)
                *replace `a`k''=. if `dead'==0
                local k=`k'+1
        }
        if "`graph'"!="nograph" {
                * Graph
                if "`more'"!="nomore" {
                        set more on
                }
                tempvar lb ub
                gen `lb'=.
                gen `ub'=.
                local k 1
                while `k'<=`p' {
                        local t1
                        if `k'<`p' { /* k=p is _cons */
                                local t1: var label `nm`k''
                                if "`t1'"=="" {
                                        local t1 `nm`k''
                                }
                        }
                        else local t1 [Constant]
                        replace `lb'=`A`k''-`zlevel'*sqrt(`VA`k'') if `dead'==1
                        replace `ub'=`A`k''+`zlevel'*sqrt(`VA`k'') if `dead'==1
                        if "`saving'"!="" {
                                local sav saving(`saving'`nm`k''`replace')
                        }
                        graph `lb' `A`k'' `ub' `time' if `a`k''!=. `iftc', sort /*
                         */ pen(323) s(iii) c(JJJ) `sav' t1title(`t1') yline(0)
`options'
                        if "`more'"!="nomore" & `k'<`p' {
                                more
                        }
                        local k=`k'+ 1
                }
        }
        * hypothesis test(s), if specified
        local ntest: word count `testwt'
        if `ntest'>0 {
                local maxtst: word `ntest' of `testwt'
                if `maxtst'>=3 {
                        tempvar SKM
                        sts gen `SKM'=s
                }
                tempvar Asm AsmV zwt
                gen `Asm'=.
                gen `AsmV'=.
                gen `zwt'=.
                gsort `time' -`dead' `vlsort'
                tokenize `testwt'
                while "`1'"!="" {
                        local w `1'
                        if `w'==1    {
                                local wtt`w' "1.0"
                                replace `zwt'=1
                        }
                        else if `w'==2 {
                                local wtt`w' "the Size of the Risk Set"
                                replace `zwt'=_N-_n+1
                        }
                        else if `w'==3 {
                                local wtt`w' "Kaplan-Meier Estimator at Time t-"
                                replace `zwt'=cond(_n==1, 1, `SKM'[_n-1])
```

```
                    }
                    else {
                          local wtt`w' "(Kaplan-Meier Estimator at Time t-
)/(Std. Dev of the Time-varying Coefficient)"
                    }
                    local k 1
                    while `k'<=`p' {
                          if  `w'==4  {
                                replace `zwt'=cond(_n==1, 1, `SKM'[_n-
1])/abs(`a`k'')
                          }
                          replace `Asm'=sum(`a`k''*`zwt')
                          replace `AsmV'=sum((`a`k''*`zwt')^2)
                          local z`k'=`Asm'[_N]/sqrt(`AsmV'[_N])
                          local k=`k'+ 1
                    }
                    noisily {
                          di in gr _n "Test `w': Uses Weights Equal to" _n
"`wtt`w'`" _n
                          di in gr "Variable" _col(17) "z" _col(27) "P"
                          di in gr "-----------------------------"
                          local k 1
                          while `k'<=`p' {
                                di in gr "`nm`k'`" in ye _col(13) %7.3f
`z`k'' /*
                                 */ _col(25) %5.3f 2*(1-
normprob(abs(`z`k'')))
                                local k=`k'+1
                          }
                    }
                    mac shift /* to process next requested test number */
             }
       } /* end of loop for hypothesis tests */
       if "`generat'"!="" {
             local keep
             local k 1
             while `k'<=`p' {
                    gen `generat'S`k'=sqrt(`VA`k'')
                    rename `A`k'' `generat'B`k'
                    lab var `generat'B`k' "Aalen cum coeff for `nm`k'`"
                    lab var `generat'S`k' "SE(Aalen cum coeff for `nm`k'')"
                    local keep `keep' `generat'B`k' `generat'S`k'
                    local k=`k'+1
             }
             if `todrop' {
                    tempfile addits
                    keep `keep'
                    save `addits'
                    use `orig'
                    merge using `addits'
                    drop _merge
                    restore, not
             }
       }
} /* end quietly */
end

*! version 1.0.0 PR 16Feb2001.
program define listsort, sclass
version 6
gettoken p 0 : 0, parse(" ,")
if `"`p'"'==""  {
      exit
}
sret clear
syntax , [ Reverse Lexicographic ]
local lex="`lexicog'"!=""
if "`reverse'"!="" { local comp < }
else local comp >
local np: word count `p'
local i 1
```

```
while `i'<=`np' {
	local p`i': word `i' of `p'
	if !`lex' { confirm number `p`i'' }
	local i=`i'+1
}
* Apply shell sort (Kernighan & Ritchie p 58)
local gap=int(`np'/2)
while `gap'>0 {
	local i `gap'
	while `i'<`np' {
		local j=`i'-`gap'
		while `j'>=0 {
			local j1=`j'+1
			local j2=`j'+`gap'+1
			if `lex' { local swap=(`"`p`j1''"' `comp' `"`p`j2''"') }
			else local swap=(`p`j1'' `comp' `p`j2'')
			if `swap' {
				local temp `p`j1''
				local p`j1' `p`j2''
				local p`j2' `temp'
			}
			local j=`j'-`gap'
		}
		local i=`i'+1
	}
	local gap=int(`gap'/2)
}
local p
local i 1
while `i'<=`np' {
	sret local i`i' `p`i''
	local p `p' `p`i''
	local i=`i'+1
}
sret local list `p'
end
```

Appendix II: estimating the indirect effect of treatment on death in the Zactima trials and bootstrapping the confidence intervals

The code given below was used to estimate the indirect effect of treatment on death in the Zactima trials, and to bootstrap the confidence intervals as described in Chapter 8. Novel commands called in this programming are reproduced below the main body of the program.

For ease of reading, the progression variable is given as [progression], the treatment variable is given as [treatment], the indicator variables for trial are given as [trial] and the baseline covariates are given as `[covs]`.

****

Estimation of the indirect effect of treatment on death via progression and its bootstrapped 95% confidence interval using the Zactima trials data

```
*load and prepare data (code not given)

*estimate the effect of treatment on progression (code for the stlhregress
*command given below, again this is a very slighly adapted version of the stlh
*command)
qui stlhregress [progression] [treatment] [trial] [covs],  gen(first)


*graph of estimated effect of treatment on progression at each death time:
gen trtprog_ub=firstb1+1.96*firsts1
gen trtprog_lb=firstb1-1.96*firsts1
#delimit ;
twoway        (line firstb1 _t, sort)
              (line trtprog_ub _t, sort lpattern(dot) lcolor(blue))
              (line trtprog_lb _t, sort lpattern(dot) lcolor(blue))
              if _t<8,
              xtitle("Time since randomisation (months)")
              ytitle("Regression coefficient") ylabel(,angle(h))
              legend(on order(1 "Treatment effect" 2 "95% confidence limits" ))
              ;
#delimit cr


*estimate the effect of progression on death using stlh_b (code for the stlh_b
*command given below, this is a very slightly adapted version of the stlh code
*reproduced in Appendix I which outputs the incremental estimates rather than
their *sums)
stlh_b  [progression] [treatment] [trial] [covs], nograph gen(second)

*graph of estimated effect of progression on death
gen progdth_ub=secondB1+1.96*secondS1
gen progdth_lb=secondB1-1.96*secondS1
#delimit ;
twoway        (line secondB1 _t, sort)
              (line progdth_ub _t, sort lpattern(dot) lcolor(blue))
              (line progdth_lb _t, sort lpattern(dot) lcolor(blue))
              if _t<8,
              xtitle("Time since randomisation (months)")
              ytitle("Cumulative regression coefficient") ylabel(,angle(h))
```

```
            legend(on order(1 "Effect of progression" 2 "95% confidence
limits" ))
            ;
#delimit cr


*estimate of the indirect effect off treatment on death via progression using
dynamic path analysis
gen g2b1=secondb1*firstb1
      gsort -_d _t [id]
      gen estG2B1 = sum(g2b1) if _d==1


*defining timepoints for evaluation of the bootstrapped confidence interval
      local t1     =0.8
      local t2     =1.6
      local t3     =2.4
      local t4     =3.2
      local t5     =4.0
      local t6     =4.8
      local t7     =5.6
      local t8     =6.4
      local t9     =7.2
      local t10    =8.0

*bootstrapping the confidence interval using bootstrap_zp.ado (code for the
ado file is given below)
      set seed 1234
            noi    bootstrap r(estG2B1bs_8)  r(estG2B1bs_16) r(estG2B1bs_24)
r(estG2B1bs_32)  r(estG2B1bs_40) r(estG2B1bs_48) /*
                  */r(estG2B1bs_56) r(estG2B1bs_64)  r(estG2B1bs_72)
r(estG2B1bs_80), reps(1000): /*
                  */bootstrap_zp, eval(`t1' `t2' `t3' `t4' `t5' `t6' `t7'
`t8' `t9' `t10')
                              estat bootstrap, all
                              matrix G=e(ci_percentile)
                              forval num=1/10 {
                                    scalar u_cip`num'=el("G",2,`num')
                                    scalar l_cip`num'=el("G",1,`num')

                        }

*outputting results from bootstrapped confidence interval

gen bstime=.
gen pc_u=.
gen pc_l=.
forval num =1/10 {
      replace bstime=0.8*`num'  in `num'
      replace pc_u = u_cip`num' in `num'
      replace pc_l = l_cip`num' in `num'
      }
replace bstime      = 0 in 11
replace pc_u        = 0 in 11
replace pc_l        = 0 in 11

*graph of estimated indirect effect of treatment on death via progression and
its bootstrapped 95% confidence interval

#delimit ;
twoway (line estG2B1 _t if _t<8, sort)
      (connected pc_u bstime , sort lpattern(dash) mcolor(blue) lcolor(blue))
      (connected pc_l bstime , sort lpattern(dash) mcolor(blue) lcolor(blue)),
      xtitle("Time since randomisation (months)")
            ytitle("Cumulative regression function") ylabel(,angle(h))
            legend(on order(1 "Effect of treatment" 2 "95% confidence limits"
))
      ;
      #delimit cr
```

****

Code for the stlhregress command

```
*!based on stlh, changed to allow ols regression at each time point
program define stlhregress
syntax varlist(min=2) [if], [GENerate(string)]

* key st chars
local id: char _dta[st_id]
local wt: char _dta[st_wt]      /* type of weight */
if "`wt'"!="" {
       di in red "weights not supported"
       exit 198
}
local time _t
local t0 _t0
local dead _d

tokenize `varlist'
local outcome `1'
macro shift
local covs `*'


quietly {
       marksample touse
       markout `touse' `varlist'
       replace `touse'=0 if _st==0
       count if `touse'
       local nobs=r(N)

       * Remove collinearities
       noi _rmcoll `covs' if `touse'
       local covs `r(varlist)'
       local nx: word count `covs'
       local p 0
       while  `p'<=`nx' {
              local p=`p'+1
              if `p'>`nx' {
                     local nm`p' "_cons"
              }
              else local nm`p': word `p' of `covs'
              tempvar a`p' se`p' natrisk
              gen `a`p''=.
              gen `se`p''=.
              gen `natrisk'=.
              if "`generate'"!="" {
                     confirm new var `generate'A`p'
                     confirm new var `generate'S`p'
              }
       }


       noi di in gr _n "Dpa ols regressions" _n _dup(43) "-"
       noi di in gr "Outcome:  " in ye "`outcome'"
       noi di in gr "Covariates:  " in ye "`covs'"
       noi di in gr "Obs:    " in ye `nobs' _n
       local Np=`nobs'-`p'

       * Handle possible ties by sorting data in order of time, censoring,
covariates.
       * Covariates are ordered lexicographically, so results can never change
even
       * if covariates are ordered differently on input.
       listsort "`covs'", lexicographic
       local vlsort `s(list)'
       * put obs with missing last then drop them
       gsort -`touse' `time' -`dead' `vlsort'
       local todrop=`nobs'<_N
```

```
	if `todrop' {
		preserve
		if "`generate'"!="" {
			tempfile orig
			save `orig'
		}
		drop if `touse'==0
	}
*	tempvar dN
*	gen byte `dN'=0
	local it 1
	while `it'<=`Np' {  /* begin it loop */
		if "`dots'"!="nodots" {
			if mod(`it',100)==0 { noi di in gr "." _continue }
		}
		if `dead'[`it']==1 {   /* begin dead==1 loop */
*			replace `dN'=(_n==`it')
			* regress for any obs for which time>=current failure time
			* and entry time (t0) is earlier than current failure time
			capture regress `outcome' `covs' if _n>=`it' &
`t0'<`time'[`it']
			count if _n>=`it'&`t0'<`time'[`it']
			replace `natrisk'=r(N) in `it'
			if e(df_m)==`nx' {  /* full rank; regression can continue
*/
				local k 1
				while `k'<=`p' {
					replace `a`k''=_b[`nm`k'']  in `it'
					replace `se`k''=_se[`nm`k'']  in `it'
					local k=`k'+1
				}
			} /* end of rss>0 */
		} /* end of the dead==1 loop */
noi di in y "regression loop `it'"
		local it=`it'+1
	} /* end it loop */


*ols regression outputs are scalar e(N) (number of obs), _b[varname]
(regression coefficient for
*varname), _se[varname] is the standard error of the regression coefficient of
varname


}

local k 1
while `k'<=`p' {
	gen `generate'b`k'=`a`k''
	lab var `generate'b`k' "Regression coeff for `nm`k''"
	gen `generate's`k'=`se`k''
	lab var `generate's`k' "SE(regression coeff for `nm`k'')"
	local k=`k'+1
	}
gen `generate'N=`natrisk'
lab var `generate'N "N at risk"
end
```

****

Code for the stlh_b command

```
*based on stlh, altered so that increments as well as cumulative sums are
reported as output
program define stlh_b
version 6
st_is 2 analysis
syntax varlist(min=1) [if] [in], [ noDOTs GENerate(string) noGRAph
LEVel(string) /*
 */ noMORE SAVing(string) TCent(real 75) TESTwt(numlist >=1 <=4 integer sort)
* ]
if "`saving'"!="" {
       tokenize "`saving'", parse(" ,")
       local s `1'
       local replace `2'`3'
       if "`4'"!="" | ("`replace'"!="" & "`replace'"!=",replace") {
              di in red "invalid saving(`saving')"
              exit 198
       }
       local saving `s'
}
* key st chars
local id: char _dta[st_id]
local wt: char _dta[st_wt]      /* type of weight */
if "`wt'"!="" {
       di in red "weights not supported"
       exit 198
}
local time _t
local t0 _t0
local dead _d

if `tcent'>100 | `tcent'<10 {
       di in red "tcent() must be between 10 and 100 (default is 75)"
       exit 198
}
if "`level'"!="" {
       confirm num `level'
}
else local level $S_level
tempname zlevel
scalar `zlevel'=-invnorm((100-`level')/200)

if "`graph'"=="nograph" & "`saving'"!="" {
       di in red "no graphs to save"
       exit 198
}

quietly {
       marksample touse
       markout `touse' `varlist'
       replace `touse'=0 if _st==0
       count if `touse'
       local nobs=r(N)
       if "`graph'"!="nograph" & `tcent'<100 {
              centile `time', centile(`tcent')
              local tp=r(c_1)
              local iftc "& `time'<=`tp'"
       }
       * Remove collinearities
       noi _rmcoll `varlist' if `touse'
       local varlist `r(varlist)'
       local nx: word count `varlist'
       local p 0
```

```
while  `p'<=`nx' {
              local p=`p'+1
              if `p'>`nx' {
                     local nm`p' "_cons"
              }
              else local nm`p': word `p' of `varlist'
              tempvar a`p'
              gen `a`p''=.
              if "`generat'"!="" {
                     confirm new var `generat'A`p'
                     confirm new var `generat'S`p'
              }
       }
       noi di in gr _n "Graphs and tests for Aalen's Additive Model" _n
_dup(43) "-"
       noi di in gr "Model:  " in ye "`varlist'"
       noi di in gr "Obs:    " in ye `nobs' _n
       local Np=`nobs'-`p'
       * Handle possible ties by sorting data in order of time, censoring,
covariates.
       * Covariates are ordered lexicographically, so results can never change
even
       * if covariates are ordered differently on input.
       listsort "`varlist'", lexicographic
       local vlsort `s(list)'
       * put obs with missing last then drop them
       gsort -`touse' `time' -`dead' `vlsort'
       local todrop=`nobs'<_N
       if `todrop' {
              preserve
              if "`generat'"!="" {
                     tempfile orig
                     save `orig'
              }
              drop if `touse'==0
       }
       tempvar dN
       gen byte `dN'=0
       local it 1
       while `it'<=`Np' {  /* begin it loop */
              if "`dots'"!="nodots" {
                     if mod(`it',100)==0 { noi di in gr "." _continue }
              }
              if `dead'[`it']==1 {   /* begin dead==1 loop */
                     replace `dN'=(_n==`it')
                     * regress for any obs for which time>=current failure time
                     * and entry time (t0) is earlier than current failure time
                     capture regress `dN' `varlist' if _n>=`it' &
`t0'<`time'[`it']
                     if e(df_m)==`nx' {  /* full rank; regression can continue
*/
                            local k 1
                            while `k'<=`p' {
                                   replace `a`k''=_b[`nm`k''] in `it'
                                   local k=`k'+1
                            }
                     } /* end of rss>0 */
              } /* end of the dead==1 loop */
              local it=`it'+1
       } /* end it loop */
       noi di
       local k 1
       while `k'<=`p' {
              tempvar A`k' VA`k'
              gen `A`k''=sum(`a`k'')
              gen `VA`k''=sum(`a`k''^2)
              *replace `a`k''=. if `dead'==0
              local k=`k'+1
       }
       if "`graph'"!="nograph" {
              * Graph
```

```
	if "`more'"!="nomore" {
			set more on
		}
		tempvar lb ub
		gen `lb'=.
		gen `ub'=.
		local k 1
		while `k'<=`p' {
			local t1
			if `k'<`p' { /* k=p is _cons */
				local t1: var label `nm`k''
				if "`t1'"==""  {
					local t1 `nm`k''
				}
			}
			else local t1 [Constant]
			replace `lb'=`A`k''-`zlevel'*sqrt(`VA`k'') if `dead'==1
			replace `ub'=`A`k''+`zlevel'*sqrt(`VA`k'') if `dead'==1
			if "`saving'"!="" {
				local sav saving(`saving'`nm`k'''`replace')
			}
			graph `lb' `A`k'' `ub' `time' if `a`k''!=. `iftc', sort /*
			 */ pen(323) s(iii) c(JJJ) `sav' t1title(`t1') yline(0)
`options'
			if "`more'"!="nomore" & `k'<`p' {
				more
			}
			local k=`k'+ 1
		}
	}
	* hypothesis test(s), if specified
	local ntest: word count `testwt'
	if `ntest'>0 {
		local maxtst: word `ntest' of `testwt'
		if `maxtst'>=3 {
			tempvar SKM
			sts gen `SKM'=s
		}
		tempvar Asm AsmV zwt
		gen `Asm'=.
		gen `AsmV'=.
		gen `zwt'=.
		gsort `time' -`dead' `vlsort'
		tokenize `testwt'
		while "`1'"!="" {
			local w `1'
			if `w'==1    {
				local wtt`w' "1.0"
				replace `zwt'=1
			}
			else if `w'==2 {
				local wtt`w' "the Size of the Risk Set"
				replace `zwt'=_N-_n+1
			}
			else if `w'==3 {
				local wtt`w' "Kaplan-Meier Estimator at Time t-"
				replace `zwt'=cond(_n==1, 1, `SKM'[_n-1])
			}
			else {
				local wtt`w' "(Kaplan-Meier Estimator at Time t-
)/(Std. Dev of the Time-varying Coefficient)"
			}
			local k 1
			while `k'<=`p' {
				if  `w'==4  {
					replace `zwt'=cond(_n==1, 1, `SKM'[_n-
1])/abs(`a`k'')
				}
				replace `Asm'=sum(`a`k''*`zwt')
				replace `AsmV'=sum((`a`k''*`zwt')^2)
				local z`k'=`Asm'[_N]/sqrt(`AsmV'[_N])
```

```
                        local k=`k'+ 1
                }
                noisily {
                        di in gr _n "Test `w': Uses Weights Equal to" _n
"`wtt`w'`" _n
                        di in gr "Variable" _col(17) "z" _col(27) "P"
                        di in gr "------------------------------"
                        local k 1
                        while `k'<=`p' {
                                di in gr "`nm`k'`" in ye _col(13) %7.3f
`z`k'' /*
                                 */ _col(25) %5.3f 2*(1-
normprob(abs(`z`k'')))
                                local k=`k'+1
                        }
                }
                mac shift /* to process next requested test number */
        }
    } /* end of loop for hypothesis tests */
    if "`generat'"!="" {
            local keep
            local k 1
            while `k'<=`p' {
                gen `generat'S`k'=sqrt(`VA`k'')
                rename `A`k'' `generat'B`k'
                lab var `generat'B`k' "Aalen cum coeff for `nm`k'`"
                lab var `generat'S`k' "SE(Aalen cum coeff for `nm`k'')"

    *output of increments as well
                rename `a`k'' `generat'b`k'
                lab var `generat'b`k' "Aalen coefficient for `nm`k'`"



                local keep `keep' `generat'B`k' `generat'S`k'
`generat'b`k'
                local k=`k'+1
            }
            if `todrop' {
                tempfile addits
                keep `keep'
                save `addits'
                use `orig'
                merge using `addits'
                drop _merge
                restore, not
            }
    }
} /* end quietly */
end

*! version 1.0.0 PR 16Feb2001.
program define listsort, sclass
version 6
gettoken p 0 : 0, parse(" ,")
if `"`p'"'==="" {
    exit
}
sret clear
syntax , [ Reverse Lexicographic ]
local lex="`lexicog'"!=""
if "`reverse'"!="" { local comp < }
else local comp >
local np: word count `p'
local i 1
while `i'<=`np' {
    local p`i': word `i' of `p'
    if !`lex' { confirm number `p`i'' }
    local i=`i'+1
}
* Apply shell sort (Kernighan & Ritchie p 58)
```

```
local gap=int(`np'/2)
while `gap'>0 {
	local i `gap'
	while `i'<`np' {
		local j=`i'-`gap'
		while `j'>=0 {
			local j1=`j'+1
			local j2=`j'+`gap'+1
			if `lex' { local swap=(`"`p`j1''"' `comp' `"`p`j2''"') }
			else local swap=(`p`j1'' `comp' `p`j2'')
			if `swap' {
				local temp `p`j1''
				local p`j1' `p`j2''
				local p`j2' `temp'
			}
			local j=`j'-`gap'
		}
		local i=`i'+1
	}
	local gap=int(`gap'/2)
}
local p
local i 1
while `i'<=`np' {
	sret local i`i' `p`i''
	local p `p' `p`i''
	local i=`i'+1
}
sret local list `p'
end
```

****

Code for the bootstrap_zp command

```
capture program drop bootstrap_zp
program define bootstrap_zp, rclass
syntax , eval(numlist)



preserve

qui {

		stlhregress [progression] [treatment] [trial] [covs],
gen(firstbs)
		stlh_b [progression] [treatment] [trial] [covs], nograph
gen(secondbs)



	*increments of indirect effect:
	gen g2b1bs=secondbsb1*firstbsb1
	gsort -_d _t [id]
	gen estG2B1bs = sum(g2b1bs) if _d==1


		foreach timepoint in `eval' {
			noi di "timepoint value is " `timepoint'
			gsort -_d _t patid
			local lab = `timepoint'*10
			noi di "macro lab contains " `lab'
			gen t`lab'tag= 1 if _d==1&
_t<=`timepoint'&_t[_n+1]>`timepoint'
			sort t`lab'tag
```

```
                return scalar estG2B1bs_`lab'=estG2B1bs
        }


restore
}


        end
```

Appendix III: simulation study investigating the performance of the extension to dynamic path analysis

The code below corresponds to simulation setting 14 in Chapter 7. The code for obtaining the bootstrapped confidence intervals is not given below.

```
**********
```

```
*Step 1: input values for simulation - the inputs below refer to simulation setting
14 in chapter 7


clear

set seed 123456

*input parameter values
local gamma0  = 1.9
local gamma1  = 0.1
local gamma3  = 0.2
local th0     = 1.8
local th1      = 0.5


*evaluation time points
local  t0     = 0
local  t1     = .25
local  t2     = .5
local  t3     = .68
local  t4     = .69
local  t5     = .75
local  t6     = 1

*number of repetitions, maximum time, number of observations
local nreps=1000
local tmax = 5

local obs=3000
set obs `obs'


**************************
*Step 2: generate the data and fit the model

tempname [tempfile]
postfile [tempfile] simnum t1time t2time t3time t4time t5time t6time g2b1_t1
g2b1_t2 g2b1_t3 g2b1_t4 g2b1_t5 g2b1_t6 /*
       */  deathsat1 deathsat2 deathsat3 deathsat4 deathsat5 deathsat6 x2at1 x2at2
       x2at3 x2at4 x2at5 x2at6 using [filename]

forval i=1/`nreps' {
di in red "cycle number is " `i'
qui {
clear
set obs `obs'
gen id=_n

*generate random variables and event times
```

```
	gen x1=rbinomial(1,0.5)

	*time of Mbin(t) event
		survsim tchange change, cumhazard((`th0':*#t):+(`th1':*x1:*#t))
	maxt(5) nodes(30)
	replace change =0 if tchange==5

	*time of death event
		survsim st1 event, cumhazard(`gamma0':*#t +`gamma1':*x1*#t+
	`gamma3':*((#t>tchange):*change:*(#t-tchange))) maxt(`tmax') nodes(30)

	replace change=0    if event==1&st1<tchange
	replace tchange=st1 if event==1&st1<tchange

	*generating time-updated binary variable x2 indicating progression
	stset st1, failure(event) id(id)
	stsplit x2 = tchange if change==1, at(0)
	replace x2=x2+1
	recode x2 .=0

	*dynamic path analysis estimate of indirect effect of treatment
	stlhregress x2 x1, gen(first)
	stlh_b x2 x1, gen(second) nograph
	gen g2b1=secondb1*firstb1
	gsort -_d _t id
	gen estG2B1 = sum(g2b1) if _d==1


	*numeric output
	forval timepoint=1/6 {

		*identifying events just before evaluation timepoints
		gsort -event _t
				gen t`timepoint'tag= 1 if event==1&
		_t<=`t`timepoint''&_t[_n+1]>`t`timepoint''
		sort t`timepoint'tag
		local t`timepoint'time     = _t

		*estimated value of G2B1_t
		local g2b1_t`timepoint'    = estG2B1

		*percentage of deaths and x2(t)s at each timepoint
		count if _d==1&_t<`t`timepoint''
		local deathsat`timepoint' = r(N)
		count if x2==1&tchange<`t`timepoint''
		local x2at`timepoint' = r(N)
		sort id _t
	}

	*output results
		post [tempfile] (`i') (`t1time') (`t2time') (`t3time') (`t4time')
	(`t5time') (`t6time') (`g2b1_t1') (`g2b1_t2') (`g2b1_t3') (`g2b1_t4')
	(`g2b1_t5') (`g2b1_t6') /*
		*/  (`deathsat1') (`deathsat2') (`deathsat3') (`deathsat4')
	(`deathsat5') (`deathsat6') (`x2at1') (`x2at2') (`x2at3') (`x2at4')
	(`x2at5') (`x2at6')



	local i=`i'+1
	}
	}

postclose [tempfile]

************************
*section 3 report results

use [filename] , clear
```

```
forval timepoint=1/6 {
	di in red "results for timepoint " `t`timepoint''
	di ""

	local trueval =  `gamma3' * exp(`t`timepoint''*(-1*(`th0'+`th1')))*((
	1/(`th0'+`th1') ) - (exp(`th1'*`t`timepoint''))/`th0'  )     - (`gamma3'
	*( 1/(`th0'+`th1')  - 1/`th0'  ))
	di in white "value of G2B1_t is " `trueval'
	di ""

	qui {
		egen   meang2b1_t`timepoint'      =      mean(g2b1_t`timepoint')
		gen    pcbias_t`timepoint'        =      (meang2b1_t`timepoint'-
	`trueval')/`trueval''*100   if g2b1_t`timepoint'<.
		}

	*mean value of estimate of G2B1
	di in white "mean estimated value of G2B1_t:"
	tab meang2b1_t`timepoint'
	di ""

	*percentage bias
	di in white "percentage bias:"
	tab pcbias_t`timepoint'
	di ""

	*percentage of deaths at each timepoint
	qui summ deathsat`timepoint'
	di in white "percentage of deaths is "  r(mean)/`obs' *100
	di ""

	*percentage of x2 at each timepoint
	qui summ x2at`timepoint'
	di in white "percentage of x2 is "  r(mean)/`obs' *100
	di ""

	*empirical SE
	qui {
		gen S_t`timepoint'                      = (g2b1_t`timepoint' -
		meang2b1_t`timepoint')^2
		egen SS_t`timepoint'                    = sum(S_t`timepoint')
				if g2b1_t`timepoint'<.
		gen empSE_t`timepoint'                  =
		sqrt((SS_t`timepoint')/(`nreps'-1))
		}
	di in white "empirical SE:"
	di ""
	tab empSE_t`timepoint'



}
```

Appendix IV: Results supplementary to chapter 7

The following sets of results are referenced in chapter 7.

Table IV-1 shows results of a repeat of simulation 1 with a sample size of n=3000.

Table IV-1 Repeat of simulation 1 based on n=3000

Time	No	0.5	1.0	1.5	2.0
	1	$p25(T_d)=p25(T_{Mbin})$, $\gamma^*_3=0.2$, $\gamma^*_0=0.6$, $\theta^*_0=0.6$			
True value of $\Gamma_3(t)$		0.1	0.2	0.3	0.4
Mean of estimates $\hat{\Gamma}_3(t)$		0.101	0.200	0.300	0.400
Mean percentage bias		0.75	0.14	-0.09	0.001
Mean % of deaths/ $M_{bin}(t)$		26.9 /22.5	47.7 /34.9	63.1 /41.7	74.3 /45.5
95% coverage		91.0	94.0	93.5	94.3
Empirical/ Model-based SE		0.067 /0.052	0.073 /0.060	0.080 /0.069	0.089 /0.081

Compared to the results of simulation 1 shown in Table 7-10, the empirical and model-based standard errors are smaller when the simulations are based on a sample size of N=3000. The coverage is improved to acceptable levels at t=1.0, and is greater at t=0.5 although still below acceptable limits.

Table IV-2 shows results obtained by repeating simulation 5 but truncating the reporting at the 99th percentile of T_{Mbin} (equivalent to t=1.4).

Table IV-2 Repeat of simulation 5 with follow-up truncated at t=1.4

Time	No	0.35	0.7	1.05	1.4
	5	$p25(T_d)=p75(T_{Mbin})$, $\gamma^*_3=0.2$, $\gamma^*_0=0.5$, $\theta^*_0=2.7$			
True value of $\Gamma_3(t)$		0.07	0.14	0.21	0.28
Mean of estimates $\hat{\Gamma}_3(t)$		0.069	0.141	0.215	0.286
Mean percentage bias		-0.08	0.44	2.19	2.14
Mean % of deaths/ $M_{bin}(t)$		18.1 /56.2	34.6 /75.3	48.4 /81.4	59.6 /83.4
95% coverage		94.2	94.6	95.2	93.7
Empirical/ Model-based SE		0.057 /0.043	0.071 /0.058	0.091 /0.083	0.136 /0.129

The results indicate that when estimation is truncated at the 99th percentile of T_{Mbin}, coverage falls within the acceptable limits of [93.6%, 96.4%].

Table IV-3 reports the results of investigation into the behaviour of dynamic path analysis estimates (aim 3) from simulation setting 13 where the 25th percentiles of T_D and T_{Mbin} are similar, so that $M_{bin}(t)$ occurs slightly more slowly than death. The simulations reported in Table IV-3 have different values of the baseline parameters, notably changing θ_1^* to $\theta_1^* = 0.1$ and $\theta_1^* = 0.8$, and changing the baseline parameters to keep the same relative event rates. A comparison of the percentage difference between $\int_0^t \beta_1(u)\gamma_3\,du$ and $\sum_{t_j \le t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$ in Table 7-14 and Table IV-3 allows the effect of changing the value of θ_1^* to be assessed. 95% coverage and the percentage difference between $\int_0^t \beta_1(u)\gamma_3 du$ and $\widehat{\Gamma_1^{\times}}(t)$ are not reported in Table IV-3.

Table IV-3 Repeat of simulation 13 with two different values of θ_1^*

	$\theta_1^* = 0.1$					
Time	$\gamma_0^* = 1.8, \gamma_1^* = 0, \gamma_3^* = 0.2, \theta_0^* = 1.8$					
	0.25	0.5	0.72 ($p75_{Mbin}$)	0.75	0.77 (p25D)	1.0
Uncensored value of $\int_0^t \beta_1(u)\gamma_3 du$	0.00046	0.0014	0.0023	0.0023	0.0024	0.0032
Mean of $\sum_{t_j \le t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$	0.00045	0.0013	0.0022	0.0023	0.0023	0.0032
Mean %age difference	-2.61	-4.28	-4.62	-4.10	-3.68	-0.82
Mean % of deaths / $M_{bin}(t)$	36.8 /30.3	60.7 /42.5	74.5 /47.2	75.6 /47.4	76.7 /47.6	85.1 /49.4
Empirical SE	0.00091	0.002	0.0032	0.0034	0.0035	0.0051
	$\theta_1^* = 0.8$					
Time	$\gamma_0^* = 1.8, \gamma_1^* = 0, \gamma_3^* = 0.2, \theta_0^* = 1.5, \theta_1^* = 0.8$					
	0.25	0.5	0.73 ($p75_D$)	0.75 ($p75_{Mbin}$)	0.76	1.0
Uncensored value of $\int_0^t \beta_1(u)\gamma_3 du$	0.0037	0.011	0.018	0.019	0.019	0.025
Mean of $\sum_{t_j \le t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$	0.0036	0.011	0.018	0.018	0.019	0.026
Mean %age difference	-0.63	-2.52	-1.18	-0.81	-0.89	1.47
Mean % of deaths / $M_{bin}(t)$	36.9 /30.8	60.7 /42.8	74.8 /47.3	75.8 /47.6	76.2 /47.7	85.1 /49.5
Empirical SE	0.0029	0.0062	0.010	0.010	0.011	0.015

In simulation setting 13, changing the value of θ_1^* has a minimal effect on the percentage difference between $\int_0^t \beta_1(u)\gamma_3\,du$ and $\sum_{t_j \le t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$. In contrast, as shown in section 7.6.3, changing the value of γ_3^* has a large effect.

Table IV-4 below, similarly, shows the results obtained by repeating simulation setting 24 but setting $\theta_1^* = 0.1$ and $\theta_1^* = 0.8$.

Table IV-4 Repeat of simulation 24 with two different values of θ_1^*

	$\theta_1^* = 0.1$					
Time	$\gamma_0^* = 0.15 \gamma_1^* = 0.1, \gamma_3^* = 0.5, \theta_0^* = 1.9$					
	0.25	0.5	0.72 ($p75_{Mbin}$)	0.75	1.0	2.4 ($p75_D$)
Uncensored value of $\int_0^t \beta_1(u)\gamma_3 du$	0.0011	0.0034	0.0054	0.0057	0.0076	0.012
Mean of $\sum_{t_j \le t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$	0.0011	0.0033	0.0054	0.0057	0.0079	0.015
Mean %age difference	-1.35	-1.27	-0.40	0.06	3.92	24.13
Mean % of deaths / $M_{bin}(t)$	7.2 /37.7	17.0 /59.8	26.0 /71.4	27.3 /72.6	37.2 /80.1	74.9 /90.2
Empirical SE	0.0015	0.0034	0.0049	0.0051	0.0066	0.012
	$\theta_1^* = 0.8$					
Time	$\gamma_0^* = 0.15 \gamma_1^* = 0.1, \gamma_3^* = 0.5, \theta_0^* = 1.6$					
	0.25	0.5	0.72 ($p75_{Mbin}$)	0.75	1.0	2.4 ($p75_D$)
Uncensored value of $\int_0^t \beta_1(u)\gamma_3 du$	0.0090	0.027	0.042	0.044	0.060	0.098
Mean of $\sum_{t_j \le t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$	0.0089	0.026	0.043	0.045	0.063	0.120
Mean %age difference	-2.02	-1.20	0.92	1.31	4.62	23.15
Mean % of deaths / $M_{bin}(t)$	7.3 /38.1	17.0 /59.9	26.0 /71.3	27.3 /72.5	37.1 /79.9	74.6 /90.3
Empirical SE	0.0019	0.0040	0.0058	0.0061	0.0077	0.015

The results shown in Table IV-4, when compared to the results of simulation setting 24 reported in Table 7-15, demonstrate that changing the value of θ_1^* has a minimal effect on the percentage difference between $\int_0^t \beta_1(u)\gamma_3\,du$ and $\sum_{t_j \le t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$ in a setting where the percentage difference is large at later evaluation timepoints.

Figure IV-1 below shows estimates of the overall effect of X $\widehat{\Gamma_1^X}(t)$ and the indirect effect of X $\sum_{t_j \le t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$ for a single simulation corresponding to simulation setting 15 (where there is no direct effect of X), with varying sample size of N=20000 and N=10000

Figure IV-1 Estimates of $\widehat{\Gamma_1^X}(t)$ and $\sum_{t_j \le t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$ for a single simulation of setting 15 where N=20000 (left) and N=100000 (right)

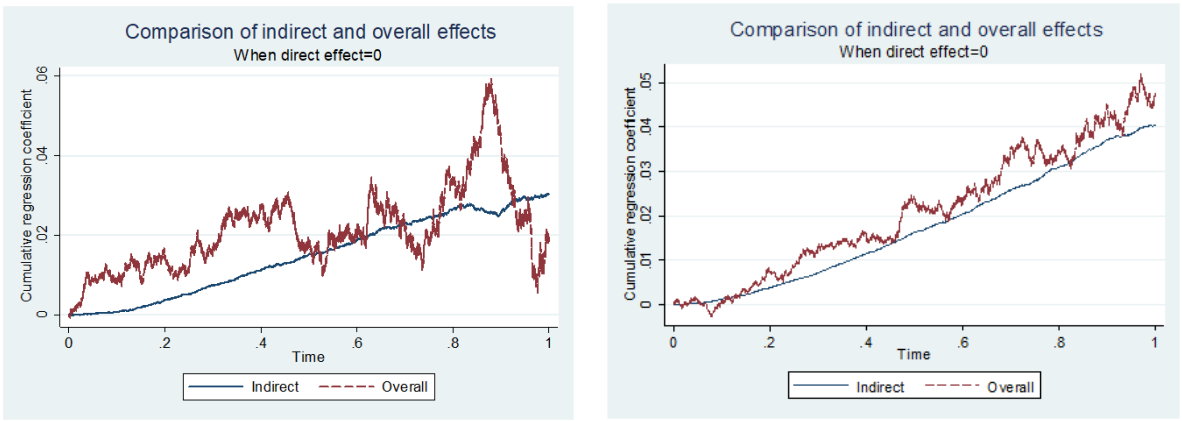

Figure IV-1 demonstrates the high variability in additive hazards model estimates of $\widehat{\Gamma_1^X}(t)$ with the smaller sample size of N=20000, decreasing with a larger sample size of N=100000. As a consequence, agreement between $\widehat{\Gamma_1^X}(t)$ and $\sum_{t_j \le t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$ is greater with the larger sample size.

Figure IV-2 below shows estimates $\widehat{\Gamma_1^X}(t)$ and t $\sum_{t_j \le t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$ for a single simulation corresponding to simulation setting 23 (where there is no direct effect of X), with varying sample size of N=20000 and N=100000.

Figure IV-1 Estimates of $\widehat{\Gamma_1^X}(t)$ and $\sum_{t_j \le t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$ for a single simulation of setting 23 where N=20000 (left) and N=100000 (right)

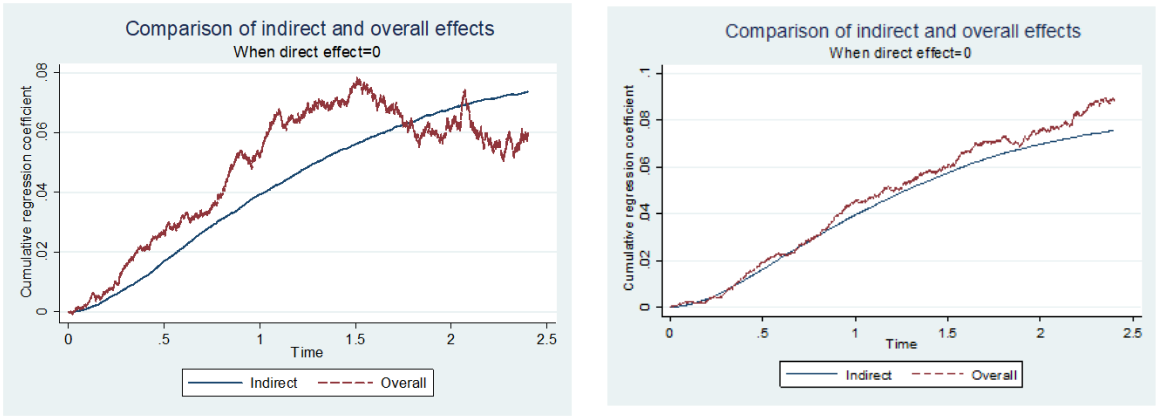

Figure IV-1 is another example of the lower variability in the estimates of $\widehat{\Gamma_1^{\times}}(t)$ that is associated with large sample sizes. It also demonstrates agreement between $\widehat{\Gamma_1^{\times}}(t)$ and $\sum_{t_j \le t_D} \widehat{\beta_1}(t_j)\widehat{\gamma_3}(t_j)$ when the sample size is large and $M_{bin}(t)$ events are not too sparse (right-hand panel). This agreement is expected, as both estimates are unbiased.