Flexible modelling for the cumulative effects of time-varying exposure, weighted by recency, on the hazard

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DEDICATION

Je dédie ma thèse à ma grand-mère, qui m' encourage et m'inspire.

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ABSTRACT

Many epidemiological studies assess the effects of time-dependent exposures, where both the exposure status and its intensity vary over time. The analysis of such studies poses the challenge of modelling the association between complex time-dependent drug exposure and the risk, especially given the uncertainty about the etiological relevance of doses taken in different time periods.

To address this challenge, I developed a flexible method for modelling cumulative effects of time-varying exposures, weighted by recency, represented by time-dependent covariates in the Cox proportional hazards model. The function that assigns weights to doses taken in the past is estimated using cubic regression splines. Models with different number of knots and constraints are estimated. Bootstrap techniques are used to obtain pointwise confidence bands around the weight functions, accounting for both the sampling variation of the regression coefficients, and the uncertainty at the model selection stage, i.e. the additional variance due to *a posteriori* selection of the number of knots.

To assess the method in simulations, I had to develop and validate a novel algorithm to generate event times conditional on time-dependent covariates and compared it with the algorithms available in the literature. The proposed algorithm extends a previously proposed permutational algorithm to include a rejection sampler. While all the algorithms generated data sets that, once analyzed, provided virtually unbiased estimates with comparable variances, the algorithm that I proposed reduced the computational time by more than 50 per cent relative to alternative methods.

I used simulations to systematically investigate the properties of the weighted cumulative dose method. Six different weight functions were considered. Simulations

showed that in most situations, the proposed method was able to capture the shape of the true weight functions and to produce estimates of the magnitude of the exposure effect on the risk that were close to those used to generate the data.

I finally illustrated the use of the weighted cumulative dose modelling by reassessing the association between the use of selected benzodiazepines and fall-related injuries, using administrative data on a cohort of elderly who initiated their use of benzodiazepines between 1990 and 2004.

ABRÉGÉ

Les études épidémiologiques évaluent fréquemment l'effet d'expositions complexes dont le statut et l'intensité varient avec le temps. L'analyse de ces études pose un défi particulier, celui de modéliser l'association entre ces expositions complexes et le risque, particulièrement lorsque la pertinence étiologique des doses prises lors de différentes périodes de temps est incertaine.

Pour aborder ce problème, j'ai développé une méthode flexible pour modéliser les effets cumulatifs d'expositions qui varient dans le temps, dans laquelle les expositions antérieures sont pondérées selon le temps écoulé depuis l'exposition, et cumulées pour obtenir une variable qui varie dans le temps dans un modèle de risques proportionels de Cox. La fonction qui pondère les doses prises rétrospectivement est estimée à l'aide de B-splines cubiques de régression. J'ai estimé des modèles avec des nombres différents de noeuds et de contraintes. Les intervales de confiance ponctuels pour la courbe de pondération ont été estimés à l'aide d'une méthode de *bootstrap* qui tient à la fois compte de la variance d'échantillonage des coefficients de régression et de l'incertitude découlant de la sélection de modèles, c-à-d. la variance additionelle découlant de la sélection *a posteriori* du nombre de noeuds.

Pour évaluer la méthode à l'aide de simulations, j'ai développé et validé un nouvel algorithme pour générer des temps d'événements conditionnels à des variables qui varient dans le temps et j'ai comparé cet algorithme avec les autres algorithmes décrits précédemment dans la littérature. L'algorithme proposé est une extension de l'algorithme permutationnel qui inclut une méthode d'échantillonage acceptation/rejet. Tous les algorithmes étudiés ont généré des jeux de données qui une fois analysés,

ont fourni des estimés de coefficents au biais minimal et dont la variance étaient semblables. Cependant, l'algorithme que j'ai proposé a réduit le temps de calcul de plus de 50 pourcent en comparaison avec les autres méthodes.

J'ai utilisé des simulations pour étudier de façon systématique les propriétés de la méthode de doses cumulatives pondérées. Six fonctions de pondération ont été envisagées. Les simulations ont démontré que dans la plupart des cas, la méthode que j'ai proposée a été capable de recapturer la vraie forme de la fonction de pondération et de produire des estimés de l'effet des doses cumulatives pondérées sur le risque qui étaient près de ceux utilisés pour générer les données.

Je conclus en illustrant la méthode de doses cumulatives pondérées afin de réévaluer l'association entre l'utilisation de quelques benzodiazépines et les blessures reliées aux chutes. Pour ce faire, j'utilise des données administratives sur une cohorte de personnes âgées qui ont initié un traitement de benzodiazépine entre 1990 and 2004.

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LIST OF ABBREVIATIONS

BIC	Bayesian information criterion
CNS	Central nervous system
CPU	Central processing unit
DDD	Defined daily dose
HR	Hazard ratio
IQR	Interquantile range
LRT	Likelihood ratio test
MR	Medical records
OR	Odds ratio
PA	Permutational algorithm
PARS	Permutational algorithm with rejection sampling
PH	Proportional hazards
PR	Prescription records
Q	Questionnaire
RMSE	Root mean squared error
SD	Standard deviation
TD	Time-dependent
TDC	Time-dependent covariate
WCE	Weighted cumulative exposure

CHAPTER 1
Preface

1.1 Format of the thesis

This manuscript-based thesis consists of a collection of three papers, for which I am the primary author, as well as separate chapters: Introduction, Literature review, Objectives, and Discussion. The three manuscripts are related and complement each other to form a cohesive body of research that addresses the objectives of the thesis.

The format of the papers respects the McGill University *Guidelines for Thesis Preparation*[1] . Each manuscript corresponds to a chapter of the thesis. A preamble to each of the manuscripts explains its rationale and its relation to the other manuscripts and to the objectives of the thesis. In addition, two of the three manuscripts are followed by a subsection that contains additional material that could not be included in the manuscript due to space limitation but is relevant to the thesis. All publications cited in each of the manuscript are listed in the References section, at the end of the thesis. Finally, the findings of the three manuscripts are discussed in the last chapter of the thesis.

This thesis has been typesetted with LaTeX within the open-source KDE Integrated Environment.

[1] `http://www.mcgill.ca/gps/current/programs/thesis/guidelines/preparation/`

1.2 Contributions of Authors

The topic, objectives and methods of my thesis was selected conjunctly with my thesis supervisor, Dr. Abrahamowicz. I conducted and wrote the literature review, which was refined in discussion with Dr. Abrahamowicz. I designed and wrote all the programs necessary to implement the new statistical methods proposed in manuscripts 1 and 2, to validate these methods in simulations, and perform all the data management and empirical analyses reported in manuscript 3.

I interpreted and summarized the results, both from the empirical analyses and simulations. I wrote the three scientific manuscripts and the other sections of the thesis. Dr Abrahamowicz provided guidance and feedback on the methods, analyses, design and interpretation of results and on the draft of all three papers.

The members of my thesis supervision committee, Dr. Pilote and Dr. Tamblyn, provided clinical and epidemiological expertise and guidance regarding the interpretation of the results. In addition, Dr. Tamblyn provided the data on benzodiazepine use in the elderly, which were analyzed in the third manuscript, using the methods developed in the second manuscript.

CHAPTER 2
Introduction

Epidemiological and medical research provides numerous examples of exposures that vary over time, both in terms of status and intensity. Examples of time and intensity varying exposures include histories of drug treatment in pharmacoepidemiology [1, 2], repeated measurements of laboratory tests in clinical research [3], socioeconomic position in social epidemiology [4], smoking patterns over time [5] in public health, or long-term exposure to a pollutant in occupational health and environmental epidemiology [6].

When modelling the association between complex patterns of exposure and the risk of an outcome, it is crucial to take into account the temporal changes in exposure status and intensity. Updating the exposure status in the model may be preferable to using the baseline values only, as the predictive ability of the baseline values may decrease over time [3]. More importantly, ignoring the timing of individual changes from the *unexposed* to the *exposed* status may lead to serious bias in the estimates of the association between the exposure and an outcome [7, 8, 9]. However, modelling the association between complex patterns of exposure and the risk of an outcome is challenging, especially given the uncertainty about the etiological relevance of exposures taken in different time periods [10, 11, 12, 13].

At the modelling stage, time-dependent covariates may be used to represent changes in exposure status and intensity [14, 15, 16]. Moreover, the specification of the time-dependent variable appropriate for a given analysis depends on the underlying assumptions about the association between exposure and the risk. A binary indicator

of current exposure status ignores the intensity of exposure, which, in the case of a true dose-response relationship, may lead to a less precise and efficient estimation and testing of the effect of exposure than current intensity of exposure [17]. On the other hand, both current measures of exposure ignore the past history of exposure and, thus, implicitly assume that exposure has no cumulative effects. Time-dependent variables such as duration of past exposure or cumulative intensity, defined as the sum of all past exposure intensities, take past exposures into account. However, these measures implicitly assume that all past exposures had the same effect on the current risk of an outcome, regardless of their timing.

These assumptions may likely be too stringent for many epidemiological and clinical applications. A more general exposure metric, the weighted cumulative exposure (WCE), has been suggested by both Breslow [18] and Thomas [19] and operationalized by Vacek [12]. It was suggested that past exposures should be weighted according to a function that assesses their contributions to the current risk, and the weighted exposures accumulated to create a cumulative weighted exposure metric. In most applications of the WCE, only a limited set of *a priori* specified parametric weight functions was considered and the weight function that had the best fit to the data was selected [12, 14]. However, the correct analytical form of the weight function is seldom known, and incorrect specification of the parametric form of the exposure metric may lead to invalid results [12, 20].

Alternatively, the weight function may be estimated using flexible techniques that avoid *a priori* assumptions about the analytical form of this function. A method has been proposed to estimate the weight function in the context of a case-control study, where only a single value of the weighted cumulative dose needs to be calculated for each subject at her or his outcome or index date [11]. Case-control studies are particularly useful when the data on the underlying cohort has not already been

collected and when it is more efficient to collect information on a sample of the cohort only [21]. In many circumstances, studies are based on cohorts that have already been assembled, such as administrative databases for pharmacoepidemiology [22]. Consequently, it might be more straightforward to analyze these data with survival models with time to event models, specifically developed for prospective designs, such as the Cox proportional hazards model [23, 24, 25, 26]. To date, no parametrization or estimation techniques have been suggested to estimate the effect of a time-dependent WCE in the Cox proportional hazards model.

The primary objective of this thesis is to develop a method for flexible estimation of the cumulative effects of time-varying exposures in Cox proportional hazards analyses of time-to-event data, while taking into account the timing of the exposure. I will develop a weighted cumulative exposure metric (WCE) that assigns different weights to past exposures according to their importance in explaining the current risk of an event. The WCE will be incorporated in a Cox proportional hazards model and the function that assigns weights to past exposure will be estimated using cubic B-splines, which avoid the need for *a priori* assumptions regarding the shape of the weight function. Modelling the WCE in the Cox model poses specific analytical and computational challenges related to changes over time in both the patterns and intensity of exposures and their recency, i.e. the distance in time from the current date. The latter implies that the relative importance of the exposure on a given date changes across risk sets.

I will use simulations to investigate and validate the properties of the proposed estimates. However, to date there is a lack of validated, efficient algorithms for generating event times conditional on complex time-varying exposures [27, 28]. Therefore, to be able to carry out the necessary simulation studies, I will extend and validate the use of the permutational algorithm, originally proposed to simulate event times

conditional on non-proportional hazards [29], to generate event times conditional on time-dependent covariates.

Once the WCE method is validated, I will then illustrate the use of this method to re-assess the associations between exposures to several benzodiazepines and fall-related injuries in the elderly. Benzodiazepine-specific analyses will be conducted to gain insights about the mechanisms that link individual patterns of use of particular benzodiazepines with fall-related injuries.

CHAPTER 3
Literature review

This thesis involves three major components: (1) the development of a new method for the flexible modelling of the cumulative effects of time-varying exposures, weighted by recency, in the Cox proportional hazards model, (2) the development of tools for validating and assessing the performance of this new method through simulations, and (3) a real-life application of the method to re-assess the association between different benzodiazepines and fall-related injuries in the elderly.

The literature review contains five separate sections, each summarizing selected literature relevant for one of the three components of the thesis. Section 3.1 presents the proportional hazards model for the analysis of time-to-event data. Section 3.2 describes selected techniques for flexible modelling of functional relationships. Section 3.3 provides an overview of the approaches used to model time-dependent exposures in epidemiology. The literature review ends with section 3.4, which summarizes the results and the methods used in published studies on the association between benzodiazepines and fall-related injuries in the elderly.

3.1 The proportional hazards model

The semi-parametric version of the proportional hazards (PH) model, proposed by Cox in 1972, is used extensively to investigate the association between covariates and time-to-event in prospective studies [30, 31]. Before describing the PH model, I will first introduce the basic concepts and notation of survival analysis.

3.1.1 Concepts and notation of survival analysis

Let X be a random variable describing the event times of a cohort of n subjects. $S(x)$ is the survival function that represents the probability that an individual survived past time x, i.e.

$$S(x) = Pr(X > x) = \int_x^{\infty} f(v)dv \tag{3.1}$$

with f the probability distribution function of the event times.

An important concept in survival analysis, that is also central to the PH model, is the notion of hazard function. The hazard function can be viewed as the instantaneous risk of an event at time x and is defined as

$$h(x) = \lim_{\Delta x \to 0} \frac{P(x \leq X < x + \Delta x | X \geq x)}{\Delta x}. \tag{3.2}$$

The associated cumulative hazard function, $H(x)$ is defined as:

$$H(x) = \int_0^x h(v)dv \tag{3.3}$$

The survival function $S(x)$ can conveniently be written either in terms of the hazard function $h(x)$ or the cumulative hazard function $H(x)$. For continuous X, the hazard can be expressed as

$$h(x) = \frac{f(x)}{S(x)} = \frac{-d\ln(S(x))}{dx}. \tag{3.4}$$

It follows from (3.3) that

$$H(x) = \int_0^x h(v)dv = -\ln[S(x)] \tag{3.5}$$

and thus that

$$S(x) = \exp[-H(x)] = \exp\left[-\int_0^x h(v)dv\right]. \tag{3.6}$$

However, because of limited duration of follow-up, sample attrition, and competing risks, event times may either be observed or censored (unobserved). Right-censoring occurs if subjects are lost to follow-up or reach the end of the study without experiencing the event. In such situations, the censoring time is shorter than the event times and thus the event times are at the right of the censoring times. Let C denote the censoring time and assume it has a cumulative distribution G(C). Under right-censoring, the *observed* event times can be written as as $T = \min(C, X)$. In addition, based on the comparison of C and X, we can construct an indicator of non-censoring that takes the value of 1 only if the event for individual i is observed during follow-up:

$$\delta_i = \mathbb{1}[X_i \leq C_i]. \tag{3.7}$$

Otherwise, $\delta_i = 0$. Given the distribution of event times and censoring times, we can construct the likelihood of the data. In constructing the likelihood, we make the critical assumption that the censoring is random (or noninformative), which states that X and C are independent [1] . Consequently, we can write the likelihood as the product of the likelihood of all observations (δ_i, T_i), $i = 1, ..., n$ [31]. Subjects censored at time t_i $(\delta_i = 0)$ survived up to time t_i so that

$$Pr(T = t_i, \delta_i = 0) = S(t_i) \tag{3.8}$$

while for subjects who experienced an event at time t_i during follow-up $(\delta_i = 1)$,

$$Pr(T = t_i, \delta = 1) = f(t_i), \tag{3.9}$$

[1] If, as required later, the event times or the censoring times are conditional on a matrix of covariates Z then we need the censoring and event times to be conditionally independent given Z.

where f is the probability distribution function of the event times. Combining (3.8) and (3.9) for each single observation, the likelihood can be written as:

$$Pr(T = t_i, \delta_i) = [f(t_i)]_i^{\delta}[S(t_i)]^{1-\delta_i}. \tag{3.10}$$

It follows that for a random sample of n subjects, assuming independence of observations, we can construct the likelihood as

$$L(t, \delta) = \prod_{i=1}^{n}[f(t_i)]^{\delta_i}[S(t_i)]^{1-\delta_i}. \tag{3.11}$$

Finally, using equations (3.4) and (3.6), we can write $f(t_i) = h(t_i)S(t_i)$ and (3.11) can be rewritten as:

$$\begin{aligned} L(t, \delta) &= \prod_{i=1}^{n}[S(t_i)h(t_i)]^{\delta_i} S(t_i)^{1-\delta_i} \\ &= \prod_{i=1}^{n}[h(t_i)]^{\delta_i} S(t_i). \end{aligned} \tag{3.12}$$

3.1.2 Overview of Cox proportional hazards model

The proportional hazards model estimates how the hazard depends on a vector of covariates values Z:

$$h(t|Z) = h_0(t)\exp(\beta' Z), \tag{3.13}$$

where $h(t|Z)$ is the hazard at time t conditional on covariate vector Z, $h_0(t)$ is the baseline hazard corresponding to $Z = 0$, and β is the vector of associated regression coefficients, i.e. logarithm of hazard ratios associated with an unit increase in a given covariate [30, 31]. The PH model relies on the assumption that the independent variables act multiplicatively on the hazard function [32]. The PH model is considered semi-parametric because a parametric form is assumed for the covariate effects, while the baseline hazard is considered as a nuisance parameter in the estimation, and no parametric assumption about its form is imposed.

The model proposed by Cox [30] assumes proportionality of the hazards, that is the hazard ratio for two vectors of covariates values, Z_1 and Z_2 is given by:

$$HR = \frac{h(t|Z_1)}{h(t|Z_2)} = \exp(\beta'(Z_1 - Z_2)), \tag{3.14}$$

and is constant over time, so that under model (3.13), any two hazard functions are proportional to each other, regardless of the change in the absolute value of the hazard over time. Violations of the proportionality assumptions may lead to biased estimates [33]. Under noninformative censoring, non-proportionality of hazards will bias the regression estimates toward the null [34]. Furthermore, the model-based variance may not be asymptotically valid [33]. Several tests and corrections for non-proportionality of hazards, including the use of time-dependent covariates, have been proposed but are not discussed here [35].

The likelihood can be derived as a profile likelihood in which the baseline hazard is considered a nuisance parameter [36, 37]. Consider the likelihood based on equation (3.12), which assumes assumes noninformative censoring, and the definition of hazard given in (3.13), which is conditional on the vector of covariates Z. Then the likelihood L can be written as:

$$L(\beta, h_0(t)) = \prod_{i=1}^{n} h_0(t)^{\delta_i} [\exp(\beta' Z_i)]^{\delta_i} S(t_i|Z_i, \beta) \tag{3.15}$$

Now, using equation (3.6),

$$S(t_i|Z_i, \beta) = \exp[-H_0(t) \exp(t_i|Z_i, \beta)] \tag{3.16}$$

so equation (3.15) becomes

$$L(\beta, h_0(t)) = \prod_{i=1}^{n} h_0(t)^{\delta_i} [\exp(\beta' Z_i)]^{\delta_i} \exp[-H_0(t_i) \exp(\beta' Z_i)] \tag{3.17}$$

Consider the profile likelihood for $h_0(t)$ obtained by fixing β. When events do not occur ($\delta_i = 0$), the profile likelihood is maximized by setting $H_0(t) = 0$. This implies that times t at which no events occur do not contribute to the likelihood and can be dropped from the profile likelihood. In fact, the profile likelihood is better known as the partial likelihood, because it does not include the nuisance parameter that is part of the full likelihood [38, 39].

Now consider the case when $\delta_i = 1$. Let the D event times be indexed as t_j, $j = 1, ..., D$ and $h_0(t_j)$ be the corresponding values of the baseline hazard at those time. Then, using (3.17) the profile likelihood for $h_0(t)$ can be written as

$$L(h_0(t_1), ..., h_0(t_D)) \propto \prod_{j=1}^{D} h_0(t_j) \sum_{k \in R(t_j)} \exp(\beta' Z_k) \tag{3.18}$$

where $R(t_j)$ is the risk set at time t_j, the set of all individuals that were still at risk at time t_j, including those who had an event at time t_j. [2]

The maximum likelihood estimator of $h_{0i}(t)$ is given by:

$$\hat{h}_0(t_j) = \frac{1}{\sum_{k \in R(t_j)} \exp(\beta' Z_k)} \tag{3.19}$$

By substituting (3.19) in (3.15), we obtain an expression of the profile likelihood that does not depend on the baseline hazard $h_0(t)$:

$$L(\beta) = \prod_{j=1}^{D} \frac{\exp(\beta' Z_j)}{\sum_{k \in R(t_j)} \exp(\beta' Z_k)} \tag{3.20}$$

[2] When multiple events occur at the same time (ties), one can express the partial likelihood by considering the ties as distinct times each of which has a risk set, which is a valid approximation when ties are few [31]. Alternative methods are available (e.g. Efron [31]) but are not discussed here.

Iterative maximization of the likelihood can be used to estimate the β coefficients [31].

The estimates of β are asymptotically normal so Wald test may be used to test the null hypothesis that a component of the vector β is zero. For large n, the likelihood ratio test may be used to test the hypothesis that several components of the β vector are zero by comparing model M_1, which is nested in model M_2 and computing the Likelihood Ratio Test (LRT) as:

$$LRT = 2(LL(M_2) - LL(M_1)) \tag{3.21}$$

and compare it with the critical value taken from a χ^2 distribution with degrees of freedom given by the difference in the number of parameters in the two models.

3.1.3 The counting processes formulation of the proportional hazards model

The PH model can accommodate time-dependent (TD) covariates, i.e. covariates that change in status or intensity over time [30]. Modelling of TD variables will be covered in section 3.3 but their inclusion in the PH model is discussed here.

Consider the following model that include a TD covariate $Z(t)$:

$$h(t|Z(t)) = h_0(t)exp\Big[\beta' Z(t)\Big]. \tag{3.22}$$

In order to estimate the PH model with TD covariates, it is helpful to describe the PH within the general framework of models for counting processes developed by Aalen and developed by Anderson and Gill for survival analysis [40, 41].

Consider $N_i(t)$, a process that counts the number of *observed* failure(s) of each subject $i, i = 1, ..., n$, up to time $t, t \geq 0$. The counting process $N_i(t)$ is a step function with $N_i(0) = 0$. Let $Y_i(t)$ be a process that indicates whether the individual i is at risk at time t, that is , $Y_i(t) = \mathbb{1}[T_i \geq t]$. Then, $N_i(t)$ has an intensity function

$\lambda_i(t)$, that represents the probability of an event occurring in the interval $(t, t+\Delta]$:

$$\lambda_i(t) = Y_i(t)\alpha_i(t) \tag{3.23}$$

where

$$\alpha_i(t) = \lim_{\Delta \to 0} \frac{Pr[N_i(t+\Delta) - N_i(t) = 1 | Y_i(t) = 1]}{\Delta} \tag{3.24}$$

is analogous to the hazard in (3.2). The process $N_i(t)$ is a Poisson process with rate $\alpha_i(t)$.

If $\alpha_0(t)$ is left unspecified, then we obtain the so called Anderson and Gill generalization of the PH model [42]:

$$\alpha(t) = \alpha_0(t) exp(\beta' Z). \tag{3.25}$$

Expressing the PH model as a counting process facilitates the inclusion of TD covariates. The data for a single subject are expressed as multiple observations (or multiple rows in the covariate matrix Z), each of which describing the interval time $[t_1, t_2)$ for which the TD covariates are constant.

The naive variance estimate of $\hat{\beta}$ in the PH model assumes that observations are independent [31]. However, in the counting process version (3.25), observations belonging to the same individual i are not independent of each other, so a robust procedure must be used to obtain a variance estimate of $\hat{\beta}$ that takes this clustering into account [41]. Robust standard errors for $\hat{\beta}$ can be obtain using grouped jackknife techniques [41]. Let $\hat{\beta}_{-i}$ be the vector of maximum likelihood estimates of the vector β obtained from a dataset from which *all* the observations pertaining to individual i have been removed. Let the matrix J be the difference between each of the $\hat{\beta}_{-i}$ estimates, $i = 1, ..., n$ and $\hat{\beta}$ the maximum likelihood estimate obtained from (3.25).

Then the variance of $\hat{\beta}$ is estimated using a sandwich estimator of the form [41]:

$$\widehat{Var}(\hat{\beta}) = (J - \bar{J})'(J - \bar{J}). \tag{3.26}$$

3.2 Flexible modelling of functions

In this section, I discuss selected methods for flexible modelling functions $f(x)$ of a continuous variable x in regression analysis. Common examples of a function to model are those of the relationship between a continuous covariate and an outcome [20, 43]. In survival analysis, flexible statistical methods have been used to model flexible functions of time representing either the hazard [44, 45] and density functions [46], or the time-dependent hazard ratio [47, 48, 49].

For simplicity, in this review, I focus on the estimation of the relationship between x and y, which is represented with the smooth function f, such that

$$y = f(x) + \epsilon \tag{3.27}$$

In some specific settings, theoretical knowledge allows the use of a fully parametric model where the functional form of $f(x)$ is explicitly specified [50], e.g. in pharmacokinetics models of drug half-life elimination. In such parametric regression models, $f(x)$ is specified *a priori* and the task of the data analyst is limited to the estimation of its parameter(s) [51].

When the functional form of f is correctly specified, using a parametric model is both simple and efficient, because the number of parameters to estimate in the parametric model is smaller than in its nonparametric counterpart, and because the former avoids the risk of overfitting bias [52]. Another advantage of parametric models is that their estimation and inference can easily be done using straightforward methods based on their likelihood function [53].

However, although many parametric models may be robust to slight departures from their own assumptions [54], more severe departures will likely cause inconsistent parameters estimates, that is, estimates that do not converge to the true maximum

likelihood value [54, 52, 55]. Incorrect assumptions regarding the form of $f(x)$ may also lead to decreased power and/or incorrect etiologic conclusions [12, 20].

In applications of regression analysis, there is typically no biological model or *a priori* knowledge to guide the choice of a single functional form of $f(x)$. In such cases, it is possible to consider several models with different functional forms for $f(x)$ [12, 56] and to select the best model using a statistical criterion such as the Akaike information criterion (AIC) [57], the Bayesian information criterion (BIC) [58] or with other methods that are based on the residual analysis [59].

Alternatively, rather than specifying an explicit parametric form for $f(x)$, it is possible to represent $f(x)$ with more flexible methods that simply assume that $f(x)$ will be a smooth function of arbitrary shape [60]. The challenge is to choose a flexible method to model $f(x)$ and to decide how smooth the estimate should be [56]. Finding the functional form of $f(x)$ involves two competing aims: obtaining a good fit to the data while avoiding overfitting bias [61]. A model is overfitting the data when it becomes too dependent on the particular feature of the sample so that it produces an estimate of $f(x)$ that fluctuates too much or too rapidly to reflect the true form of f in the underlying population [61]. Models that are too flexible or too complex for the data will likely produce overfitting bias. As the complexity of a model increases, larger and larger amount of data are required to avoid unacceptably large increases in variance [51, 62]. In fact, this issue should be considered while keeping in mind the principle of Occam's razor, as expressed by Clayton and Hills: *when considering two explanations for a given problem, the simplest explanation consistent with the known fact should be preferred* [36].

In this section, I discuss several methods that model $f(x)$ smoothly, namely regression polynomial, fractional polynomials, regression splines and smoothing splines,

while highlighting some of their strengths and weaknesses. These methods were selected because of their use in epidemiology and clinical research [56, 49, 63, 64] and because they are available in most statistical software such as R, SAS, S and Stata [65, 66, 67, 68]. Due to space restrictions, the following overview represents a somewhat arbitrary selection of topics partly related to the relevance of specific issues of my thesis research.

3.2.1 Polynomial regression

Polynomial functions of the form

$$f(x) = \sum_{i=0}^{n} a_i x^i \tag{3.28}$$

where $n \in \mathbb{N}$, represents the degree of the polynomial, provide a simple method to represent functions [69]. The functions in the polynomial basis x^i, $i = 1, ..., n$ are easy to compute from the data and the resulting polynomial (3.28) is linear in the parameters to estimate $(a_1, ..., a_n)$ [60]. However, polynomial functions have several limitations. First, the set of shapes that polynomials can represent is limited [70]. Polynomials of high order are required to model more complex shapes, which implies that a large number of parameters must be estimated. This may cause overfitting bias and unstable estimates if there are not enough data points [70]. Second, high order polynomials are particularly prone to local bias [60]: a change in the behaviour of $f(x)$ near a given point x^* may cause important changes around distant points x. This causes polynomials to be sensitive to outliers [71]. Finally, while polynomial models may give a good fit to the observed data, they have poor extrapolation properties, especially for higher order models [70]. Finally, for positive-valued argument x, polynomials of different orders are highly correlated. This makes this approach inefficient and increases the risk of near-multicollinearity.

Fractional polynomials

The fractional polynomial approach provides a more refined approach to the flexible modelling of functions [63].

A fractional polynomial of degree m is a function of $\phi_m(x, \beta, \boldsymbol{p})$ for $x > 0$, such that[3] :

$$\phi_m(x, \beta, \boldsymbol{p}) = \sum_{j=0}^{m} \beta_j H_j(x) \tag{3.29}$$

where for $j = 1, ..., m$:

$$H_j(x) = \begin{cases} x^{(p_j)} & \text{if } p_j \neq p_{j-1} \\ H_{j-1}(x) \ln(x) & \text{if } p_j = p_{j-1} \end{cases} \tag{3.30}$$

and where p_j and p_{j-1} belong to a vector of powers $\boldsymbol{p} \in \mathbb{R}$, and $\boldsymbol{\beta} = \{\beta_0, ..., \beta_m\}$ is a vector of real-valued coefficients. If $p_j = 0$, then x^{p_j} in (3.30) is replaced by $\ln x$ [72]. Conditional on the values of m and $\boldsymbol{p}$, $\phi_m(x, \beta, \boldsymbol{p})$ is a linear function of $H_j(x)$ with coefficients $\boldsymbol{\beta}$ to be estimated.

In practice, polynomials of degree $m \leq 2$ are believed to be sufficient to model most applications [72]. Consequently, equations 3.29 can be conveniently re-written as two functions, $FP1(x)$ and $FP2(x)$:

$$FP1(x) = \beta_1 x^{(p_j)} \tag{3.31}$$

and

$$FP2(x) = \begin{cases} \beta_1 x^{(p_1)} + \beta_2 x^{(p_2)}, & \text{if } p_1 \neq p_2 \\ \beta_1 x^{(p)} + \beta_2 x^{(p)} \ln x & \text{if } p_1 = p_2 = p, \end{cases} \tag{3.32}$$

[3] If $x \leq 0$, a change in the origin $(x - \psi)$ or a more complicated quasi-linear transformation can be applied [72]

Proponents of this technique suggest using the set of powers:

$$p = \{-2, -1, -\frac{1}{2}, 0, \frac{1}{2}, 1, 2, 3\}. \tag{3.33}$$

Thus, in addition to the shape of conventional polynomials, fractional polynomials of degree m can represent curves with asymptotes, as well as curves with rapid curvatures [72].

The model building strategy involves finding the best fitting models for $FP1(x)$ and $FP2(x)$ using the deviance $D = -2 \times$ log-likelihood, with lowest deviance indicating a better fit [72].

Once the best models for $FP1(x)$ and $FP2(x)$ are selected, they are compared using a test where the best fitting model for $FP2(x)$ is preferred over the best fitting model for $FP1(x)$ if

$$D(FP1(x)) - D(FP2(x)) < \chi^2_{2,0.90} \tag{3.34}$$

The test in (3.34) has two degrees of freedom, respectively for the additional variable due to the use of $FP2(x)$ and the additional parameter p_2 to estimate.

In a similar fashion, one can test whether the best fitting $FP1(x)$ has a better fit than a straight line model by using comparing the difference in the deviance of the two models in a fashion similar to (3.34).

In cases where a subset of models have similar deviances and tests do not select an overall best-fitting model, the final choice of a model depends on the appearance of the curves in relation to the data and on *a priori* knowledge of the problem [72].

Fractional polynomials have the similar disadvantages than conventional polynomials, although often at a lesser extent: their lack of flexibility may lead to a poor fit and they are also prone to local bias because each function in the basis spans the entire range of argument values [63].

3.2.2 Regression B-splines

Regression B-splines is an alternative to the flexible modelling of functions. A regression B-spline function is a curve that is represented as a linear expression of a B-spline basis, which is a set of piecewise polynomials of degree p, each defined over a limited domain [73, 60]. A spline is formed of a sequence of adjacent polynomial pieces, each covering a limited interval of x values, which are joined smoothly at pre-specified points called knots. The smoothness of the spline is ensured because the polynomials and their first and second derivatives are constrained to be equal at the knots [45, 60]. For example, Figure (3–1) shows how a cubic B-spline (solid line) can be constructed from four polynomial pieces (dotted lines). The vertical lines indicate the knots where adjacent polynomials and their first and second derivatives are equal.

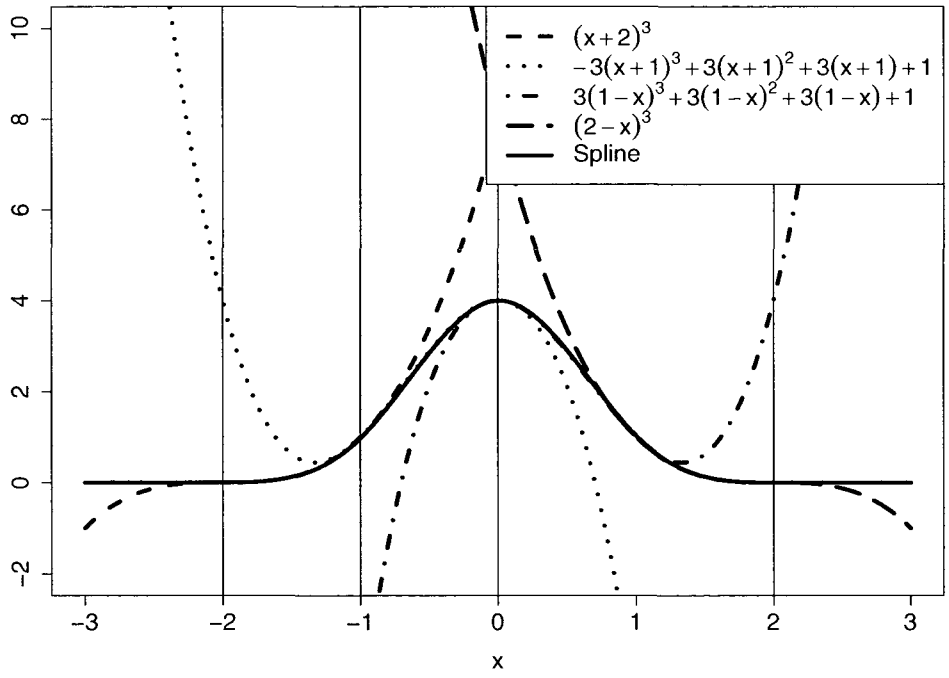

Figure 3–1: Four piecewise cubic polynomials forming a cubic spline (order 4)

A B-spline basis is a collection of such splines. For example, in Figure (3–2), a cubic B-spline basis is represented using dotted curves with arrows pointing at the knots.

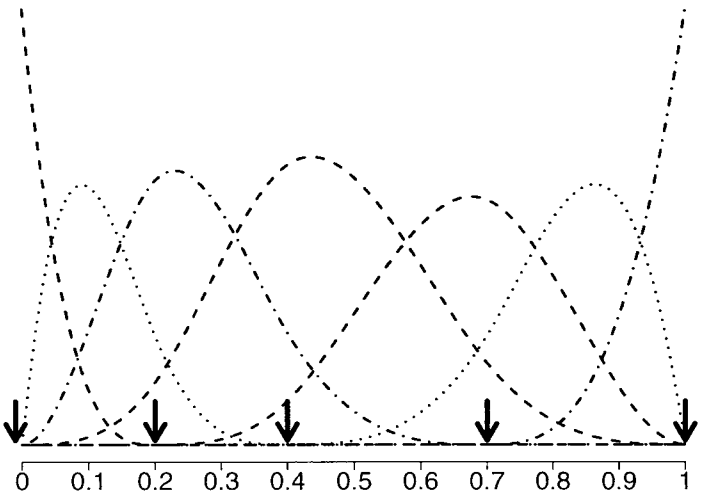

Figure 3–2: Cubic B-spline basis with arrows pointing at knots position

The B-spline basis can be constructed as follows. Consider a B-spline basis of order p defined over the interval $[a, b]$. Given m *interior* knot(s) k_j, $j = 1, ..., m$, such that $a < k_j < b$, the B-spline basis will consist of $m + p$ polynomials of degree p [74]. To construct such basis, we need to set p exterior knots on each side of the interval $[a, b]$ over which the spline basis is defined [11]. Assume, without lost of generality, that $k_{j-1} = a$, ... $k_{j-p} = a - p - 1$ and that $k_{j+1} = b$, ... $k_{j+p} = a + p - 1$. Then, the B-spline basis functions can be defined recursively as [11]:

$$B_{j,0}(x) = \begin{cases} 1, & \text{if } k_j \leq x < k_{j+1}, \\ 0 & \text{otherwise} \end{cases} \tag{3.35}$$

and

$$B_{j,p}(x) = \frac{x - k_j}{k_{j+p} - k_j} B_{j,p-1}(x) + \frac{k_{j+n+1} - x}{k_{j+n+1} - k_{j+1}} B_{j+1,p-1}(x) \tag{3.36}$$

where $a < x < b$.

Figure (3–3) shows example of B-spline bases of order 1-4 (degrees 0-3), each defined over the interval $[0, 1]$, and each using three interior knots at 0.2, 0.4, and 0.7. Basis functions of degree 1 are step functions and degree 2 are broken lines, which ensure continuity of the function but not of its derivatives. The first and second derivatives of bases of degree 3 are continuous.

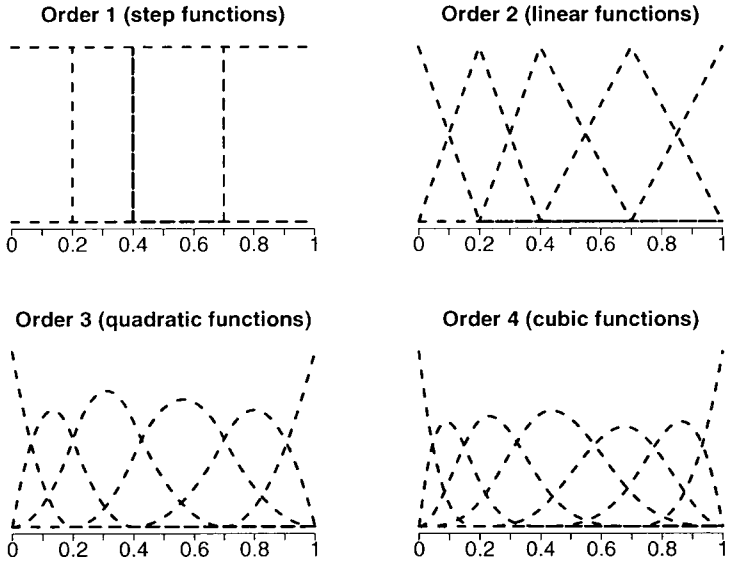

Figure 3–3: B-spline basis functions of order 1 to 4 with interior knots at 0.2, 0.4, and 0.7

Given pre-specified the B-spline basis, the spline function $f(x)$ is defined as a linear combination of the basis functions:

$$f(x) = \sum_{j=1}^{m+p} \alpha_j B_j(t) \tag{3.37}$$

where α_j are coefficients that need to be estimated. Figure (3–4) shows the spline functions associated with each of the B-spline bases of Figure (3–3) for arbitrary[4] values of α_j. Functions obtained from quadratic and cubic B-spline bases are smoother than those obtained with the basis of order 1 or 2 and are, therefore, more clinically plausible.

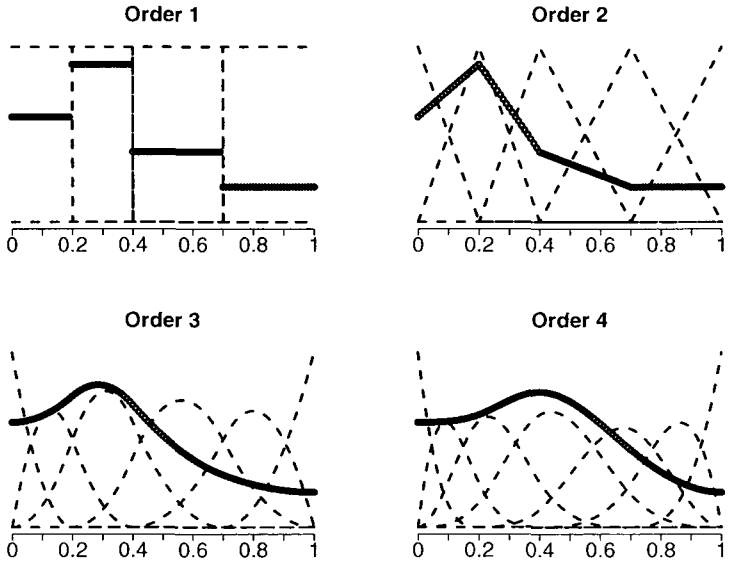

Figure 3–4: Spline functions associated with the bases in Figure (3–3)

Choice of the number and location of knots

Given the pre-specified order of the B-spline basis, the flexibility of the estimated spline function depends on the number of knots selected, with a larger number of knots leading to a greater flexibility [60]. While there is no theoretical basis for selecting a specific number of knots, parsimony is often preferred because the variance

[4] Values of α_j for the bases of order 1 to 4 were, respectively: $\{0.6, 0.9, 0.4, 0.2\}$, $\{0.6, 0.9, 0.4, 0.2, 0.2\}$, $\{0.6, 0.6, 0.9, 0.4, 0.2, 0.2\}$, $\{0.6, 0.6, 0.6, 0.9, 0.4, 0.2, 0.2\}$.

of the estimated spline function and the risk of overfitting increases with the number of knots [73]. In practice, up to 5 knots are deemed sufficient to model most nonlinear functions of interest [75].

In settings where there is some prior information on the function to model, for example when modelling the change in the incidence of a disease following the introduction of a new treatment, knots may be placed where the estimated curve is expected to show more curvature [73]. In most settings, however, the interest is in the general shape of the curve and not the positions of the knots [73]. In these cases, interior knots can be placed at equal distances over the interval over which the spline basis is defined. Alternatively, the interior knots k, $k = 1, ..., K$ can be placed at the $\frac{k}{K+1}$ quantile of the distribution of x [45]. This approach ensures that each segment of $f(x)$ has comparable support from the data [45]. Then, several models with different number of knots can be estimated and compared using criteria such as the AIC or BIC to select the appropriate number of knots, and thus flexibility, for the problem at hand [45, 11].

An alternative is to consider the knot location as an additional meta-parameter that needs to be estimated. The main issue with doing so is that knots enter into the regression problem in a nonlinear fashion, giving rise to all the known problems of estimation and inference about models that are nonlinear in their parameters [76]. Furthermore, methods that attempt to estimate the number and position of knots are quite computer-intensive and require specialized software [73].

Other regression spline bases

The previous section focused on B-spline basis but several other basis options exist for regression splines [71, 60]. One option is the truncated power basis, which

is based on the truncated power functions of order p defined as [71]:

$$(x - k_j)_+^p = \begin{cases} (x - k_j)^p & \text{if } x > k_j, \\ 0 & \text{if } x \leq k_j, \end{cases} \tag{3.38}$$

where k_j are the knots. For a given set of knots, more coefficients need to be estimated for the truncated power basis than for the B-spline basis [77]. In addition, B-spline bases have a better numerical stability than truncated power bases because of the collinearity between truncated power functions [78].

Another useful basis is the M-spline basis, which, like the B-spline basis, can be defined recursively [60]. Each M-spline of degree m has the properties of a probability density function over the interval between the knots k_j and k_{j+m}, is positive and satisfies the normalizing property that [60]

$$\int_{k_j}^{k_j+m} M_j(t)dt = 1. \tag{3.39}$$

Therefore, by constraining the spline coefficients α_j in $\sum \alpha_j M_j(t)$ such that, $\alpha_j > 0$ and $\sum \alpha_j = 1$, the resulting spline estimate also satisfy the properties of a density function [79]. The main difference between the M-spline and B-spline bases concerns the way they are normalized.

In some applications, the estimated function should be constrained to monotonicity, while their other properties are unknown. For such situations, Ramsay proposed the I-spline basis, whose basis functions are obtained by integration of the M-splines:

$$I_j(x) = \int_{k_j}^{k_j+m} M_j(t)dt. \tag{3.40}$$

Because each M-spline is positive over its entire support interval, its integral, the I-spline, is a monotonically increasing function of the argument t [60].

Smoothing splines

An alternative approach to spline modelling involves smoothing splines. The level of smoothness of regression spline estimates is controlled by the number and location of their knots [77], while for smoothing splines, control over the smoothness of the estimated curve is done by adding a penalty term to the regression equation [80].

Suppose that the relationship between y_i and x_i, $i = 1, ..., n$ is such that $y_i = f(x_i)$, and we want to estimate the functional form of f as in equation (3.27). For simplicity, assume that both x and y are continuous, and that their relationship is estimated through least squares [61]. The estimate that minimizes

$$\sum_{i=1}^{n}\Big[y_i - f(x_i)\Big]^2 \tag{3.41}$$

will be a jagged curve that interpolates the data, which is unlikely to represent the reality and will be seriously affected by overfitting bias [80]. To impose some smoothness on the $\hat{f}(x)$, the estimate of $f(x)$ a roughness penalty term λ is added to (3.41), so that the criterion to minimize in the estimation becomes [80] :

$$\sum_{i=1}^{n}\Big[y_i - f(x_i)\Big]^2 + \lambda \int \Big[f''(z)\Big]^2 dz. \tag{3.42}$$

Indeed, the integral of the second derivative of $f(x)$ is a measure of rapid local variations [61], and penalizes models that fluctuate too much [80]. A linear estimate has $[f''(x)]^2 = 0$, as its second derivative is 0 for all values of x, while nonlinear curves have $[f''(x)]^2 > 0$. While other forms of penalty terms have been proposed, $\int \Big[f''(z)\Big]^2 dz$ is commonly used [61, 80]. Reinsch has showed that $\hat{f}(x)$ obtained from minimizing (3.42) is a cubic spline with knots at the observed points x_i and that $\hat{f}(x)$ will be linear outside the range of the data [61].

The coefficient λ is the smoothing parameter that controls the size of the smoothness penalty imposed [20]. In fact, $\lambda \to \infty$ leads to a straight line estimate of $f(x)$ while $\lambda = 0$ provides an unpenalized spline estimate that interpolates the data [80]. The smoothing parameter λ can be selected *a priori* by the user [20] or estimated [80].

A common method to estimate the value of λ is cross-validation [61]. The general idea is to remove a datum $\{x_i, y_i\}$ from the dataset used for estimation and find the value of λ such that the corresponding $\hat{f}(x_{-i})$ is the best predictor of y_i [61]. This is done in turn for each i, $i = 1, ..., n$, and the estimate of λ is found by minimizing the cross-validation score [61]:

$$XVSC(\lambda) = \frac{1}{n}\sum_{i}^{n}\left[y_i - f_{\lambda}^{-i}(x_i)\right]^2. \tag{3.43}$$

Cross-validation techniques such as (3.43) may be computationally cumbersome [80]. An alternative form of (3.43), the general cross-validation criterion, along with numerical approximation algorithms, have been suggested to make the cross-validation process less computationally-intensive [61].

3.2.3 Properties of regression splines versus other flexible modelling methods

Modelling a function $f(x)$ using regression B-splines may offer several advantages. First, the fact that splines are linear in the coefficients to be estimated implies that standard methods of estimation and inference are implemented in commonly used statistical software packages [73]. Second, regression splines are less sensitive to local bias than polynomials or fractional polynomials [60, 72]. This arises from the property that each of the B-spline basis of order m functions B_j is nonnegative only between the knots k_j and k_{j+m}, and zero outside this interval. This implies that a change in the coefficient α_j of the basis function B_j in (3.37) will only affect $f(x)$ within the interval $[k_j, k_{j+m}]$ [60]. Thus, outliers have a more local effect on the

splines than on polynomials, because they will only affect the spline estimate over a limited interval [71]. Third, regression spline functions can easily be constrained at their boundaries [60]. For example, a cubic spline function can easily be constrained to smoothly go to zero at the right-hand-side boundary of its support interval by setting the coefficients α_{m+3} and α_{m+3} in the spline function equation (3.37) to zero. Alternatively, one can force a spline function to be linear in the tails where there is less data and where the unconstrained spline estimates are quite unstable [64].

On the other hand, a disadvantage of regression spline modelling is that the fit of the model depends on the number and the position of knots [56]. Finally, smoothing splines are more flexible locally than regression splines. However, the estimation and inference in regression spline models are more straightforward than for the smoothing splines, which require a penalized maximum likelihood estimation [80]. Indeed, once the number of knots and their position is selected, the regression spline function becomes a linear combination of known B-spline basis functions, which avoids the cross-validation process required to select the value of the penalty parameter for smoothing splines [60].

3.3 Modelling time-dependent exposure

3.3.1 Time-dependent exposure

Many exposures in epidemiology vary with time, both within and across individuals, whether in terms of duration of exposure, pattern of changes in exposure intensity over time, or time of exposure initiation [19]. For example, Bartlett *et al.* assessed the 5-year patterns of use of benzodiazepine in the elderly in Québec, and observed a large individual variability in the number of periods of uninterrupted use, the average duration of uninterrupted use, the average duration of interruptions between periods of use, and of the patterns of change in dose over time [2]. Indeed, time-related factors, if modelled appropriately, may provide insights regarding the etiology and mechanisms of health-related outcomes [19].

In addition, in some settings, ignoring the time-varying aspect of an exposure may create bias in its association with an outcome, which may be as severe as reversing the association [3, 7, 8, 9]. An example of this is immortal time bias in cohort studies in which subjects intiate their exposure at different times during the follow-up [81]. If a fixed-in-time binary indicator is used to classify subjects into *exposed/unexposed* groups, irrespective of when they started their exposure, the individual person-times of exposure will not be accounted for properly [9]. Specifically, the period of time between the beginning of follow-up and the beginning of exposure will be wrongly classified as time exposed, and the lack of events during this time period will be unduly attributed to the effect of the exposure on the time to event [9, 7, 8]. If this is not taken into account in the analysis, then the survival time of exposed will be artificially large, which may create a spurious protective effect of the exposure [9].

The use of time-dependent (TD) variables, for which the status or the intensity of the exposure is updated at each time t, may prevent such biases [8, 16]. In many

cases, however, the time-dependent variables used is restricted to a binary indicator of the status of exposure, which may cause loss of power and residual confounding [82]. Moreover, when included in a model, TD variables such as the intensity of exposure, $x(t)$, or an indicator of the state of exposure, $\mathbb{1}[x(t)]$, assume that the effect of exposure does not accumulate over time. Alternatively, measures like the cumulative intensity $\int_0^u x(t)dt$ or the cumulative duration of exposure $\sum_0^u \mathbb{1}[X(t)]dt$ assume that exposures cumulate over time, at a constant rate. Equivalently, using these cumulative measures in a model implies that the timing of exposures that occurred in the past is irrelevant to how the current cumulative exposure affects the current response variable.

Several methods have been proposed to model multiple features of time-varying exposures such as duration, intensity and potential cumulative effects [12, 83]. I first present the so called *sliding time window methods*, and exploratory method to investigate the potential cumulative effects of time-varying exposures [83]. I then discuss two exposure metrics that were proposed to represent exposures that are both intensity and time-varying [12].

3.3.2 Sliding time window method

Hauptmann *et al.* proposed an exploratory method to investigate the potential cumulative effects of a time-varying exposure $x(t)$ on an outcome y in a case-study [83]. The method consist in estimating a series of models of the form

$$logit[Pr(y_j = 1|x(t), t \in [0, T])] = \beta_0 + \beta_1 \int_0^T x(t)dt + \beta_2 \int_{c-\frac{k}{2}}^{c+\frac{k}{2}} x(t)dt. \quad (3.44)$$

The two variables in (3.44) are cumulative variables that sum exposures over different time windows. The first variable sums exposures over a time windows corresponding to the study follow-up $[0, T]$, while the second cumulative variable sums exposures over a shorter time window, centered at c and of width k. A series of models are

estimated, each of which corresponding to a different time window $c \pm \frac{k}{2}$ for the second variable. As a result, the time window covered by different models covers different sections of the follow-up time, hence the name of *sliding window method.*

The fit of the models with different boundaries $c \pm \frac{k}{2}$ are compared using statistical criteria to obtain insight on the effect of exposure on the risk at different periods of time. For simplicity, equation (3.44) only includes the variables representing the time-dependent exposure of interest, but covariates may easily be added to the model. Simulations show that the method is rather robust to random measurement error in the pattern of exposure [83]. The principal drawback with this method is that it assumes that exposures cumulate over time, at a constant rate.

3.3.3 Weighted cumulative dose metric

To alleviate this assumption of exposures cumulating at a constant rate, several authors have proposed a more general cumulative exposure metric that takes the timing of the exposures into account. Indeed, in separate publications, Breslow, Vacek and Thomas discuss the concept of a time weighted cumulative exposure $z(u)$:

$$z(u) = \int_0^u x(t)w(u-t)dt, \tag{3.45}$$

where $x(u)du$ represents the additional exposure received during a time interval $[u, u+du]$ and $w(u-t)$ is a function that assigns weights to exposure in the past [18, 19, 12]. If exposure is measured at discrete time intervals, such as days or weeks, then the WCE can be expressed as:

$$z(u) = \sum_{t=1}^{u} w(u-t)x(t) \tag{3.46}$$

This metric is flexible in the sense that it allows the user to specify how exposures accumulate over time thought the choice of the weight function w. In its simplest

case, where $w(u-t) = 1$, (3.46) is equivalent to the unweighted cumulative intensity discussed earlier.

The exposure metrics in (3.46) require the user to define the form of the weight function w. The weight function w can be selected *a priori* based on specific pathophysiologic models, that is, parametric models that are derived from theory. Examples of weight functions are the exponential weight function $w(u) = 1 - \exp(-\lambda u)/u$ used by Berry *et al.* to model how asbestos fiber is eliminated from the lung at rate λ [84]. Lundin *et al.* used a lognormal distribution to weight cumulative exposure to radiation in uranium miners [85]. However, the validity of such analysis depends greatly on that of the underlying biologic models [86].

Alternatively, several different parametric form of w may be estimated in a model and compared with a statistical criterion that indicates the model with the best fit. For example, Vacek used a set of weight functions in her analysis of the relationship between exposure to asbestos and lung cancer in Canadian asbestos workers [12]. She tested four time weight functions: a lagged weight function where exposure previous to time C has no effect on the risk of outcome, but exposures at times after C have all equal weights, an exponential function, a Gaussian cumulative distribution, and a Gaussian density function [12]. Since all the models considered had the same number of parameters to estimate, they were compared using the deviance statistics. In the same spirit, in their analysis of the association between time-dependent use and dose of specific benzodiazepines and fall-related injuries in the elderly, Abrahamowicz *et al.* [14] used two half-Gauss curve functions:

$$w(u) = \exp\left[\frac{-1}{2\sigma}u^2\right], \tag{3.47}$$

with σ selected *a-priori* to reflect either the 4-day half-life of benzodiazepine, $w(4) = 0.5$, or the clinical recommendation that benzodiazepine consecutive use should not

exceed 30 days, $w(30) = 0.5$ [14]. Models of different dimensions were compared using the AIC criterion [14].

A limitation of these approaches is that they require *a priori* selection of weight functions. Yet, the correct analytical form of the weight function is seldom known, while incorrect specification of the parametric form of the exposure metric may lead to invalid results [20, 12].

The third approach to select a functional form for the weight function w consists in estimating the functional form of the weight function from the data, using flexible non- or quasi- parametric methods. Hauptmann *et al.* suggested estimating the weight function using constrained regression splines within a generalized linear model, which required a constrained maximization algorithm to jointly estimate the regression parameters and the coefficients of the spline basis [11].

3.4 Benzodiazepines and fall-related injuries

This section of the literature review focuses on the epidemiological studies on the association between the use of benzodiazepines and fall-related injuries. The pharmacology and pharmacokinetics of benzodiazepines are briefly presented. The methodology and results of studies on the association between benzodiazepines and fall-related injuries are then summarized and discussed.

3.4.1 Pharmacology and pharmacokinetics of benzodiazepines

Benzodiazepines are drugs that inhibit or depress the central nervous system (CNS) via its major neurotransmitter, the GABA receptors (γ amino butyric acid)[87]. Benzodiazepines are prescribed to decrease the symptoms of anxiety or panic disorders, to treat insomnia, and to manage seizure disorders [88, 87]. However, benzodiazepines may cause adverse effects, mostly CNS-related, such as ataxia, dizziness, lightheadedness, drowsiness, weakness, and fatigue [87].

Currently, more than a dozen of different benzodiazepines are available for prescriptions [89]. Table 3–1 lists the benzodiazepines that are available in Canada [87]. The decision of which benzodiazepine to prescribe for a specific condition depends mainly on the pharmacokinetic profiles of the different products. Pharmacokinetics describes the way the body affects the action of the medication over time and includes properties such as the absorption, distribution, metabolism and excretion of a drug [87, 90].

All the benzodiazepines have a similar short absorption rate, which implies that the onset of the clinical effect of benzodiazepine is generally quick (0.5 to 4 hours after ingestion) [88]. However, once they are absorbed, different benzodiazepines will have different duration of action. The duration of action of a single dose depends on how the drug circulates in the body and penetrates tissues to act and on its rate of elimination [88]. As shown in Table 3–1, benzodiazepines can be classified in

Table 3–1: Selected benzodiazepines with their main indication and half-lives [87]

Generic	**Brand name**	**Anxiety**	**Panic**	**Insomnia**	**Seizure**	**Half-life** (hours)
		Long half-life				
Chlordiazepoxide	Librax	X				100
Clorazepate	Tranxene	X	X		X	100
Diazepam	Valium	X			X	100
Flurazepam	Dalmane			X		100
		Medium half-life				
Clonazepam	Rivotril				X	20-80
Nitrazepam	Mogadon			X	X	16-55
Alprazolam	Xanax	X	X			12-15
Clobazam	Frisium				X	10-46
Temazepam	Restoril			X		10-20
Lorazepam	Ativan	X			X	10-20
Bromazepam	Lectopam	X				8-30
Oxazepam	Serax		X			5-15
		Short half-life				
Triazolam	Halcion			X		1.5-5

short (1-5 hours), medium (6-90 hours), and long (> 90 hours) half-life categories [87, 91]. Half-life is defined as the time required for the concentration of the drug in the blood to decrease to half of its initial value. In fact, the accumulation rate varies inversely with the half-life, with shorter half-life benzodiazepines accumulating more rapidly then long half-life [88] products. For example, although diazepam has a long half life (100 hours) it has a rapid distribution from blood into fatty tissues, which implies that a single-dose effect will be short [92]. Lorazepam, on the other hand, has a shorter elimination half-life of about 15 hours, but its distribution from blood into fatty tissues is less rapid, and so an effective concentration may persist in the blood for many hours [92].

In the case of a therapy in which consecutive doses of benzodiazepines are taken, the drug will accumulate in the body until it reaches a steady-state plasma level [88]. It usually takes the equivalent to 4-5 half-life periods after the treatment initiation for benzodiazepines to accumulate to a steady-state level [88, 87]. However, the extent

or the amount of accumulation will depend on drug dosage and on the half-life of each benzodiazepines [88, 87].

There may be important variability in clinical effects of benzodiazepines because pharmacokinetics properties vary from an individual to another [88]. In addition, the clinical effects of a benzodiazepine do not necessarily vary in proportion to blood concentration of the drug when multiple doses are taken [88]. Tolerance may balance out drug accumulation in the blood. It should also be noted that pharmacokinetics are likely to be altered in the elderly because of the changes in organ function that occur with the aging process [93]. With increasing age, the liver size, and thus its activity, are decreased, delaying the extraction of drugs [93, 87]. As a result, the prolonged effects produced by long-term use of benzodiazepines may be stronger in the elderly than in younger users. In addition, by age 60, there is an exponential decline in the ability of the kidney to excrete toxic substances, which puts the elderly users at a higher risk of drug adverse events [93].

3.4.2 Summary of the methods and results of epidemiological studies of the association between benzodiazepine use and risk of fall-related injuries in the elderly

Benzodiazepine use is common in the elderly, with annual prevalence estimates ranging from 10% to 30% [94, 95, 96, 97, 98]. Reported use of benzodiazepines show important variation within and across individuals [99, 100, 2]. Elderly users also tend to use benzodiazepines more than once and for longer periods [99, 100, 2]. In a large cohort of new elderly users of benzodiazepines followed for up to five years, the average duration of an uninterrupted period of use of benzodiazepines was 75.5 days (SD 137.2), which is significantly longer than the recommended maximum of 30 days [2, 101]. Elderly users had, on average, three uninterrupted periods of benzodiazepine use (median of 2 periods, SD 3.3 periods) during the 5 years of follow-up [2]. In

addition, the likelihood of receiving a higher dose of benzodiazepine in a subsequent prescription increased with age [2].

Benzodiazepine use started to be linked to fall-related injuries in the late eighties, in studies assessing predictors of falls in the elderly [102, 103, 104, 103]. Over the last 20 years, two dozens observational studies were published on the topic (randomized control trials cannot be conducted for obvious ethical reasons). The review presented in this section is based on the 22 observational studies that reported adjusted measures of association of the association between benzodiazepine use and fall-related injuries in the elderly.

Early studies focused on the association between the *current* use of *any* benzodiazepine and the risk of falls or fractures. *Current users* were defined as having taken a dose of benzodiazepine or having a prescription of benzodiazepine when the fall occurred or at the index date. Table 3–2, at the end of this section, summarizes the design, sample size, measures of benzodiazepine use, outcome measures and results of theses studies. Many of these studies reported a statistically significant increase in risk of fall-related injuries in benzodiazepine users compared with non-users, with OR ranging from 1.34 to 2.05, irrespective of the type of outcome selected (fall[5] , hip fracture or femur fracture). However, an appreciable proportion of studies did not find any association between benzodiazepine use and the risk of falls in the elderly.

Several factors need to be considered in explaining the discrepancy in the early study results. First, the quality of assessment of exposure may have had an effect on the observed results. Studies either used questionnaires or prescription databases to assess the current use of benzodiazepine. Questionnaires are prone to recall bias,

[5] Fall was defined as an unintentional change in position resulting in coming to rest on the ground or other lower level.

which occurs when respondants incorrectly recall and assess their histories of drug use [105]. The degree of recall bias may be influenced by the frequency and duration of the drug use, the time since the last prescription was filled, the number of drugs used, the age, and the type of questions [106, 105]. While exposure assessed from medical or prescription records is not affected by patients recall, it may still be biased. Indeed, prescriptions records provide information on the dispension of the drug but not on the actual consumption of the medication [107]. These biases lead to exposure misclassification and induce bias [105]. In both cases if the misclassification in exposure is random, i.e. not related to the risk of fall-related injuries, then the measure of association will be biased towards the null [108]. Otherwise, the magnitude and sign of the bias will depend on the underlying mechanism. However, there were not systematic differences between the results of studies that used questionnaires versus prescription records to assess exposure to benzodiazepines, suggesting that the method of assessment, in and of itself, could not have explained the discrepancy in the results.

The second factor that needs to be considered is the number of falls assessed in each of the studies. A lack of statistical power can prevent a study from detecting a statistically significant association that is present in the data. However, this is not sufficient to explain why some studies did not detect an effect. In the studies summarized in Table 3–2, however, there were both small scale studies that detected an association [109, 104], and large scale studies that did not [110, 111].

Finally, it is possible that the assumptions underlying the choice of the measure of exposure that some of these studies used were not appropriate. Using a current use indicator of benzodiazepine makes three underlying assumptions about the effect of benzodiazepines. First, by combining all the benzodiazepines in one measure of exposure, one assumes that all the benzodiazepines have the same physiological

effect, irrespective of the differences in their pharmacokinetics properties such as their half-life. The studies considered in Table 3–2 did not investigate the same groups of benzodiazepines, which might have influenced the results if different benzodiazepines have different effects on the risk of falls.

Moreover, modelling exposure using a binary indicator of current use ignores the potential effect of the dose of the benzodiazepine on the risk of fall. If there is a dose-response relationship in the association between benzodiazepine use and fall-related injuries, then ignoring it by using an indicator of current can be seen as an extreme case of dichotomizing a continuous variable at the cutpoint of zero. Doing so leads to a decrease in precision and efficiency of the estimation in comparison to a parametrization in the continuous scale [112]. Simulations have shown that the loss in efficiency due to dichotomizing a continuous variable may be large [113, 112]. This may be a severe problem in studies that have low power [17].

In fact, modelling benzodiazepine use with a current use indicator ignores the history of prior use of benzodiazepine. Consequently, this approach assumes that there is no cumulative effect of using benzodiazepine over time, thus that the risk of fall associated with the exposure to benzodiazepine is acute or instantaneous. As discussed earlier, some benzodiazepines accumulate in the body [88], which can potentially lead to a cumulating effect. If it is the case, using an indicator of current use will bias the results because the *current users* category will combine both long term and short term users of the drug, whose risk of fall may be very different.

Later studies attempted to address each of these modelling pitfalls, although often in a different and separate ways. Several studies grouped the benzodiazepines in categories based on short versus long half-life (in general, the cutoff of >24 hours was used to indicate long half-life). These studies are summarized in Table 3–3. Results were again discrepant. Most studies found a higher risk of falls for users

of long half-life benzodiazepines, with OR associated with current use ranging from 1.45 to 2.18, [114, 115, 116, 117, 118] but other studies either did not find an effect even if they had a large sample size [110] or found a larger risk for the use of short half-life benzodiazepines [119, 120].

Five studies estimated separate effects of individual benzodiazepines, but still, there is a large difference across studies for the same benzodiazepines [117, 119, 121, 122, 123]. For example, the OR for Lorazepam, varied from 1.2 [123] to 5.5 [117]. When considered separately, the OR for short half-life products did not seem markedly smaller than that of long half-life benzodiazepines. However, a major issue with these results is that most of the benzodiazepine-specific analyses relied on a very small number of events and, thus, had very wide confidence interval. The study of Tamblyn *et al.* was the only study with large number of cases for most individual benzodiazepines and it reported some variations in ORs associated with current use of specific benzodiazepines [123].

A few studies investigated the effects of dose of benzodiazepine use on the risk of fall-related injuries by converting the dose into defined daily dose (DDD) equivalents [124, 110, 119, 118]. The defined daily dose (DDD) is a comparative unit of drug use, which is robust across therapeutic classifications, dosing forms, and populations [125]. These studies are summarized in Table 3–5. All but one of theses studies grouped the benzodiazepines together and found a dose-response pattern with higher dose associated with higher risk of falls [124, 110, 119]. However, it is unclear to what extent these results may be due to the differences in the effects of individual benzodiazepines.

A small number of studies assessed the impact of the timing of the benzodiazepine exposure on the risk of falls by categorizing subjects depending on when they used the drug and are summarized in Table 3–6. Ray and Neutel both found that

the likelihood of a fall was higher in the 1-2 weeks following treatment initiation than it was afterward [124, 121]. Neutel found an association between the duration of treatment and the risk of fall [121].

Tamblyn *et al.* estimated several benzodiazepine-specific Cox PH models that represented both the [123] current doses and past use of the drugs as time-dependent variables. Model 1 estimated the effects of current use of benzodiazepines. In addition to the current use indicators of Model 1, Model 2 included benzodiazepine-specific indicators of past use so that hazard ratio for current use represented the risk associated with periods of use compared with periods of non-use in persons previously prescribed the same benzodiazepine. Model 3 expanded Model 1 by including a standardized dosage so that HR for the indicator of current use represented the risk associated with the current use at a common mean dose, relative to non-use, assuming a common dose-response relationship for all benzodiazepines [123]. Finally, Model 4 estimated separate dose-risk relationships for each individual benzodiazepines. Out of the ten benzodiazepines considered, four had a statistically significant association with the risk of falls, a result that was robust across models 1 to 4 [123] . Two of these benzodiazepines had short half-life, suggesting that short versus long half-life was not an important factor in assessing the risk of fall associated with the use of a specific benzodiazepines. While Tamblyn *et al.* modeled the separate effects of current dose and of the past use of benzodiazepines, they did not investigate possible cumulative effects of exposure [123].

Finally, Abrahamowicz *et al.* used the weighted cumulative exposure framework (discussed in section 3.3.3 of the literature review) to reassess the associations between exposure to three benzodiazepines and fall-related injuries in the elderly within the Cox proportional hazards model [14]. Exposure to three different benzodiazepine

were modeled using a TD weighted cumulative exposure defined as:

$$z(u) = \sum_{t=1}^{u} w(u-t)x(t) \tag{3.48}$$

where $x(t)$ represents the dose of benzodiazepine taken on day t and $w(u-t)$ is a function that assigns weights to exposure in the past. The parametric form of the weight functions was defined *a priori* as:

$$w(u) = \exp(\frac{-1}{2\sigma}u^2). \tag{3.49}$$

Two versions of model 3.49 were considered with σ selected *a priori* to reflect either the 4-day half-life of benzodiazepine ($w(4) = 0.5$) or the clinical recommendation that benzodiazepine consecutive use should not exceed 30 days ($w(30) = 0.5$) [14]. Additional models, with exposure represented as (i) the weighted cumulative duration of treatment, which ignored the dose, and (ii) the current dose in addition to the the weighted cumulative duration of treatment, were considered and their fit was compared using the AIC criterion.

The results suggested a different mechanism linking the drug exposure and the risk of falls for each of the three benzodiazepines considered. For Temazapam, which had the shortest half-life (8-24 hours), the best-fitting model represented exposure using the current dose and the weighted cumulative duration with $w(30) = 0.5$. For Flurzepam, which was the benzodiazepine with the longest half-life (40-100 hours), the best model was the weighted cumulative dose with $w(4) = 0.5$. Finally, the third benzodiazepine considered, Nitrazepam (half-life of 20-40 hours), was better represented with the cumulative dose with $w(30) = 0.5$. Interestingly, for the three benzodiazepine considered, models that only included current use or current dose did not detect a statistically significant association with the risk of falls, which would suggest that the recent use of benzodiazepine is *not* relevant in the

current risk of falls. However, one limitation of this study, recognized by the authors, related to the *a priori* selection of parametric form of the weight function [14]. This *a priori* restriction does not allow an assessment of the validity of the modelling assumption that the impact of benzodiazepine exposure decreases monotonically with time since exposure. Moreover, incorrect specification of the parametric form of the exposure metric may lead to biased results, decreased power and/or incorrect etiologic conclusions [12, 20].

In conclusion, the studies reviewed clearly suggest an association between at least some benzodiazepines and fall-related injuries. However, it is still unclear whether this association is present for each benzodiazepine, and whether there is a systematic difference between products with short versus long half-lives. While studies suggest a dose-response relationship between current dose of benzodiazepine and the risk of fall, other suggest an effect of the duration of treatment or past exposure to benzodiazepines. Therefore, both dose and timing of use must be taken into account in the estimation of the risk of fall related to the use of benzodiazepines, and the possibility of a cumulative effect must be evaluated.

Table 3–2: Summary of findings on the association between benzodiazepine use (yes-no) and fall-related injuries in the elderly

Study	Country and time period	Sample size	Benzodiazepine Measure	Outcome measure	Results
Cohort studies					
Ray [124]	USA 1993-1996	2,510 3,706 falls in 1,544 p-y	Current Recent(last1-7days)[PR]	Fall [MR]	Current **1.44 (1.33-1.56)** Recent **1.23 (1.07-1.42)**
Ray [126]	USA 1993-1996	2,510 3,706 falls in 1,544 p-y	Current Baseline use [PR]	Fall [MR]	Current **1.44 (1.33-1.56)** Baseline 1.02 (0.95-1.10)
Ensrud [115]	USA 1992-1994	8,127 women 2,241 falls	Used in the past 2 weeks [Q]	Fall [Q]	**1.34 (1.09-1.63)**
Landi [116]	Italy 2000-2002	2,854 women 1,061 falls	Current [Q] + [MR]	Fall [Q]	**1.36 (1.08-1.71)**
Cummings [103]	USA 1986-1990	9,516 women 192 falls	Current [Q]	Hip fracture [MR]	HR **1.6 (1.1-2.4)**
Tromp [127]	Netherlands 1995-1996	1,285 428 falls	Recorded medication from container	Fall [Q]	**1.6 (1.1-2.2)**
Ebly [111]	Canada 1991-2001	2,035 486 falls	Current [Q]	Fall [Q]	No association
Chaimowicz[109]	Brazil 1998	161 27 falls	Use in the past year [Q]	Fall [Q]	Association with **p=0.05**

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Table 3–2 – continued from previous page

Study	Country and time period	Sample size	Benzodiazepine Measure	Outcome measure	Results
Case-control in the community					
Cumming [128]	Australia 1990-1991	209 cases 207 controls	Current [Q]	Hip fracture [MR]	1.55 (0.95-2.54)
Panneman [129]	Netherlands 1985-2000	9,081 cases 9,081 controls	Current [PR]	Fall [MR]	**1.6 (1.4-1.7)** 85+ **3.6 (2.9-4.5)**
Case-control in hospitals					
Stevens [102]	UK 1985	173 cases 143 controls	Current [Q] corroboted by physicians	Hip fracture [MR]	1.03 (0.60 -1.75)
Lichtenstein [104]	Canada	129 cases	Current	Hip fracture	**2.05 (1.05-3.77)**
	1976-1985	234 controls	[PR]	[MR]	
Pierfitte [122]	France 1996-1997	245 cases 817 controls	Current [Q]+ [PR] + Plasma	Hip fracture [MR]	[Q] 1.00 (0.92-1.09) [PR] 1.19 (0.88-1.63) Plasma 1.06 (0.78-1.43)
Nested case control					
Sgadari [110]	USA 1992-1996	9,752 cases 38,564 controls	Last 7 days [PR]	Femur fracture [MR]	1.09(0.98-1.20)

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Table 3–2 – continued from previous page

Study	Country and time period	Sample size	Benzodiazepine Measure	Outcome measure	Results
Herings [119]	Netherlands 1986-1992	493 cases 1,479 controls	Current Recent (last 1-365 days) [PR]	Femur fracture [MR]	Current **1.6 (1.2-2.1)** Former 1.1(0.8-1.6)
Wang [118]	USA 1993-1995	1,222 cases 4,888 controls	Current [PR]	Hip fracture [MR]	**1.47 (p=0.0001)**

1. Bold indicates statistically significant results at $\alpha = 0.05$.
2. The abbreviation [Q] indicates Questionnaire, [PR] Prescription Records, and [MR] Medical Records.
3. Reference is non-user unless stated otherwise.
4. Measures are OR unless stated otherwise.

Table 3–3: Summary of findings on the association between benzodiazepine use and fall-related injuries in the elderly, by half-life categories

Study	Country and time period	Sample size	Benzodiazepine Measure	Outcome measure	Results
Cohort studies					
Ray [124]	USA 1993-1996	2,510 3,706 falls in 1,544 p-y	Current [PR]	Fall [MR]	Short 1.15 (0.94-1.40) Medium **1.45 (1.33-1.59)** Long **1.73 (1.40-2.14)**
Ensrud [115]	USA 1992-1994	8,127 women 2,241 falls	Used in the past 2 weeks [Q]	Fall [Q]	Short 1.19 (0.92-1.54) Long **1.61 (1.17-2.2)**
Passaro [120]	Italy 1991-1993	7,908 174 falls	Current [PR]	Fall [MR]	Very short **1.9 (1.03-3.3)** Short **1.8 (1.2-2.8)** Long 0.8 (0.4-1.8)
Landi [116]	Italy 2000-2002	2,854 women 1,061 falls	Current [Q] + [MR]	Fall [Q]	Short **1.32 (1.02-1.72)** Long **1.45 (1.00-2.19)**
Case-control in the community					
Cumming [130]	USA 1987-1988	108 cases (2 falls) 250 controls (0-1 falls)	Current [Q]	Fall [Q]	Short 0.79 (0.28-2.22) Long **2.18 (1.06-4.49)**
Nested case control database					
Ray [131]	Canada 1977-1985	4501 cases 24,041 controls	Used in the past 30 days [PR]	Hip fracture [MR]	Short 1.1 (0.9-1.3) Long **1.7 (1.5-2.0)**

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Table 3–3 – continued from previous page

Study	Country and time period	Sample size	Benzodiazepine Measure	Outcome measure	Results
Sgadari [110]	USA 1992-1996	9,752 cases 38,564 controls	Last 7 days [PR]	Femur fracture [MR]	Long 1.19 (0.97-1.46)
Herings [119]	Netherlands 1986-1992	493 cases 1,479 controls	Current [PR]	Femur fracture [MR]	Short **1.5 (1.1-2.0)** Long 1.3 (0.7-2.4)
Wang [118]	USA 1993-1995	1,222 cases 4,888 controls	Current [PR]	Hip fracture [MR]	Long **1.35 (p=0.001)**

1. Bold indicates statistically significant results at $\alpha = 0.05$.
2. The abbreviation [Q] indicates Questionnaire, [PR] Prescription Records, and [MR] Medical Records.
3. Reference is non-user unless stated otherwise.
4. Measures are OR unless stated otherwise.

Table 3–4: Summary of findings on the association between selected benzodiazepine use and fall-related injuries in the elderly

Study	**Cumming** [128]	**Herings** [119]	**Neutel** [121]	**Pierfitte** [122]	**Tamblyn** [123]
Chlorazepoxide					**1.83 (1.04-3.22)** 12 events
Clorazepate				0.6 (0.3-1.1) 13 events	
Diazepam	0.59 (0.21-1.64) 7 events		**1.8 (1.3-2.5)** NA		0.99 (0.76-1.28) 57 events
Flunitrazepam				1.4 (0.5-4.4) 5 events	
Loprazolam				2.7 (0.5-13.6) 4 events	
Flurazepam			**3.4 (2.5-4.7)** NA		**1.78 (1.48-2.14)** 113 events
Nitrazepam	1.21 (0.54-2.72) 14 events	1.1 (0.7-1.8) 28 28 events		2.2 (0.4-13.4) 2.2 2 events	1.34 (0.97-1.84) 38 events
Alprazolam				0.8 (0.2-2.7) 3 events	1.10 (0.87-1.38) 72 events
Clobazam				3.1 (0.6-15.6) 33 events	
Temazepam	**3.78 (1.60-8.92)** 29 events	**2.8 (1.3-5.8)** 14 events		2.7 (0.7-10.9) 4 events	**1.26 (1.03-1.55)** 94 events
Lorazepam		**5.5 (1.3-23.1)** 6 events	**2.0 (1.3-3.1)** NA	**1.8 (1.1-3.1)** 25 events	**1.20 (1.12-1.29)** 830 events
Bromazepam				1.02 (0.6-1.7) 21 events	1.03 (0.80-1.32) 60 events
Oxazepam	0.79 (0.32-1.93) 14 events	5.1 (0.5-57.2) 2 events	**2.2 (1.4-3.4)** NA	1.7 (0.2-2.2) 5 events	**1.24 (1.12-1.36)** 392 events
Triazolam			**2.7 (2.0-3.6)** NA		1.32 (0.98-1.79) 42 events

1. Bold indicates statistically significant results at $\alpha = 0.05$.

Table 3–5: Summary of findings on the association between benzodiazepine dose and fall-related injuries in the elderly

Study	Country and time period	Sample size	Benzodiazepine Measure	Outcome measure	Results
Cohort studies					
Ray [124]	USA 1993-1996	2,510, 3,706 falls in 1,544 p-y	Current dose DDD [PR]	Fall [MR]	≤2mg **1.30 (1.12-1.52)** 2-4 mg **1.34 (1.20-1.51)** 4-8 mg **1.38 (1.20-1.51)** >8mg 2.**21 (1.89-2.60)**
French [132]	USA 1999-2001	13745 users 1,1000 falls	Current dose DDD and duration [PR]	Fall [MR]	Dose **1.06 (1.047-1.073)**
Nested case control database					
Sgadari [110]	USA 1992-1996	9,752 cases 38,564 controls	DDD [PR]	Femur fracture [MR]	DDD < 1 **1.11 (1.03-1.96)** DDD > 1 1.14 (0.95-1.96)
Herings [119]	Netherlands 1986-1992	493 cases 1,479 controls	Current DDD Recent (last1-365days) [PR]	Femur fracture [MR]	1-74% of DDD 1.0 (0.6-1.5) 75-124% of DDD **1.9 (1.3-2.7)** >124% of DDD **2.3 (1.2-4.1)**
Wang [118]	USA 1993-1995	1,222 cases 4,888 controls	Current dose Diazepam equivalent [PR]	Hip fracture [MR]	0-2.9 mg 1.32 (no CI) 3.0-5.9 mg 1.54 6.0-8.9 mg 1.52

1. Bold indicates statistically significant results at $\alpha = 0.05$.
2. The abbreviation [Q] indicates Questionnaire, [PR] Prescription Records, and [MR] Medical Records. DDD indicates standard daily recommended dose for adults.
3. Reference is non-user unless stated otherwise.
4. Measures are OR unless stated otherwise.

Table 3–6: Summary of findings on the association between benzodiazepine timing of use and fall-related injuries in the elderly

Study	Country and time period	Sample size	Benzodiazepine Measure	Outcome measure	Results
Cohort studies					
Ray [124]	USA 1993-1996	2,510, 3,706 falls in 1,544 p-y	Days since started use [PR]	Fall [MR]	<7 days **2.96 (2.33-3.75)** 7-29 days **2.23 (1.64-3.03)** ≥30 days **1.30 (1.17-1.44)**
French [132]	USA 1999-2001	13745 users 1,1000 falls	Current dose DDD and duration [PR]	Fall [MR]	Duration **1.044 (1.024 1.064)** and duration squared 0.999(0.980-1.000)
Nested case control database					
Neutel [121]	Canada 1979-1986	468 cases 936 controls	Time after 1st use [PR]	Fall [MR]	< 15 days: sedative: **3.6 (2.5-5.2)**; tranquilizers **2.6 (1.7-3.7)**; 15-28 days: sedatives: **2.3(1.6-3.4)**; Tranquilizers 1.4 (0.9-2.1); 29-60 days: sedatives: **1.4 (1.1-1.9)**; Tranquilizers 1.1 (0.9-1.5)

1. Bold indicates statistically significant results at $\alpha = 0.05$.
2. The abbreviation [Q] indicates Questionnaire, [PR] Prescription Records, and [MR] Medical Records. DDD indicates standard daily recommended dose for adults.
3. Reference is non-user unless stated otherwise.
4. Measures are OR unless stated otherwise.

CHAPTER 4
Objectives of the thesis

The primary objective of the present thesis is to develop and evaluate a flexible method for modelling cumulative effects of time-varying exposures, weighted by recency, represented by time-dependent covariates in the Cox proportional hazards model.

Secondary objectives include: (i) developing an algorithm to generate event times conditional on complex time-dependent and intensity-varying exposures to validate the method described in the primary objective; and (ii) applying the method developed in the primary objective to re-asses the association between selected benzodiazepines and fall-related injuries in the elderly.

CHAPTER 5
Manuscript 1: Comparison of algorithms to generate event times conditional on time-dependent covariates

5.1 Preamble

This article addresses the specific question of generating time-to-event data conditional on time-dependent covariates. This issue is essential for the simulations that are presented in the manuscript 2, where the performance of the proposed weighted cumulative exposure method was investigated and validated. The design of the simulation studies presented in manuscript 2 comprised many scenarios, each requiring the estimation of several models. As a result, I needed a data-generating algorithm that was fast, yet precise and stable.

In this article, I first review the two classes of algorithms available in the literature, which could be used for generating event times conditional on time-dependent covariates, (i) the permutational algorithm, and (ii) algorithms based on a binomial model. I then proposed a modification of the permutational algorithm to incorporate a rejection sampler, which was expected to enhance the efficiency of data generation. Finally, I designed and carried out simulations which compared the accuracy, stability, flexibility and computational speed of the alternative algorithms.

Based on the results of this article, I used the permutational algorithm to generate the data required for the simulation reported in manuscript 2, which addressed the main objective of this thesis.

This article was accepted for publication in *Statistics in Medicine* in August 2007 (DOI 10.1002/sim.3092) and is available electronically at `http://www3.interscience.wiley.com/cgi-bin/abstract/116327580`. The letter of acceptance is included

in Appendix A, while the permission from the publisher to reproduce the manuscript is in Appendix B.

The publications cited in Manuscript 1 are listed in the general reference section at the end of the thesis. The R code for the permutational algorithm with and without the rejection sampler can be found in Appendix A.

Manuscript 1: Comparison of algorithms to generate event times conditional on time-dependent covariates

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CHAPTER 6
Manuscript 2: Flexible modelling of the cumulative effects of time-dependent exposures on the hazard

6.1 Preamble

This article addresses the primary objective of the thesis, which is to develop and evaluate a flexible method for modelling cumulative effects of time-varying exposures, weighted by recency, on event times analyzed in prospective studies.

I propose a new method for estimating the weighted cumulative exposure metric and model it as a time-dependent covariates in the Cox proportional hazards model. The function that assigns different weights to past exposures is modeled using cubic B-splines because they provide smooth estimates that are flexible enough to represent a variety of clinically plausible shapes, and can easily be computed by any statistical package. The choice of the number of knots and their location is discussed. Several alternative spline models of different complexity are considered and the BIC criterion is used to select the best-fitting model. I estimated both models that constrained the weight function to decrease smoothly to zero after some pre-specified time intervals and others that did not impose any constraint on the shape of the estimated function. Pointwise confidence intervals around the estimated weight functions are obtained using a non-parametric bootstrap re-sampling routine that accounts for both the sampling variation of the regression coefficients, and the uncertainty at the model selection stage. A LRT-based procedure is proposed to test the two relevant null hypothesis of (a) no association, and (b) equal (constant) weights of all past exposures. I discuss how to estimate the hazard ratios for the WCE corresponding to specific patterns of exposure.

Simulations are used to validate the proposed method. To this end, I rely on the novel algorithm for generating event times conditional on time-dependent covariates, which has been developed and validated in Manuscript 1. In the manuscript 3, the method is applied to re-assess the associations between the use of several benzodiazepines and fall-related injuries in the elderly.

The publications cited in Manuscript 2 are listed in the general reference section at the end of the thesis. Additional material is provided at the end of the chapter.

Manuscript 2: Flexible modelling of the cumulative effects of time-dependent exposures on the hazard

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Abstract

Many epidemiological studies assess the effects of time-dependent exposures, where both the exposure status and its intensity vary over time. One example that abundantly attracts public attention concerns pharmacoepidemiological studies of the adverse effects of medications. The analysis of such studies poses challenges for modelling the impact of complex time-dependent drug exposure, especially given the uncertainty about the way effects cumulate over time and about the etiological relevance of doses taken in different time periods. We present a flexible method for modelling cumulative effects of time-varying exposures, weighted by recency, represented by time-dependent covariates in the Cox proportional hazards model. The function that assigns weights to doses taken in the past is estimated using cubic regression splines. We validate the method with a simulation study.

KEYWORDS: Proportional hazards model; regression splines; simulations; survival analysis; time-dependent covariates; pharmacoepidemiology

6.2 Introduction

The aim of many epidemiological studies is to assess the effects of time-dependent exposures, where both the exposure status and its intensity vary over time. Adequately modelling such complex time-dependent exposures poses a particular challenge, especially given the uncertainty about whether and how exposure effects cumulate over time and about the etiological relevance of doses taken in different time periods [10, 12, 11].

Ignoring the complex time-varying nature of exposure, or restricting its modelling to a subset of its components, such as current dose or duration of exposure, may miss more complex forms of association between exposure and outcome, or lead to etiologically incorrect conclusions [144]. A slightly more comprehensive measure of exposure is the cumulative exposure, calculated as un-weighted sum of past exposures [152, 153, 154], assumes that all the exposures in the past had the same impact on the current risk, which may be debatable in many instances.

Both Breslow and Thomas have discussed the general framework of weighted cumulative exposure (WCE), that combine information about duration, intensity and timing of exposure into a summary measure [18, 19]. In this framework, the WCE at time u is formed by assigning weights to past exposures up to time u and then summing up over time. Consider $x(t)$, the instantaneous intensity of exposure at time t. Let $w(u-t)$ be a function that assigns weights to exposures in the past, based on their impact on the risk of event occurring after the time interval $u-t$. If exposure is measured at discrete time intervals, then the WCE can be expressed as:

$$z(u) = \sum_{t=1}^{u} w(u-t)x(t) \tag{6.1}$$

Vacek proposed parametric modelling of the weight function in case-control studies, where u was fixed at the index date and a single value of the WCE for

each subject was incorporated in a conditional logistic regression model [12]. Four alternative parametric forms for the weight function were selected *a priori* and the fit of the resulting models were compared to select the specification most consistent with the data [12]. In the analysis of a case-control study of the impact of smoking on lung cancer, Hauptmann *et al.* used the WCE framework to summarize the individual smoking histories up to the date of cancer diagnosis for cases or index time for controls [11]. They estimated the weight function using constrained regression splines within a generalized linear model, which required a constrained maximization algorithm to jointly estimate the regression parameters and the coefficients of the spline basis.

Abrahamowicz *et al.* used the parametric WCE framework within the Cox proportional hazards model to refine the assessment of the associations between exposure to three benzodiazepines and fall-related injuries in the elderly [14]. The parametric form of the weight function was *a priori* selected to reflect assumptions about the pharmacokinetics properties of benzodiazepines and had two alternative parameter values to represent different windows of clinically relevant exposure. The weighted cumulative exposure models provided better fit to the data then models that represented exposure using time-dependent variables for current dose or current duration. In addition, the best-fitting WCE model was different for each of the three benzodiazepines, possibly reflecting the differences in their elimination half-life and/or withdrawal effects [14, 101].

However, modelling strategies that require selecting the parametric form of the weight function in the absence of any prior knowledge about its shape may lead to invalid results if the function is incorrectly specified [12, 86, 20]. An alternative approach consists in estimating the functional form of the weight function from the data, using flexible non- or quasi- parametric methods [11]. In the current article,

we propose the regression spline based method for modelling the WCE as a time-dependent covariate in the Cox PH model. This involves calculating the WCE at each time t of the follow-up, in contrast to computing its value only once at the end of follow-up, as it is done in the case-control framework [11, 12]. We propose a parametrization of the WCE in the Cox proportional hazards (PH) model that does not require constrained optimization, so that it can be readily estimated using most statistical software packages.

Section 6.3 discusses the estimation of our model, the pointwise confidence bands for the weight function, and hypothesis-testing procedures. Section 6.4 presents the design and results of the simulations, which evaluated the performance of our method. We finish with concluding remarks in Section 6.6.

6.3 Methods

6.3.1 Cox model with time-dependent weighted cumulative exposure

Consider a cohort in which individual exposure $X_i(t)$ varies over time. At any time u during the follow-up, we represent the joint effect of the past exposures by the weighted cumulative exposure (WCE) metric

$$WCE(u) = \sum_{t=1}^{u} w(u-t)X(t), \tag{6.2}$$

where t indexes times of exposure preceding u, and $w(u-t)$ is the function assigning weights to past exposures based on time elapsed since the exposure occurred. The WCE is then modeled as a time-dependent covariate in the Cox proportional hazards model [30]:

$$h(u|\boldsymbol{X}(t), \boldsymbol{Z}(u)) = h_0(u) \exp\left[\gamma \sum_{t=1}^{u} w(u-t)X(t) + \sum_{s=1}^{q} \beta_s Z_s(u)\right], \tag{6.3}$$

where $X(u)$ represents the time-vector of the past exposure for $0 \leq t \leq u$ and each $Z_s(u)$ is a vector of fixed-in-time or time-dependent covariates.

We propose to estimate the weight function $w(u-t)$ using cubic regression B-splines [74]:

$$w(u-t) = \sum_{j=1}^{m} \theta_j B_j(u-t), \tag{6.4}$$

where B_j, $j = 1, ..., m$, represent the m functions in the cubic spline basis and θ_j, $j = 1, ..., m$, represent the estimable coefficients of the linear combination of the basis splines.

Conceptually, $w(u-t)$ in (6.3) estimates the shape of the weight function, and γ estimates the magnitude of the effect of cumulative exposure on the hazard. However, both γ in (6.3) and θ_j, in (6.4) reflect the strength of the association between the exposure and the risk. Therefore, to avoid identifiability problem when jointly estimating the parameters γ and θ_j, we define:

$$\alpha_j = \theta_j \gamma. \tag{6.5}$$

Furthermore, estimation of model in (6.3) is largely facilitated by introducing artificial time-dependent covariates [49]:

$$D_j(u) = \sum_{t=1}^{u} B_j(u-t)X(t), j = 1, ..., m. \tag{6.6}$$

Given (6.5) and (6.6), the model in (6.3) is redefined into a familiar form of the PH regression model with time-dependent covariates $D_j(u)$:

$$h(u|\boldsymbol{X}(t), \boldsymbol{Z})(u) = h_0(u) \exp\left[\sum_{j=1}^{m} \alpha_j D_j(u) + \sum_{s=11}^{q} \beta_s Z_s(u)\right] \tag{6.7}$$

Once the m artificial time-dependent covariates $D_j(u)$ are calculated, any standard statistical software for Cox regression with time-dependent covariates can be used to estimate the parameters of the model (6.7).

It should be noted that since γ is absorbed in the α vector, the magnitude of the effect of cumulative exposure on the risk of an event cannot be summarized by a single parameter. However, measures of relative risks, such as hazard ratios (HR), may easily be calculated from model (6.7) by comparing the risk of event evaluated for two different histories of exposure, keeping other variables constant:

$$\hat{HR} = \exp\left[\sum_{j=1}^{m} \hat{\alpha}_j \sum_{t=1}^{u} B_j(u-t)[X_0(t) - X_1(t)]\right] \tag{6.8}$$

where $B_j(u-t)$ is the spline basis, $\hat{\alpha}_j$ are parameters estimated from model (6.7), while $X_0(t)$ and $X_1(t)$ represent the two exposure histories to compare. Depending on the selected exposure histories, one can estimate the HR resulting from, for example, (i) changing the dose, (ii) changing the duration and timing of exposure, or (iii) any combination of (i) and (ii). Corresponding 95% confidence interval may be obtained via bootstrap, as described in Section 6.3.4.

6.3.2 Choice of the cubic regression spline basis

We estimate the weight function in (6.4) using cubic regression splines because they provide smooth estimates with continuous first two derivatives, that are flexible enough to represent a variety of clinically plausible shapes [76], and can easily be computed by any statistical package [155]. The number of knots determines the flexibility of the estimated spline function and the model's degrees of freedom. A cubic B-spline basis with $m-4$ interior knots consists of m curves, whose linear combination provides the estimated spline function. In general, not more than five knots are enough to model a smooth uni- or bi-modal curve while reducing the risk of major over-fitting bias [51]. In addition, the tail of a spline function can be constrained to go smoothly to zero by setting the first (or last) two coefficients of the linear combination of the spline basis to zero.

Regression splines have a finite support interval, which has to be defined by the user [60]. In our framework, the support interval corresponds to the time window $[u-a, u]$ of exposures that are considered potentially etiologically relevant at time u. Outside of this interval, i.e. for $t < u - a$, the exposures are *a priori* believed to be too remote in time to influence the risk of an outcome at time u so that $w(u-t)$ is *a priori* set to 0 for $t < u - a$. Therefore, the weight function in (6.4) is estimated over the limited interval $[0, a]$ only. Accordingly, we place three exterior knots at 0 and three others at a. In the absence of prior knowledge about the potential shape of the weight function, we place the interior knots at equal distances within the time window $[0, a]$.

In many, but not all applications, it may be *a priori* evident that very early exposures that occurred near the beginning of the etiologically relevant window have no impact on the current risk. Therefore, in addition to the unconstrained weight function models, in which the coefficients α_j for all m artificial time-dependent variables in (6.6) are estimated, we also considered constrained models in which the coefficients of the last two artificial time-dependent variables in (6.6), α_{m-1} and α_m, are set to zero, which results in constraining the weight function, and its first derivative, to reach 0 at $t = u - a$.

We *a priori* limit the number of the interior knots to be between one and three, which implies that five to seven spline coefficients had to be estimated in the unconstrained model, and three to five in the constrained model. We then rely on the BIC to select the unconstrained and/or constrained model(s) that achieved the best fit, as determined by the lowest BIC. Following [156], we define the BIC for a given model as:

$$BIC = -2\ln(PL) + p\ln(d) \tag{6.9}$$

where PL represents the partial likelihood function for the model, while p is the number of estimable parameters in (6.7), and d corresponds to the number of uncensored events.

6.3.3 Hypothesis testing procedures

When significance tests are performed on the results of the model selected by some data-dependent criteria based on goodness of fit, standard inference procedures may be invalid because of inflated type I error [157, 158, 159].

The distribution of the test statistics conditional on an *a posteriori* selected model and its unconditional distribution may be significantly different [157]. In the context of our method, it implies that standard inference about the effects of exposure based on the BIC-optimal model needs to take into account the uncertainty at the model selection stage, and the interdependence of tests conditional on alternative WCE models with different numbers of knots an/or different several time windows of clinically relevant exposure $[u - a, u]$ [159, 47, 49].

To obtain valid likelihood ratio tests for the association between the WCE represented by m time-dependent variables $D_j(u)$, $j = 1, ..., m$ in (6.7), and the risk of an event, we propose a simulation-based approach. Our approach is similar to that employed by Mahmud *et al.* to correct the significance level α^* of the likelihood ratio tests (LRT) of the effect of a continuous covariate on the hazard for *a posteriori* selection of the functional form of the dose-response curve [159]. We first generated 1,000 datasets under the assumption of no association between exposure and outcome (data generation procedures are discussed in section 6.4), and then selected the BIC-optimal WCE model for each simulated sample. We computed a LRT for the joint effect of the m variables $D_j(u)$,

For the i^{th} simulated sample, we computed the $m_i - df$ LRT statistic, where m_i denotes the number of splines coefficients α estimated in the BIC-optimal model for

this specific sample, and establish the corresponding, un-corrected, p-value. Next, we construct the empirical distribution of the 1,000 resulting so-called conditional p-values, across 1,000 samples generated under the null hypothesis. This distribution will be shifted to the left, i.e. towards lower p-values, relative to the uniform distribution that would be obtained if a single model was selected *a priori* [159]. Therefore, using an un-corrected significance level, e.g. $\alpha = 0.05$, would lead to inflated type I error, with the magnitude of inflation increasing as the sampling variation in the BIC model selected increases [49]. However, the empirical distribution of conditional p-values directly accounts for such inflation [159]. Therefore, we used the 5^{th} percentile of the empirical distribution of the conditional p-values as the significance level α^* in the reported LRT to ensure a type I error rate of 0.05. Indeed, under the null hypothesis, about 5% of the conditional p-values will be expected to fall below the new significance level α_0^*.

Because the spline space also includes the constant weight model, we used a similar procedure to test whether the WCE models provided a better fit to the data then the conventional unweighted cumulative exposure model [49]. This time, the corrected critical cutoff value α_1^* was selected to be the 5^{th} percentile of the empirical distribution of the conditional p-values obtained from samples simulated while assessing that the true model was the unweighted cumulative dose, i.e. that all past exposures had the same weight, regardless of their timing.

6.3.4 Pointwise confidence bands for the estimated weight function

To assess the precision of the estimated weight function $w(u-t)$, we relied on non-parametric bootstrap re-sampling [160]. The bootstrap routine should account for both (1) the sampling variation of the regression coefficients, and (2) the uncertainty at the model selection stage, i.e. the additional variance due to *a posteriori* selection of the number of knots [45, 49]. Accordingly, for each of the B bootstrap

samples, alternative versions of model (6.7) with 1-3 interior knots are estimated and the BIC is use to select the best estimate of $w(u-t)$ for a given bootstrap sample. The percentile method can then be used to compute a 95% pointwise confidence band, for each $w(u-t)$. Next, for each $0 \leq t \leq u$, the empirical distribution of the B point estimates of $w(u-t)$, each corresponding to the BIC-optimal model for a given bootstrap sample, is constructed.

6.3.5 Software specification

The algorithms for the data generation and for computing the time-dependent covariates in 6.7 were coded in R version 2.6.1 [65] with the *Mersenne-Twister* random number generator [150]. To analyze the simulated data, we used the R procedure `coxph` [161] with Efron method for tie handling. The scripts are available from the authors.

6.4 Design of simulations and data generation

We validated our model and investigated its properties using simulations. We simulated a hypothetical prospective cohort study, which aims at assessing the association between exposure to a single drug and time to an event. The cohort consisted of 500 new users of the drug, and time zero was defined as the first day of the drug use as in [123]. Individuals could interrupt and resume their treatment repeatedly thereafter. The follow-up was limited to a year. In the next three sub-sections, we describe: (i) the generation of a matrix of individual drug use patterns that we kept fixed across the simulations; (ii) the selection of alternative weight functions and parameters used in different data-generation scenarios; and (iii) the generation of adverse event times conditional on the weighted cumulative doses.

6.4.1 Exposure generation

The drug treatment was assume to vary in dose and duration both between individuals and over time within an individual. The duration of the initial treatment

for individual i, was defined in multiple of 7 days and was generated from a lognormal distribution :

$$duration_i = \frac{7}{365} \times \left[1 + round\left(logN\left(\log \mu = \frac{187}{365}, \log \sigma = \frac{292}{365}\right)\right)\right] \quad (6.10)$$

with mean of log(0.5) and standard deviation of log(0.8). A subsequent period of interruption, when the subject was assumed not to be exposed to the drug, was generated using a similar distribution. Successive periods of use and interruptions were generated similarly until the end of follow-up was reached (365 days). For each uninterrupted period of use, the standardized daily dose [123] was assumed to remain constant across the entire period. The daily dose corresponded to the time-dependent variable $X(t)$ in Equation (6.3), with $X(t) = 0$ for all periods of interruption. Specifically, the dose was generated to be 0.5, 1, 1.5, 2, 2.5, or 3 times the recommended dose, with each of the six values assigned with equal probability of $\frac{1}{6}$.

6.4.2 Weight functions

We first considered 6 different scenarios, each corresponding to a different true weight function that were defined over a $[0, 1]$ interval, corresponding to one year. The six true weight functions are shown in Figure (6–1). Notice that the time axis in Figure (6–1) runs backwards, so that $u - t = 0$ corresponds to the current exposure. The first two scenarios assumed that weights decreased monotonically as time since exposure increased. For scenario 1, we used an *exponential* decay function with $w(u - t) = 7e^{-7(u-t)}$ while for scenario 2, we used a *Bi-linear* function $w(u - t) = 1 - \frac{u-t}{50/365}$ for $u - t \leq \frac{50}{365}$ and zero otherwise. Scenarios 3 and 4 corresponded to functions with a bump within the interval $[u, u-180/365]$ so that the weights increase until $t = 0.2$ year and then decrease as time since exposure increases. The *Inverted U* function for scenario 3 corresponded to the density function of a $N[0.2; 0.06]$

distribution, while *Early peak* function of scenario 4, to the density of a $N[0.04; 0.05]$ distribution, both left-truncated at $t = 0$. In comparison with the *Inverted U*, in the *Early peak* scenario, the maximum weight was assigned to more recent doses and the weights declined more sharply afterward. Scenario 5 corresponded to a *Constant* weight function with $w(u-t) = \frac{1}{365}$, so that the resulting WCE was in fact a standard un-weighted time-dependent cumulative dose variable over the follow-up period. In the last scenario (Sc 6), we considered a weight function that intially increased, reached a plateau at around $u - t = 180/365$ and then started to decrease to zero around $u - t = 240$. This function was labeled *Hat* and was specifically designed to investigate the impact of constraining the weight function to go to zero around $u - 180/365$ where the true weight function was actually at its maximum value. To enhance comparability, the weight functions were standardized so that the area under each six true weight functions summed up to 1 over the interval $[u, u - 180/365]$.

Finally, we investigated type I error by considering the case where there was no association between weighted cumulative dose and the outcome. In this case, the event times were generated from the marginal distribution described in the next section and randomly assigned to individuals independently of their exposure pattern.

6.4.3 Events generation

For each scenario and each subject, $i = 1, ..., 500$, we calculated the vector $WCE_i(u)$ of the true value of the time-dependent variable WCE in (6.2), based on individual patterns of drug exposure and the relevant weight function, for each day of potential follow-up: $u = 0, \frac{1}{365}, ..., 1$. Next, we assumed that the strength of the exposure impact on the hazard corresponded to $\gamma = \ln 4$ in (6.3), i.e. that an unit increase in WCE corresponded to a 4-fold increase in the hazard (HR=4). Notice that because the weight function was standardized, an unit increase in WCE corresponded to, e.g., a difference between (a) an individual prescribed a standard

dose of 1 for the entire year, and (b) a subject not exposed at any time during the year.

Finally, we generated event times conditional on the WCE, using the permutational algorithm, specifically developed and validated for simulating event times conditional on time-dependent covariates and/or effects [29, 162]. The permutational algorithm involves three major steps: (i) generating individual covariate values over time; (ii) generating the event times from the pre-specified marginal distributions, independent of covariates; (iii) matching individual event times with individual covariate vectors based on pre-specified assumptions about the covariates impact on hazard [49]. Matching at step (iii) is performed so that probability of a subject, who remained at risk until time t, with a particular covariate vector $x_i(t)$ being matched with the event at time t is proportional to the subject's current hazard $h(t|x_i(t))$ [29, 162]. A detailed description of the algorithm and its validation can be found in [162]. We generated event times assuming their marginal distribution is uniform $U[0, 1]$ and assumed a 50% rate of right random censoring, resulting in approximately 250 events per simulated sample.

6.4.4 Analysis of the simulated datasets

For each of the 1,000 samples simulated for a given scenario, we estimated unconstrained and constrained models with 1 to 3 interior knots, and used the BIC to select the best fitted model. Regardless of the true shape of the weight function, we assumed that the user would select a six-month interval $[0, \frac{180}{365}]$ as the window of etiologically relevant exposure. Accordingly, we used $a = \frac{180}{365}$ for all spline models estimated in our simulations.

We first assessed the accuracy of our estimates of the exposure impact on the hazard, we simply reconstructed $\hat{\gamma}$ as

$$\hat{\gamma} = \sum_{\tau=0}^{a} \sum_{j=1}^{m} \hat{\alpha}_j B_j(\tau). \tag{6.11}$$

When generating the data, we used the true weight functions defined so that

$$\int_0^a w(t)dt = 1. \tag{6.12}$$

This implied that γ used to generate events represented the $\ln(HR)$ between a subject exposed at a constant dose $X(t) = 1$ for the entire window of the relevant exposure $[u - a, u]$ against an unexposed subject $X(t) = 0$, $u - a \leq t \leq u$. We then compared the distribution of the estimated γ, across simulated samples, with the true γ by calculating the relative bias $\frac{\bar{\hat{\gamma}} - \gamma}{\gamma}$ and the standard deviation (SD) of the estimates obtained from (6.11).

Next, we assessed the accuracy of the simulated weight functions. To this end, we obtained the normalized version of the estimated weight function, which respected the constraint:

$$\hat{w}^*(u - t) = \sum_{j=1}^{m} \frac{\hat{\alpha}_j}{\hat{\gamma}} B_j(u - t) \tag{6.13}$$

where $\hat{\gamma}$ was calculated from (6.11). We then plotted a random sample of 100 normalized weight functions against the true weight functions to investigate the ability of the method to recover the shape of the true weight function used to generate the data.

We also estimated two alternative simpler models in which the exposure was expressed with a time-dependent variable: (1) current dose, $DOSE = X(u)$ and (2) cumulative (unweighted) dose $CUMDOSE = \sum_{t=0}^{u} X(u)$. The fit of all of these

models were compared using the BIC. Finally, we performed a likelihood ratio test (LRT) on each of the models to evaluate type-I error.

6.5 Simulation results

In this section, we report the results of the analysis of 1,000 simulated datasets for each of the six *true* weight functions described in Section 6.4.2.

6.5.1 Accuracy of the estimated weight functions

We calculated the normalized estimated weight functions as described in section 6.4.4 from each of the BIC-optimal unconstrained and constrained WCE models and plotted them against the true weight functions used to generate the data. Figures 6–2 and 6–3 show a random sample of 100 normalized estimated weight functions obtained from the unconstrained and constrained models, respectively. In each of the Figures' panels, the true weight function used to generate the data is plotted in white. In every scenario, except for the *Hat* and the *Constant* functions, most of the estimated weight functions were able to capture the shape of the true weight functions, albeit with some variation in the amplitude of the curves. In the unconstrained models, the estimation was less satisfactory in the right tail of the plot, especially in scenarios when the exposures that occurred relatively long ago had little impact on the risk. Instability at the tails of the estimated function is a known feature of B-splines [56]. As Figures 6–2 and 6–3 show, constraining the weight functions to smoothly go to zero at the end of the exposure time window considerably reduced the variation of the estimates, even if the window $[0, \frac{180}{365}]$ was selected *a priori* and was often much longer than the time window of relevant exposures (with non-zero impact).

6.5.2 Model selection

For each scenario, we used the BIC to select the overall best model among the unconstrained and unconstrained spline-based WCE models, and the two alternative

models with time-dependent exposure (current dose and cumulative dose), as described in section 6.4.4. Table 6–1 shows the number of times, out of 1,000, that each of the models was selected as the best model by scenario. Table 6–2 shows similar results, stratified by WCE versus alternative models. Table 6–2 also shows, in parenthesis, the proportion of simulated samples that found a statistically significant association between the exposure and the outcome using the likelihood ratio test with the corrected critical cutoff value $\alpha_0^* = 0.039$.

For scenarios 1-4, corresponding to the weight functions that decreased to zero near $u - t = 180/365$, the constrained WCE models had the best fit in more than 90% of the simulated data sets. The number of knots selected for these models depended on the curvature of the weight function. For monotone functions like the *Bi-linear* and the *Exponential* functions, the BIC selected models with 1 interior knot in more than 90% of the samples (Table 6–1). This reflected the fact that for monotone functions, the additional flexibility provided by adding extra knots did not improve the fit enough to compensate for the penalty due to increasing the model dimension.

Models with 2 knots were selected more frequently for the two weight functions that had a bump within the support interval $[u - 180/365, u]$, namely the *Early peak*, and the *Inverted U* (Table 6–1). This reflected the need for a greater flexibility in modelling functions that had a local extremum and one or two inflexion points within the support interval. Constrained models with two knots were selected as the best fit models in more than half of the simulated samples for the *Inverted U* scenario, while in the case of the *Early peak* weight function, more than two thirds of the models with the lowest BIC were the constrained models with 1 knot. The *Early peak* weight function had a narrow and sharp peak around $u - t = \frac{30}{365}$ which, in many samples, was not detected by the WCE method. Indeed, as Panels (c) of Figures 6–3 and 6–2

show, several estimated weight functions for the *Early peak* scenario were decreasing monotonically and required only one knot.

In addition, for Scenarios 1-5, the alternative non-spline based models were never selected as the best model, except for the unweighted cumulative dose model, which had the best fit in 58 and 22 samples out of 1,000 for the *Exponential* and *Inverted U* functions, respectively. Using the corrected $\alpha_1^* = 0.039$, the LRT indicated that the WCE models provided a better fit to the data then the unweighted cumulative exposure model in more than 95% of the simulated samples for the *Bi-Linear*, *Exponential*, *Early Peak* and *Inverted U* scenarios.

In scenarios 1-4, where the true weight functions decreased to zero within the $[u - 180/365, u]$ interval, all of the LRT tests for both constrained and the unconstrained modeled rightfully detected a statistically significant association between the exposure and the event. In comparison, the unweighted cumulative dose model missed a statistically significant association in about 70.9% of the simulated samples. The current dose model was usually able to detect an association in the majority of Scenarios 1, 2 and 4 but yielded statistically significant results in less than 5% of the samples for Scenario 3. This is because, unlike in Scenarios 1, and 4, the *Inverted U* weight function in Scenario 3 does not assign large weights to current or very recent doses (Figure 6–1).

In the scenario where the true model was the unweighted cumulative exposure (*Constant* weight in Figure 6–1), the correct model with the cumulative unweighted exposure variable (CUMDOSE) had the best fit in 924 out of 1,000 simulated samples. In comparison, the spline based WCE models did not perform well because of their larger number of estimated parameters penalized their BIC values. While the CUMDOSE model had a statistically significant LRT tests in 75.1% of the times, the spline based WCE models detected an association between the exposure and

the outcome in about only 40% of cases on average. This relatively low power, even for the correct CUMDOSE model, reflect the fact that in this scenario, the true association was more difficult to detect. Since the area under the true *weight* function summed to 1 over the $[u - 180/365, u]$ interval, the weight assigned to exposures on a single day was relatively small, as shown in Figure 6–1. That and the fact that the generated average duration of the exposure periods was relatively short (21 days), implied that, for most simulated subjects, the effective hazard ratios in the *Constant* weight scenario were relatively small and more difficult to detect than those associated with the other weight functions.

Finally, in Scenario 6, the true weight function *Hat* increased until 180/365 and decreased after $u = 180/365$. This example was specifically selected to assess the performance of the method in a difficult situation when the selected support interval for the estimated weight function, $[u - 180/365, u]$, was not wide enough to capture the entire time window of etiologically relevant exposure. As Panel (f) of Figure 6–3 shows, in this scenario, the constrained weight function estimates were forced to go to zero at $u - t = 180/365$, where the true function was in fact at its maximum. Accordingly, the constrained WCE models provided very biased estimates. On the other hand, in contrast to other scenarios, in Scenario 6, the unconstrained models, were performing better in approximating the true shape of the weight function, at least within the $[u-180/365, u]$ window, selected as the best model in 158 simulated samples out of 1,000. In the remaining samples, the best model was that with the unweighted cumulative dose variable.

Both the unweighted cumulative dose model and the unconstrained WCE estimates showed in panel (f) of Figure 6–3 suggest that even those exposures at the right end of the support window, near $u-180/365$, which occurred about half a year earlier, have a marked impact on the current risk. Moreover, the shapes of almost all

unconstrained weight functions suggest that exposures that occurred more than half a year ago may be much more important than most of the more recent exposures. This should provide a strong suggestion that the support interval $[u - 180/365, u]$, *a priori* set by the hypothetical user, is actually much too short. In this sense, these results suggest that if the true situation corresponded to our *Hat* scenario, then the use of alternative models would provide a strong evidence that the initially selected support interval is too short. We believe that, given such evidence, most users would re-analyse the data while using a considerably larger support interval. Therefore, we carried out additional sensitivity analyses, linked to the Scenario 6. Specifically, we modified the window of the support interval for the splines from $[u - 180/365, u]$ to$[u - 1, u]$ and the the constrained WCE models were selected as the best model in more than 90% of the case (Results not shown).

6.5.3 Estimated regression coefficient for the weighted cumulative dose

We also investigated whether the estimated magnitude of the effect of the WCE on the risk of an event that were estimated by WCE models reflected the true value of γ in Equation 6.3, i.e. the regression coefficient used to generate the simulated data sets. To this effect, we compared the normalized estimates of γ, obtained by summing the estimated values of the weight function over the 180 days, with the true value of γ. The results are shown in the left-hand-side of Table 6–3, under the *All models* heading. We repeated the analysis, this time on the subset of simulated samples for which the WCE model had the best fit (lowest BIC). The results are shown in right-hand-side of Table 6–3, under the *Best BIC models* heading.

For Scenarios 1-4, the relative bias for $\hat{\gamma}$ were relatively small (-2.9% to 2.8% for unconstrained models and -5.0% to 5.8% for constrained models). When only the models with the best BIC were considered, the bias was reduced to less than

1% for the constrained models. In comparison, the number of unconstrained models with the lowest BIC is too small to assess the relative bias accurately.

6.6 Discussion

We proposed flexible method for modelling cumulative effects of time-dependent exposures, weighted by recency, in the Cox's proportional hazards model. Our method avoids making *a priori* assumptions about the shape of the function that assigns weights to exposures in the past, by estimating it with cubic regression B-splines. The proposed parametrization of our flexible WCE model allows its estimation with any standard statistical package.

Our simulations illustrated that the WCE model is able to capture a variety of clinically plausible shapes of the true weight function and to produce relatively accurate estimates of the strength of the association between exposure and outcome. We proposed a strategy to test if the WCE model detects a statistically significant cumulative exposure effect and provides a better fit to the data than the conventional unweighted cumulative exposure model. This simulation-based testing strategy accounts for sampling variation at the model selection stage and, thus, can be for hypothesis-testing in other flexible models where the test is conditional on the BIC-optimal spline model [49]. Pointwise confidence bands may be obtained using a bootstrap method that also accounts for data-dependent BIC-based selection of the number of interior knots and/or length of the etiologically relevant exposure window. Even if the estimated spline coefficients do not have a meaningful interpretation, the strength of the cumulative effect may be assessed by estimating hazard ratios corresponding to contrasts between pre-specified patterns of exposure histories.

While the method is generally able to capture the overall shape of the weight function, it may fail to accurately reflect sudden and rapid change in the function, resulting in high local curvature. In cases where such functional behavior is expected,

the user may improve the fit of the model by adding knots where the change in the function is expected to occur. Otherwise, the location of the knots inside the window of etiologically relevant exposure needs to rely on some arbitrary rule. It has been suggested to place the interior knots t_k, $k = 1, ..., K$ at the $\frac{k}{K+1}^{th}$ quantiles of the distribution of the exposure variable, to ensure that each segment of $f(x)$ has comparable support from the data [45]. However, this generic approach may be of limited use in our context. Indeed, in our model, the individual values of the time-dependent WCE variable need to be calculated every time a risk set is formed due to the occurrence of an event. At the time of each event, past exposures that occurred during the pre-specified time window of etiologically relevant exposure are used to construct the WCE variable. The accuracy of the weight function estimation depends on the variance in the observed exposure status and/or dose during this window. In most applications, past periods of exposure versus non-exposure, as well as past doses, are randomly distributed over the entire follow-up. Thus, one may expect that local variance in the exposure status and dose will be proportional to the length of the support interval. Such considerations motivated our decision for equal spacing of the knots within this window.

Among many alternative smoothing techniques, we opted for regression B-splines to model the weight function mainly because they allowed a simple parametrization of the WCE model. Conditional on the choice of the number and location of knots, regression B-splines are linear in the coefficients to be estimated, which implies that standard methods of estimation and inference may be used [73]. Polynomials and fractional polynomials are also linear in the coefficients to estimate, but they are more sensitive to local bias than regression splines [60, 72]. In addition, regression spline functions can easily be constrained at their boundaries [60]. The latter property

is of particular importance in our context as, in most applications, the weight function will be *a priori* expected to smoothly decay to 0 in its right tail. Indeed, in our simulations, the constrained spline model fit the data almost uniformly better than the unconstrained model whenever the true weight function assigned weights close to 0 for exposure that occurred in relatively remote past. Finally, while smoothing splines are more flexible locally than regression splines [80], the penalty term required to estimate the smoothing spline function would not have allowed the use of artificial time-dependent variables, which are essential to implement the WCE model with widely available software.

While our simulations mimic a hypothetical study of the adverse events of a drug, where exposure is measured daily, applications of the WCE method are not limited to pharmacoepidemiological studies. Possible applications of the method include any exposure that vary over time and may have cumulative effects with different impacts of exposures that occurred a different times in the past. Pharmacoepidemiological studies based on prescription databases have the advantage of providing individual time-dependent measures of exposure over a fine time grid [163]. Additional simulations studies are required to evaluate the behaviour of the proposed WCE method when the individual measures of exposure over time are more sparse or coarsely measured.

In addition, the use of the weighted cumulative exposure metric is not restricted to the investigation of the effect of cumulative intensity of exposure (or doses) on the event of interest. Extensions of the model presented here include using a similar approach for the weighted cumulative duration of past treatment, in which the exposure history is represented with a time-dependent binary indicator of the status of exposure instead of its intensity. As proposed in [14], models that include both a time-dependent variable representing the current intensity of exposure and

the weighted cumulative duration of treatment can also be fitted to disentangle the effects of the current dose from that of the duration of past treatment.

In conclusion, although the concept of the recency-weighted cumulative dose metric has been present in the literature over more than twenty years [18, 19], its use has been restricted to a couple of studies [12, 11, 84, 85, 14], practically all of which represented individual exposure history with a time independent covariate. Yet, the prospective cohort design with time-dependent covariates provides a natural setting for evaluating the impact of longitudinal changes in exposure status and intensity. We hope that our implementation of the flexible modelling of the weighted cumulative dose in the familiar Cox proportional hazards model will motivate a more widespread use of this metric. We also believe that the WCE model can provide useful insights regarding the mechanisms linking the history of time-dependent exposure with the risk of events investigated in clinical and epidemiological studies.

6.7 Acknowledgments

M-P S. holds a Canadian Institutes for Health Research Doctoral Award. M.A. is a James McGill Professor at McGill University. This research was supported by grants from the National Sciences and Engineering Research Council of Canada (#228203) and the Canadian Institutes for Health Research (#MOP-8127).

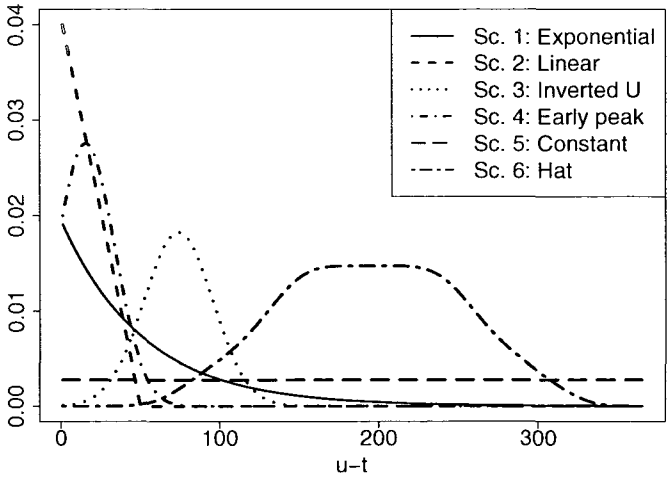

Figure 6–1: True weight functions corresponding to scenarios 1-6

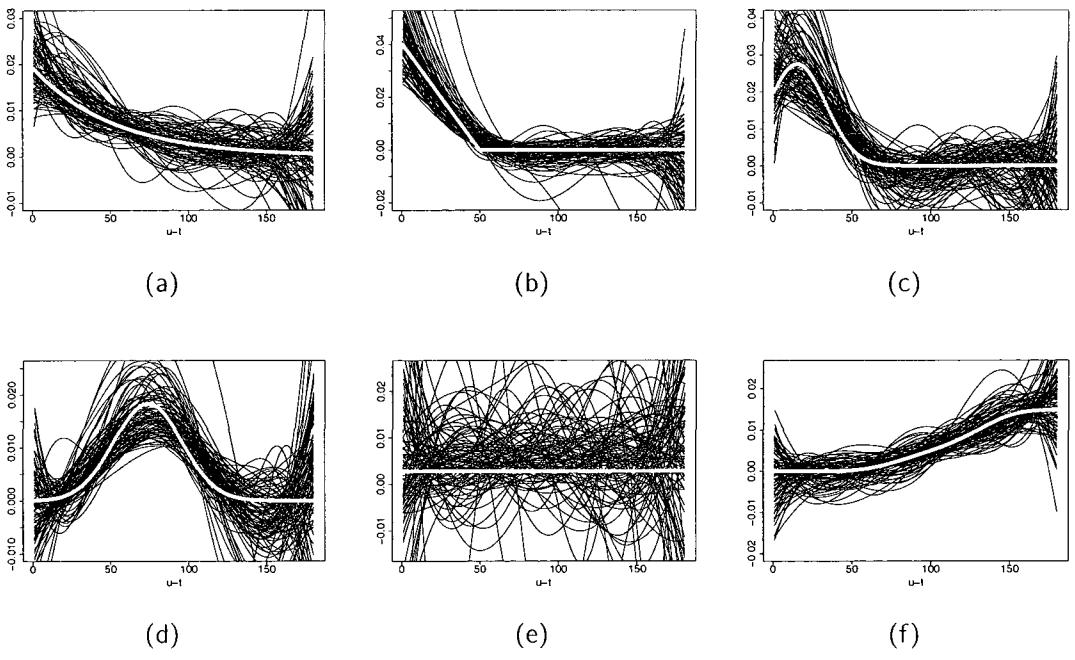

Figure 6–2: A random sample of 100 normalized estimated weight functions for the unconstrained models with the true weight function in thick white: *Bi-linear* (b); *Exponential* (a); *Early peak* (c); *Inverted U* (d); *Constant* (e); *Hat* (f)

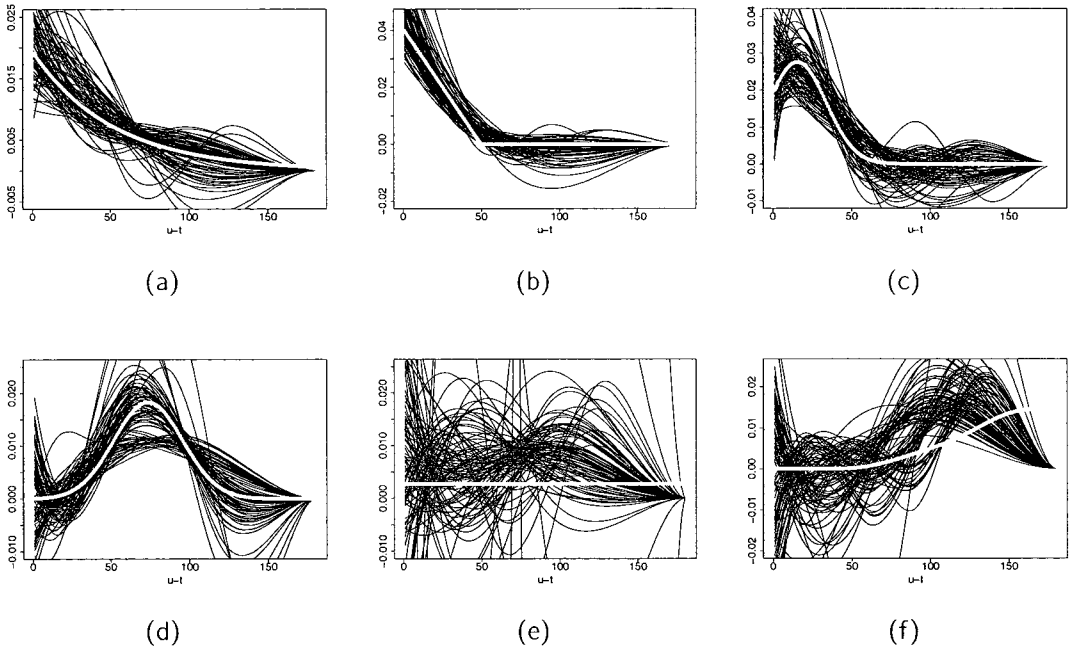

Figure 6–3: A random sample of 100 normalized estimated weight functions for the constrained models with the true weight function in thick white: *Bi-linear* (a); *Exponential* (b); *Early peak* (c); *Inverted U* (d); *Constant* (e); *Hat* (f)

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Table 6–1: BIC-optimal model, by scenario, for each of the 1,000 simulated samples

	Weight functions						
Models	Exponential	Bi-linear	Inverted U	Early peak	Constant	Hat	Null
			Unconstrained models				
1 knot	3	4	25	5	0	151	0
2 knots	0	1	1	1	0	7	0
3 knots	1	0	1	0	0	0	0
Total	4	5	27	6	0	158	0
			Constrained models				
1 knot	926	925	396	648	5	8	0
2 knots	11	56	541	275	0	10	0
3 knots	1	14	14	71	0	2	0
Total	938	995	951	994	5	20	0
			Other models				
DOSE	0	0	0	0	70	0	236
CUMDOSE	58	0	22	0	924	822	277
Total	58	0	22	0	995	822	1,000

Table 6–2: Frequency of BIC-optimal models among the WCE models and the alternative models, (% statistically significant likelihood ratio test for the exposure, corrected $\alpha_0^* = 0.039$)

	Weight functions						
Models	Exponential	Bi-linear	Inverted U	Early peak	Constant	Hat	Null
			Unconstrained models				
1 knot	3 (100%)	4 (100%)	25 (100%)	5 (100%)	8 (39.2%)	690 (98.6%)	3 (3.9%)
2 knots	0 (100%)	1 (100%)	1 (100%)	1 (100%)	0 (35.9%)	10 (97.7%)	0 (3.1%)
3 knots	2 (100%)	0 (100%)	1 (100%)	0 (100%)	0 (34.4%)	1 (96.4%)	1 (3.0%)
			Constrained models				
1 knot	983 (100%)	925 (100%)	413 (100%)	648 (100%)	962 (41.4%)	201 (76.0%)	979 (4.0%)
2 knots	12 (100%)	56 (100%)	546 (100%)	275 (100%)	25 (38.4%)	87 (88.2%)	16 (3.7%)
3 knots	1 (100%)	14 (100%)	14 (100%)	71 (100%)	5 (36.5%)	11 (90.1%)	1 (3.9%)
Total	1000	1000	1000	1000	1000	1000	1000
			Other models				
DOSE	21 (100%)	403(100%)	0 (0%)	44(100%)	70 (28.6%)	3 (100%)	481 (9.14%)
CUMDOSE	979 (100%)	597(100%)	1000 (100%)	966(100%)	930 (75.1%)	977 (92.3%)	519 (6.74%)
Total	1000	1000	1000	1000	1000	1000	1000

Table 6–3: Estimated γ from 1,000 simulations for each of the weight function scenarios

		All models			Best BIC models			
Weight	True γ	mean($\hat{\gamma}$)	SD($\hat{\gamma}$)	% Bias	mean($\hat{\gamma}$)	SD($\hat{\gamma}$)	% Bias	#Samples
				Unconstrained models				
Exponential	1.386	1.346	0.328	-2.886%	0.987	0.963	-28.788%	3
Bi-linear	1.386	1.390	0.385	0.289%	0.672	1.123	-51.515%	4
Inverted U	1.386	1.425	0.352	2.814%	1.344	0.511	-3.030%	25
Early peak	1.386	1.385	0.361	-0.072%	1.671	0.686	20.563%	5
Constant	1.386	0.689	0.315	-50.289%	0.000	-	-100.000%	1
Hat	1.386	1.388	0.304	0.144%	1.515	0.323	9.307%	151
Null	0	-0.024	0.322	-2.400%	0.000	-	0.000%	1
				Constrained models				
Exponential	1.386	1.317	0.269	-4.978%	1.318	0.271	-0.068%	938
Bi-linear	1.386	1.372	0.299	-1.010%	1.373	0.298	-0.938%	995
Inverted U	1.386	1.467	0.322	5.844%	1.470	0.324	0.084%	951
Early peak	1.386	1.372	0.305	-0.014%	1.372	0.305	-0.014%	994
Constant	1.386	0.546	0.251	-60.606%	0.993	0.337	-28.355%	5
Hat	1.386	0.785	0.287	-43.362%	0.815	0.329	-41.198%	20
Null	0	-0.009	0.259	-0.099%	0.000	-	0.000%	1

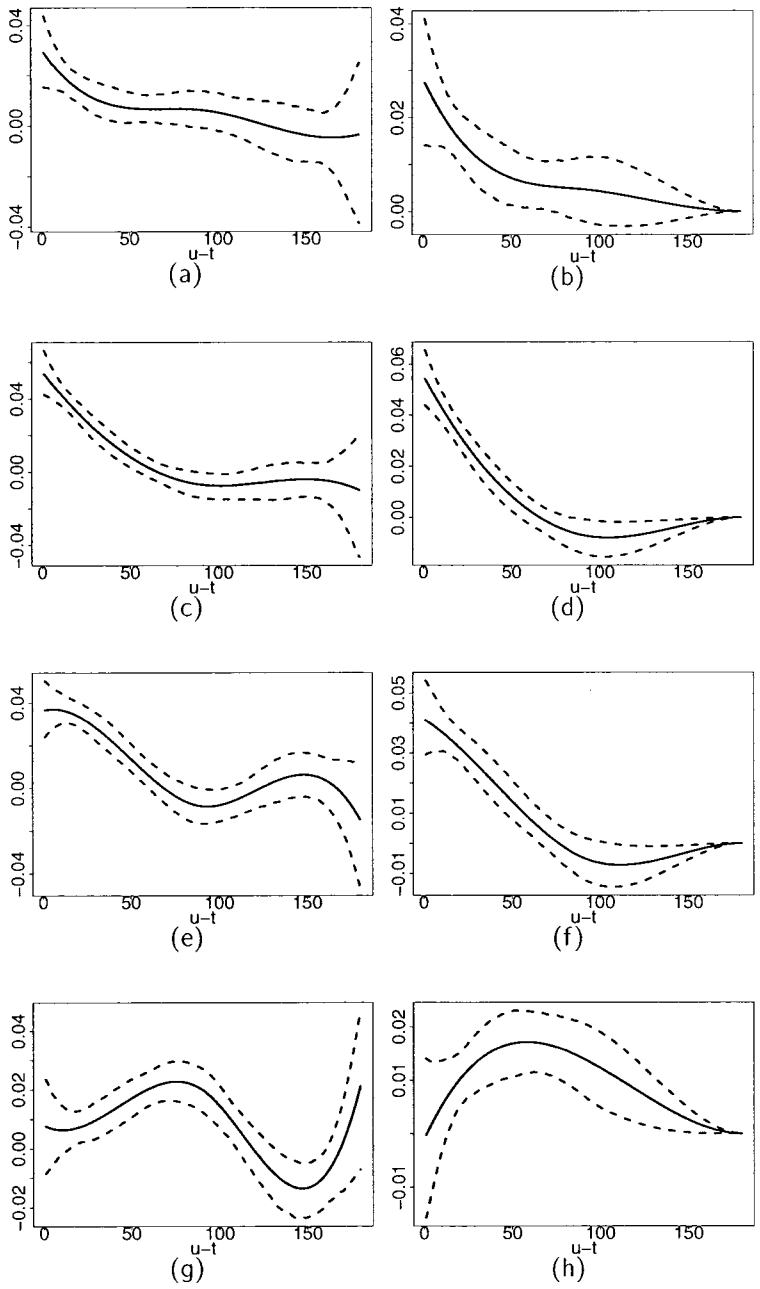

Figure 6–4: Estimate of the weight functions (solid line) and pointwise 95% bootstrap confidence interval (dashed line): *Bi-linear* Unconstrained (a) and Constrained (b); *Exponential* Unconstrained (c) and Constrained (d); *Early peak* Unconstrained (e) and Constrained (f); *Inverted U* Unconstrained (g) and Constrained (h)

6.8 Additional material

In manuscript 2, I generated time-dependent exposure patterns and I the value of $\gamma = \ln 4$ to generate the event times conditional on the exposure. This may seem like a large magnitude of effect, but in reality, it leads to plausible magnitude of effects once the individual patterns of exposure are considered, using the method describe in equation (6.8). Table (6–4) shows, for 1 simulated sample and for every scenario considered, the individual HR resulting from contrasting each of individual patterns of use over 180 days with periods of non-use. The corresponding histograms are showed in Figure 6–5.

Table 6–4: Quantiles for the distribution of individual hazard ratios for Scenarios 1-6 from 1 simulation

Estimated weight functions	**Minimum**	**25%**	**50%**	**75%**	**Maximum**
Bi-Linear	1.00	1.42	2.05	3.47	19.36
Exponential	1.00	1.42	1.81	2.45	11.40
Early peak	1.00	1.42	2.04	3.30	18.90
Inverted U	1.00	1.12	1.61	2.22	11.15
Constant	1.00	1.12	1.26	1.39	2.11
Hat	1.00	1.00	1.13	1.62	5.88

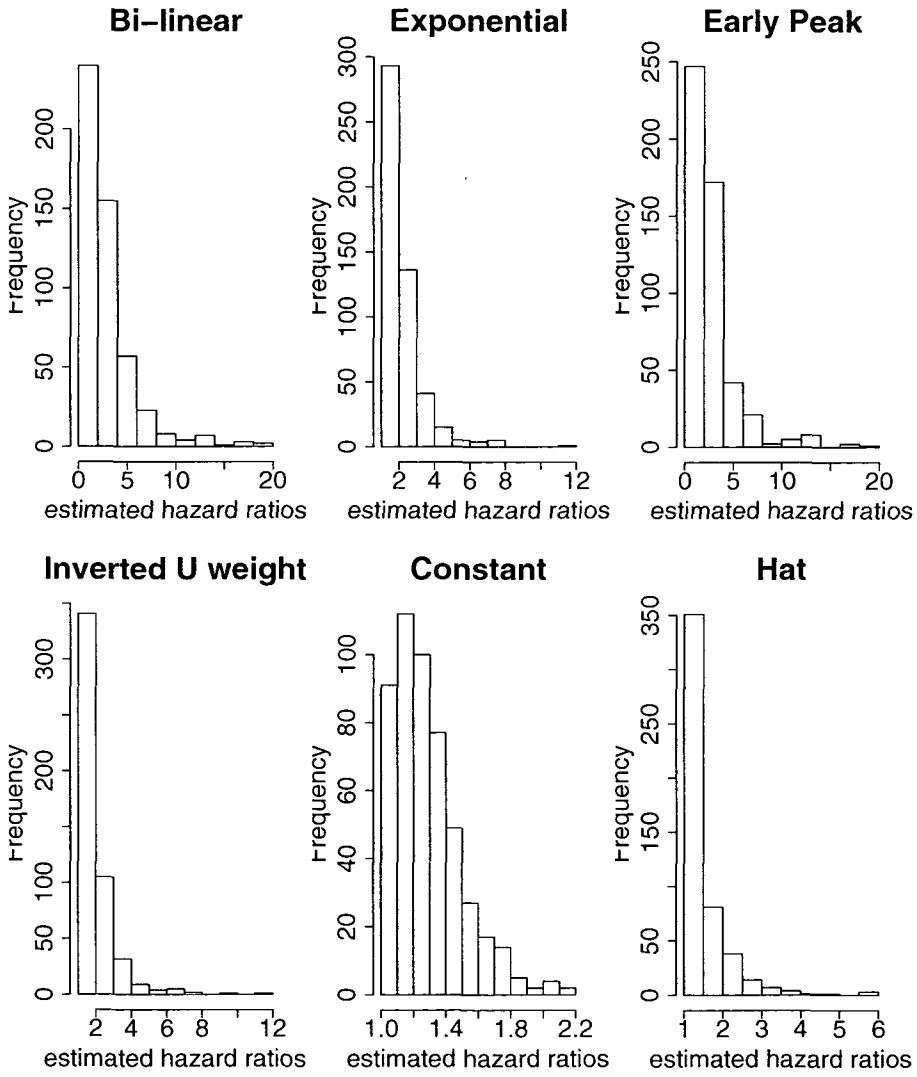

Figure 6–5: Histograms for the distribution of individual hazard ratios for Scenarios 1-6 from 1 simulation

CHAPTER 7
Manuscript 3: Re-assessing the associations between selected benzodiazepines and fall-related injuries in the elderly

7.1 Preamble

In manuscript 2, I proposed a novel method for modelling the weighted cumulative exposure (WCE) metric in the Cox proportional hazards model where the function that assigns weight to past exposures is estimated using cubic B-splines. Using the simulations methods developed in the manuscript 1, the proposed approach was validated in manuscript 2. In the present manuscript 3, I illustrate the use of the WCE method by re-assessing the associations between the use of selected benzodiazepines and fall-related injuries in the elderly.

The choice of this real-life example was motivated by both discrepant results reported in pharmacoepidemiological studies of benzodiazepines and the pharmacological literature that indicated that pharmacokinetics properties differed among benzodiazepines. The latter findings implied that some benzodiazepines accumulated in the body for a longer time, suggesting the potential for cumulative effects, which likely differed across different benzodiazepines. I wanted to investigate this hypothesis by using the weighted cumulative exposure methodology developed in manuscript 2 separately for each of the eight benzodiazepines available in the dataset. I used three alternative representations of the past history of benzodiazepine use, each based on the proposed WCE methodology: (1) weighted cumulative dose; (2) weighted cumulative duration of past use; and (3) a combination of weighted cumulative duration of past use and current dose. I also estimated alternative models with unweighted time-dependent representations of current and cumulative exposure.

The publications cited in Manuscript 3 are listed in the general reference section at the end of the thesis. Additional material is provided at the end of the chapter. The R code for the WCE models can be found in Appendix B.

Manuscript 3: Re-assessing the association between benzodiazepine use and the risk of fall-related injuries using a weighted cumulative exposure metric

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Abstract

Purpose: Evidence suggests that the use of benzodiazepines increases the risk of fall-related injuries in the elderly. However, the possibility of cumulative effects have not be thoroughly investigated.

Methods: The associations between the use of eight benzodiazepines and the risk of fall-related injuries is assessed using a weighted cumulative exposure metric that assigns to each dose taken in the past a weight that represents the importance of that dose in explaining the current risk of fall.

Data: Administrative database for a cohort of 23963 new users of benzodiazepines, aged 65 and older, in Québec, Canada, between 1990 and 1994.

Results: Current dose of Flurazepam was associated with an increased risk of fall-related injuries (HR = 1.67, 95% CI 1.14-2.46). The first day of use of Nitrazepam was associated with a HR of 1.82 (95%CI 1.22-2.22) but the HR increased to 6.35 (95%CI 3.25-11.17) after a week of uninterrupted use. The effect of a 30-day exposure to Alprazolam was 1.27 (1.13-1.42).

Conclusion: Mechanisms affecting the risk of falls differ across benzodiazepines so benzodiazepine-specific analyses should be preferred over simpler analyses that group all benzodiazepines together or assume the effects are similar within categories of half-life.

KEYWORDS: benzodiazepines, elderly, injuries, pharmacoepidemiology; proportional hazards model; time-dependent covariates, cumulative exposure.

7.2 Introduction

There is mounting epidemiological evidence supporting the link between the use of benzodiazepines and fall-related injuries in the elderly [114, 115, 116, 117, 127, 129, 104, 119, 118]. This is of particular concern since benzodiazepine use is common in the elderly, with annual prevalence estimates ranging from 10% to 30% [94, 95, 96, 97, 98], and elderly users tend to use benzodiazepines repeatedly and for longer periods than recommended [99, 100, 2].

However, what constitutes a high risk use of benzodiazepines is still uncertain. Indeed, it remains unclear whether the risk of fall is present for each benzodiazepine [128, 119, 121, 122, 123], and whether there are systematic differences between products with short versus long half-lives [114, 115, 116, 117, 118, 110, 120]. In addition, while some studies suggest a dose-response relationship between current dose of benzodiazepine and the risk of fall [110, 119], others suggest an effect of the duration or timing of the treatment of benzodiazepines [124, 121]. These findings underline the need for further benzodiazepine-specific analyses, in which both the dose and the timing of exposure are taken into account. The possibility of a cumulative effect must be evaluated, as the pharmacokinetics literature suggests that effective concentrations of some benzodiazepines may persist in the blood for many hours after their intake [92, 88].

Yet, adequately modelling exposure to benzodiazepines poses a particular challenge, especially given the uncertainty about the etiological relevance of doses taken in different time periods, and the potential cumulative effects of exposure over time [10, 12, 11]. To address this challenge, we propose to combine the information about duration, intensity and timing of exposure into a time-varying summary measure, the weighted cumulative exposure (WCE) [18, 19, 12]. The WCE is obtained by (i) multiplying each dose taken in the past by a weight that represents the importance

of that dose in explaining the current risk of fall, and (ii) summing the weighted past doses up to the current time.

The use of the WCE framework already offered insights regarding the risk of falls associated with the use of three benzodiazepines (Flurazepam, Nitrazepam, and Temazepam) [14]. In that study, Abrahamowicz *et al.* provided empirical evidence that the effect of recent doses of benzodiazepines on the risk of fall was cumulating over time, a feature that conventional models that accounted for only current use or current dose of benzodiazepine could not capture [14]. Furthermore, their results suggested a different mechanism linking the drug exposure and the risk of falls for each of the three benzodiazepines considered, possibly reflecting the differences in their elimination half-life and/or withdrawal effect [14]. However, as the authors recognized, their modelling approach was limited by the *a priori* selection of the parametric form of the function that assigns the weights to the benzodiazepine doses taken in the past [14]. Indeed, an incorrect specification of the parametric form of such weight function may lead to biased estimation, decreased statistical power and/or incorrect etiologic conclusions [12, 20].

We have recently proposed and validated a flexible method that addresses this limitation by estimating the weight function used in the WCE framework directly from the data, without the need for arbitrary *a priori* assumptions regarding its parametrization [164]. In addition to avoiding the issues related to potential mis-specification of the form of the weight function, the new method provides empirical insights regarding the mechanisms linking the pattern of medication use with the risk of outcomes.

In the current paper, we re-assess the associations between the use of eight benzodiazepines and the risk of fall-related injuries using the new flexible WCE method.

7.3 Methods

7.3.1 Data source

We re-analyzed a cohort of new users of benzodiazepines that was previously assembled by Tamblyn *et al.* from administrative databases from the province of Québec, Canada, where all residents aged 65 years and older have public insurance coverage for prescription drugs, and hospital and medical care [123]. Specifically, four RAMQ (Régie de l'assurance maladie du Québec) databases were linked with encrypted individual identifiers. The physician claims dataset provided information on the date, diagnosis and medical services supplied at each medical visit, while the hospitalization database provided admission and discharge dates as well as diagnostic causes for admission (International Classification of Diseases, Ninth Revision (ICD-9)). The prescription database provided information on the drugs prescribed, the dose, the duration of the treatment, and the date when the prescription was filled. Finally, demographic information contained in the beneficiary database included sex, age and date of death. The use of these administrative databases for pharmacoepidemiological studies has been validated elsewhere [165, 166, 167].

7.3.2 Study population

The initial cohort consisted of a random sample of 517,450 community-dwelling elderly people, who were listed in the administrative database and were aged 65 years or older on January 1, 1989 [123]. The prescription, hospitalization and medical services records of the cohort members were retrieved for the following five year period, ending on December 31, 1994. A cohort of 78,367 new users of benzodiazepines was formed by selecting all of elderly persons who had been prescribed at least one benzodiazepine between January 1st, 1990 and the end of follow-up, but had not been prescribed any benzodiazepine in 1989 [123]. Elderly who had died in 1989 or who were institutionalized for the complete follow-up period were excluded.

We then formed eight mutually-exclusive sub-cohorts, each of which included users of a particular benzodiazepine. Individuals were assigned to a given sub-cohort based on the first benzodiazepine prescribed during follow-up. Subjects who switched to another benzodiazepine during follow-up, or those who were prescribed two or more different benzodiazepines, were censored at the time when the second benzodiazepine was prescribed.

7.3.3 Fall-related injuries

The outcome was defined as the first fall-related injury occurring between January 1 1990 and December 31, 1994. Fall-related injuries consisted of a fracture of the hip, upper or lower extremity, pelvis, skull and thorax, or soft tissues-injuries [123].

7.3.4 Benzodiazepine use

We considered eight benzodiazepines (Alprazolam, Bromazepam, Chlordiazepoxide, Clonazepam, Flurazepam, Lorazepam, Nitrazepam, and Temazepam). Each individual history of benzodiazepine exposure was reconstructed from the drug type, date, dosage, number of pills, and duration of consecutive benzodiazepine prescriptions. Whenever two prescriptions of the same drug overlapped by less than 5 days, we assumed that the the second prescription represented an early refill, and that it would only start when the first prescription had been completed [123].

Daily dosage of each benzodiazepine was computed by first dividing the number of pills in a prescription by the duration of the prescription, and then multiplying that by the dose of a single pill [123]. To allow comparisons across benzodiazepines, for each product, we calculated a standardized daily dose by dividing the daily dosage by the World Health Organization recommended daily adult dose for that benzodiazepine [123, 168].

7.3.5 Statistical analysis

We used the Cox proportional hazards model with time-dependent covariates to assess the effect of exposure to benzodiazepines on the risk of fall-related injuries [30]. Time zero corresponded to January 1st, 1990. Elderly subjects were followed up until the first fall-related injury, or the end of follow-up (December 30, 1994), whichever came first. Since subjects initiated their first benzodiazepine use at different periods during follow-up, they enter the risk set only on the date they started their benzodiazepine prescription. We censored individuals who died, moved out of the province, or were institutionalized before their first fall-related injury.

Because of the uncertainty about the potential mechanisms linking the benzodiazepine exposures and fall-related injuries, for each product, we estimated seven alternative Cox models, each of which represented benzodiazepine exposure differently. All seven models was also adjusted for sex, age at baseline and the occurrence of an injury in 1989 [123, 14].

The first four models considered used conventional time-dependent variables to represent benzodiazepine exposure. *Model 1* included an indicator of current use, taking the value of 1 when the elderly person was using a benzodiazepine and 0 otherwise. *Model 2* represented exposure using the the current daily dose. *Model 3* included the cumulative (unweighted) duration of use, a variable that counted the number of days within the last 90 days for which the benzodiazepine was prescribed. Finally, *Model 4* represented expsure using a cumulative (unweighted) dose variable, calculated as the sum of all past daily doses in the last 90 days, from the beginning of the first relevant prescription to the current day. For each model, we used a likelihood ratio test to test for an association between the corresponding measure of benzodiazepine exposure and the hazard of fall-related injury, using a critical value

of $\alpha = 0.05$. We used the BIC [156] for time-to-event analysis to select the best-fitting model for current exposure (between *Model 1* and *Model 2*) and the best best-fitting model for cumulative exposure (between *Model 3* and *Model 4*), for each of the benzodiazepines.

7.3.6 Weighted cumulative benzodiazepine exposure

In addition to four aforementioned, conventional models, we estimated three models that relied on weighted cumulative exposure metrics (WCE) [12, 14, 11, 164]. Each metric assigns differential weights to past exposures, according to the time elapsed since the exposure. These weights represent the relative importance that exposures at different times have on the current risk of fall [12, 14, 11, 164]. In each WCE models, exposure to benzodiazepine of each subject was represented by a time-dependent weighted cumulative exposure metric, that was updated at each time u from the beginning to the end of follow-up.

Model 5 represented the exposure by the weighted cumulative dose. Standardized daily doses taken prior to time u, represented by $X(t)$, $t = 1, ..., u$ were assigned a weight $w(u - t)$ that was based on the time elapsed since the current time u and that represented the importance of the dose at time $(u - t)$ on the risk of fall-related injury at time u. For example, a decreasing weight function would assign smaller weights to doses more remote in time and, thus, would assume that the recent doses were more important in explaining the current risk of fall-related injuries than doses taken in the past. At each time u, the corresponding past weighted doses, prior to time u, were summed to form a time-dependent weighted cumulative dose variable:

$$WCDose(u) = \sum_{t}^{u} w(u - t)X(t), \tag{7.1}$$

The weight function, $w(u-t)$, was estimated using cubic regression B-splines, i.e. piecewise cubic polynomial functions [74, 60]. Cubic regression splines provide smooth estimates that are flexible enough to represent a variety of clinically plausible shapes [76], and that can easily be computed [155]. The flexibility of the spline function is determined by the number of interior knots, which are the points where adjacent polynomial pieces join each other.. We estimated models with 1 to 3 knots, which is generally considered sufficient to model a smooth uni- or bi-modal curve and reduces the risk of major over-fitting bias [51]. Knots were placed at equal distances within the etiologically relevant exposure window (see below).

We *a priori* assumed that doses taken three or more months ago could not affect the current risk of falls. Accordingly, we restricted the weight function to smoothly decrease to zero for exposures that occurred 90 or more days ago. In sensitivity analyses, we also considered alternative etiologically relevant exposure windows of 60 and 180 days. The fit of alternative models, with different number of knots, and different sizes of the etiologically relevant exposure window, was compaired using the BIC, and the best-fitting WCE model for a given benzodiazepine was selected.

In a similar fashion, in *Model 6*, we constructed a weighted cumulative duration of treatment variable (WCDur), obtained by replacing the standardized daily doses $X(t)$ in equation (7.1) by binary time-varying indicators of exposure status, that were taking the value of 1 on days where the subject was prescribed a benzodiazepine and 0 otherwise.

In *Model 6* it was represented by the weighted cumulative duration of treatment (WCDur); in *Model 7* exposure to benzodiazepine was represented by two time-dependent variables: the current dose and the weighted cumulative duration.

To assess the precision of our estimates, pointwise confidence intervals for the weight function $w(u-t)$ were obtained using non-parametric bootstrap re-sampling

technique [160] that accounted for both the sampling variation of the regression coefficients, and the uncertainty at the model selection stage [45, 49]. In each model, we tested the association between the corresponding WCE and fall-related injury using the likelihood ratio test with the appropriate degrees of freedom [49]. For *Model 7*, we tested the hypothesis that the two measures of benzodiazepine exposure, current dose and weighted cumulative duration, improve the fit to the data, by using the joint likelihood ratio test with degrees of freedom calculated as the degrees of freedom for the weighted cumulative duration plus 1 for the current dose effect.

To illustrate the implications of the estimated association between WCE and the risk of fall-related injury, for each model we computed different histories of exposure, keeping other variables constant. As showed in Table (7–1), for the spline-based models, we estimated five hazard ratios corresponding to following five comparisons: (i) we estimated the effect of a single dose of the benzodiazepines by comparing a current user at the recommended daily dose who has not used the benzodiazepine previously to a non-user over that same period; (ii) similarly, we estimated the effect of short-term use of benzodiazepine by comparing a current user, at the recommended daily dose who has used the benzodiazepine for the last 7 days versus a non-user over that same period; (iii) we estimated the effect of the timing of the exposure by comparing a current user at the recommended dose who has used the benzodiazepine for 7 days and a past user who has used the benzodiazepine for a week, between 14 and 7 days ago, at the recommended dose; (iv) we estimated the effect of the duration of the treatment by comparing a current user at the recommended dose who has used the benzodiazepine for 30 days and a current user at the recommended dose who has used a benzodiazepine for 7 days; (v) we estimated the joint effect of differences in both the timing and the dose by comparing a current

user at the recommended dose who has used the benzodiazepine for 14 days and a past user who used the benzodiazepine at twice the recommended dose 7 days ago for 14 days.

7.4 Results

The baseline characteristics of each of the benzodiazepine users are reported in Table 7–2. The Chlordiazepoxide cohort had the smallest number of fall-related injuries (50 falls, 6.4%), while the Lorazepam cohort had the largest (841 falls, 15.8%). In fact, since the cohort for Lorazepam had both a large sample size and the highest number of events, we stratified the analysis of its effects by sex. The mean age in 1989 was very similar across cohorts, and varied between 72 and 73 years (SD around 5 years). The proportion of subjects who had an injury in 1989 ranged from 4.1% in the Bromazepam cohort to 6.4% in the Chlordiazepoxide cohort. The proportion of males varied between 38.6% in the Bromazepam cohort to 55.9% in the Flurazepam cohort.

We analyzed each of the cohorts with both the conventional and the weighted cumulative exposure (WCE) models, and compared the fit of the models using the BIC. Table 7–3 shows the three best-fitting, among the seven candidate models, for each benzodiazepine. For the second and third best models, we show the difference in BIC (Δ BIC) relative to the minimum BIC model. Aserisks indicate models for which the variable(s) representing the benzodiazepine exposure had a statistically significant association, at $\alpha = 0.05$, with the fall-related injuries. Table 7–4 shows the estimated hazard ratios (HR) obtained from the conventional models (*Models 1-4*) representing current or cumulative measures of exposure or dose. The weight functions estimated with the best-fitting WCE models for Alprazolam, Flurazepam, Nitrazepam and Temazepam are shown in Figure 7–1. Finally, Table 7–5 shows the

estimated HR for the five comparisons summarized in Table (7–1) from the WCE models for selected benzodiazepines.

For two of the benzodiazepines (Flurazepam and Nitrazepam), the best-fitting models were those that represented exposure using the WCE metric. For Flurazepam, the best model was *Model 5*, which represented exposure using the weighted cumulative dose over 60 days. The estimated weight function, as well as its 95% pointwise confidence band, is shown in Panel (a) of Figure 7–1. The estimated weight function was relatively flat in the first 10 days but decreased thereafter. This shape suggests cumulative effects of exposures to flurazepam during first 10 days. On the other hand, doses more than 20 days ago were given weights close to zero, suggesting the effect did not last beyond three weeks after exposure.

Hazards ratios obtained from the conventional models indicated that while the higher current dose of Flurazepam was associated with an increased risk of fall-related injuries (*Model 2* HR = 1.67, 95% CI 1.14-2.46), the cumulative dose over 90 days was not (*Model 4* HR = 1.12 95% CI 0.94-1.34). This pattern of findings is consistent with the estimated weight function for Flurazepam, which suggests that the effects of Flurazepam cumulate only during the first 20 days of use, with higher weights assigned to recent doses (Panel (a) of Figure 7–1). This suggests that *Model 4*, which represented unweighted cumulative Flurazepam dose over 90 days, summed the doses over periods of use that were not contributing to the current risk of falls, resulting in a very weak association. The HR obtained from the best-fitting weighted cumulative dose model (*Model 5*) for comparing the risk associated with the use of Flurazapam for the last 7 days, at the recommended daily dose, relative to a period of non-use was 1.68 (95% CI 0.68-3.05). The uncertainty in the estimation of the early part of the Flurazapam curve, as indicated by the large width of the 95% pointwise bootstrap confidence band in Panel (a) of Figure 7–1, explained the

wide 95% CI for this association. Still, the WCE curve showed in Panel (a) of Figure 7–1 fitted the data slightly better ($p < 0.001$) than the model that assumed no association, which emphasizes the importance of short-term, cumulative effects of Flurazepam.

The best-fitting model for Nitrazepam was *Model 6*, which represented exposure using the weighted cumulative duration over an exposure window of 60 days. The estimated weight function for Nitrazepam is shown in Panel (b) of Figure 7–1. In comparison to that of Flurazepam, the weight function for Nitrazepam assigned much higher weights to very recent doses, and decreased more rapidly, so that exposures that occurred more than a week ago were given a weight close to zero. Thus, *Model 6* indicated that the higher risk of fall was associated with the use of Nitrazepam in the previous week. This finding was consistent with the conventional *Model 1*, which had a statistically significant hazard ratio of 4.68 (95% CI 2.91-7.52) for current use of Nitrazepam. However, the weighted cumulative duration model fit these data better (Table 7–3) and provided more accurate assessment of the impact of recent use of Nitrazepam.

According to the weighted cumulative duration of exposure model, the first day of use of Nitrazepam was associated with about 80% risk increase (HR=1.82 95%CI 1.22-2.22) but the relative risk increased to about 6 after a week of uninterrupted use (HR=6.35 95%CI 3.25-11.17) and to about 15 after a month of uninterrupted use (HR=15.31 95%CI 7.29-34.10) (Table 7–5). This large HR associated with a 30-day period of uninterrupted Nitrazepam use is in part due to the bump in the estimated weight function that occurred at around 25 days after the initiation of Nitrazepam use (Panel (b) of Figure 7–1). As a results, on a given day, exposures to Nitrazepam that occurred from 20 to 35 days ago are assigned positive weights, which resulted in a large hazard ratio. It is unclear whether the bump in the estimated weight function

for Nitrazepam is due to overfit bias, or whether it reflects the true mechanism that links Nitrazepam use to fall-related injuries. However, the weight functions estimated by the three best models for Nitrazepam (Table 7–3) had a similar shape (graphs not shown), and the pointwise bootstrap confidence band around the estimated weight function in Panel (b) of Figure 7–1 is fairly narrow, indicating that the estimation of the weight function for Nitrazepam was relatively robust.

In the case of Alprazolam, the best-fitting model was the conventional model that represented exposure by its unweighted cumulative duration, and produced a HR of 1.27 (95%CI 1.13-1.42) for the effect of a 30-day exposure to Alprazolam. Interestingly, *Model 6*, which represented exposure using the weighted cumulative duration of treatment over 180 days, was selected as the third best-fitting model by the BIC, and also detected a statistically significant association between Alprazolam and fall related injury. The estimated weight function for Alprazolam is shown in Panel (c) of Figure 7–1. Compared to the other weight functions shown in Figure 7–1, the weight function for Alprazolam was relatively flat with weights decreasing very slowly with increasing time since exposure. Thus, the WCE estimate is consistent with the best-fitting unweighted cumulative duration model, which corresponds to using the WCE metric with a constant weight function, which assigns the same weight to all exposures in the past.

Similarly, the best-fitting model for Clonazepam was the unweighted cumulative duration of treatment. The increase in risk of fall-related injuries associated with 30 days of uninterrupted use of Clonazepam was around 20% (HR = 1.23 (95%CI 1.01-1.46). None of the WCE models were selected as the three best models for Clonazepam.

Finally, the BIC-optimal models failed to detect a statistically significant association with fall-related injuries for the other four benzodiazepines (Chlordiazepoxide,

Lorazepam, Temazepam and Bromazepam). On the other hand, the previous study that used the parametric WCE metric had found that it accurately described the association between Temazepam and fall-related injuries [14]. Therefore, we investigated further the results obtained from the best WCE model for Temazepam, which was *Model 7* with a relevant exposure time window of 180 days. Similarly to the best-fitting model in [14], *Model 7* included both the current dose of Temazepam, and the weighted cumulative duration of exposure. A likelihood ratio test applied the joint effects of both the current dose and the cumulative use detected statistically significant association with the risk of fall-related injury (p=0.017).

Interestingly, while the effect of the current dose was protective (HR=0.38), the estimated weight function, as shown in panel (d) of Figure 7–1, decreased as time since exposure increased, suggesting an increase in risk of falls with cumulating use of Temazepam. The joint effect of the current dose and the weighted cumulative duration of Temazepam use was summarized by the HR showed in Table 7–5. The HR associated with cumulative use of Temazepam at the recommended daily dose for 1, 7, and 30 days was, respectively, 0.42 (95% CI 0.16-0.97), 0.63 (95% CI 0.29-1.15), and 1.17 (95% CI 0.66-2.01) (Table 7–5). Overall, *Model 7* suggested that there is no risk of fall-related injuries associated with cumulative use of Temazepam.

7.5 Discussion

We re-assessed the associations between the use of selected benzodiazepines and fall-related injuries using both conventional models (current exposure, unweighted cumulative exposure) and models that represented exposure using weighted cumulative exposure (WCE) metrics. In the WCE framework, past exposures are weighted according to a function that assesses their contributions to the current risk, depending on the time elapsed since exposure. Then, the weighted exposures are accumulated to create a time-dependent covariate representing the current value of the WCE

[12, 11, 14, 164]. We used a recently developed flexible method [164] that allowed us to estimate the weight function directly from the data, thus avoiding making *a priori* assumptions about the form of this function.

Our results highlight the importance of considering the hypothesis that the effects of benzodiazepines may cumulate over time. Indeed, while previous studies did not detect any association between the *current* use of Nitrazepam and Alprazolam [117, 119, 122, 123], our results suggest statistically significant and clinically important associations between cumulative use of these benzodiazepines and fall-related injuries. Indeed, our estimates show that subjects who used Nitrazepam for a week, at the recommended daily dose, may have a six-fold increase in the risk of fall-related injuries. Furthermore, the lower bound of the 95% confidence interval suggests that the risk is increased by a factor of a least three (scenario (ii) in Table 7–5).

In addition, similar to previous studies, we provide evidence of a statistically significant association between the use of Flurazepam and the risk of fall-related injuries [122, 123, 14]. However, the use of the weighted cumulative dose metric offered additional insights regarding the mechanism linking Flurazepam use to the risk of falls, by suggesting that, on a given day, the window of etiologically relevant exposure for Flurazepam is limited to approximately the 10 previous days.

All but one [122] of the previous studies that investigated the effect of Temazepam on fall-related injuries detected a statistically significant association [117, 119, 123, 14]. Consistent with [14], we find that the use of Temazepam only has a statistically significant association with the risk of fall-related injuries when both the current dose and the cumulative use are taken into account. However, the corresponding hazard ratios suggest that there is no risk of fall-related injuries associated with cumulative use of Temazepam.

Our results for Bromazepam are consistent with other studies, who also did not find any association between Bromazepam use and fall-related injuries [122, 123]. Unlike the current study, the only study that considered the effect of current use of Chlorazepoxide on the risk of fall-related injury detected a statistically significant association (HR = 1.83 (1.04-3.22)) [123]. Our cohort of Chlorazepoxide users had the smallest number of fall-related injuries (n=50), and the low statistical power might have prevented us from detecting a statistically significant association. Finally, unlike other studies, our results did not suggest a statistically significant association between Lorazepam and fall-related injuries [122, 119, 123].

It has been suggested that the use of benzodiazepines with a long half-life was riskier than shorter half-life benzodiazepines because a prolonged elimination half-life implied a longer presence of the drug in the body [131]. Our results agree with two previous studies that did not support the hypothesis that the half-life of benzodiazepines explains the differences in the risk associated with their use [110, 119]. Similarly, our results do not suggest any systematic effect of the dose of benzodiazepine. In fact, while dose seem to be an important risk factor for Flurazepam, it is not for other benzodiazepines such as Alprazolam, Nitrazepam and Clonazepam, for which the duration of treatment seems to be a more important determinant of the risk of fall-related injuries.

Although the WCE models provided more insight than the conventional models regarding the associations between exposure to selected benzodiazepines and the risk of falls, they tended to produce estimates with slightly wider 95% confidence intervals than the conventional models. This is common to nonparametric methods, where attempts to avoid incorrect specification of the parametric form of the exposure metric lead to more complex models, which in turn result in increased variance and wider confidence intervals [63].

In addition, the interpretation of our results should account for the limitations related with the use of administrative datasets for pharmacoepidemiological studies. First, our measure of exposure was based on prescriptions of benzodiazepines, and not on their actual use [163, 169, 26]. This, combined with the fact that benzodiazepines may be prescribed on an as-needed basis (PRN *pro re nata*), could cause misclassification of the exposure [123]. It was reported that the proportion of falls in users of PRN and non PRN benzodiazepines was relatively similar [110], which would imply that the exposure misclassification was non-differential, and, thus, would lead to attenuated estimates of the hazard ratios [163, 123]. Furthermore, although our analyses controlled for age, sex, and previous falls, we did not account for other factors that could have partly confounded the association between benzodiazepine exposure and falls-related injuries, such as other medication use or co-morbidity [163, 169].

In conclusion, our study highlights the importance of considering the possibility that the effects of use of some benzodiazepines on fall-related injuries may cumulate over time. It also indicates that mechanisms affecting the risk of falls differ across benzodiazepines. This suggests that benzodiazepine-specific analyses, which consider both the dose and the timing of the exposure, should be preferred over simpler analyses that group all benzodiazepines together, assume the effects are similar within categories of half-life, and/or limit exposure measurement to current use or current dose. These methodological recommendations might likely apply to the studies of other medications, where the patterns of use and/or dose vary over time.

Table 7–1: Scenarios for estimating the relative risks (adjusted hazard ratios) from the weighted cumulative exposure models

	Pattern of use			**Reference**		
	Dose	Duration	Timing	Dose	Duration	Timing
Scenario (i)	1	1 day	current	not exposed	180 days	current
Scenario (ii)	1	7 days	current	not exposed	180 days	current
Scenario (iii)	2	7 days	current	1	7 days	current
Scenario (iv)	1	7 days	current	1	7 days	14 to 7 days ago
Scenario (v)	1	14 days	current	2	14 days	seven days ago

Table 7–2: Descriptive statistics by benzodiazepine

Benzodiazepine		**Half-life (hours)**	**Sample size**	**Events Number (%)**	**Mean age (SD)**	**Males Number (%)**	**Injury in 1989 Number (%)**
Flurazepam		100	4,666	252 (5.4%)	72.4 (5.3)	2,608 (55.9%)	224 (4.8%)
Chlordiazepoxide		100	777	50 (6.4%)	72.4 (5.3)	397 (51.1%)	50 (6.4%)
Clonazepam		20-80	1,549	101 (6.6%)	72.4 (5.6)	690 (44.5%)	74 (4.8%)
Nitrazepam		16-55	1,056	104 (9.8%)	73.5 (5.7)	481 (45.6%)	47 (4.5%)
Alprazolam		12-15	3,614	268 (7.5%)	72.1 (5.3)	1,435 (39.7%)	156 (4.3%)
Lorazepam		10-20	10,197	841 (8.25%)	73.2 (5.8)	3,996 (39.2%)	504 (4.9%)
	Men		3,996	195 (4.88%)	72.9 (5.6)	-	195 (4.9%)
	Women		6,201	646 (10.42%)	73.5 (5.9)	-	309 (5.0%)
Temazepam		10-20	3,418	165 (4.9%)	73.2 (5.8)	1769 (51.7%)	148 (4.3%)
Bromazepam		8-30	3,544	191 (5.4%)	72.1 (5.3)	1,367 (38.6%)	146 (4.1%)

Table 7–3: Three best models for each of the benzodiazepines

Benzodiazepine (Number of events)	**Best model**	**Second best model**	**Third best model**
Flurazepam (252)	WCDose, 1 knot, 60 days***	WCDose, 1 knot, 90 days***	WCDur, 1 knot, 60 days***
		Δ BIC[1] = 0.5	Δ BIC = 1.3
Chlordiazepoxide (50)	Unweighted cum. dose	Unweighted cum. dur	Current dose
		Δ BIC = 0.32	Δ BIC = 7.8
Clonazepam (101)	Unweighted cum. dur.*	Unweighted cum. dose	Current use
		Δ BIC = 3.9	Δ BIC = 5.0
Nitrazepam (104)	WCDur, 2 knots, 60 days***	Current dose + WCDur 2 knots, 60 days***	WCDur, 3 knots, 60 days***
		Δ BIC= 1.8	Δ BIC = 7.5
Alprazolam (268)	Unweighted cum. dur.***	Current use**	WCDur, 1 knot, 180 days***
		Δ BIC = 10.3	Δ BIC = 10.6
Lorazepam (men) (195)	Unweighted cum. dur.	Unweighted cum. dose	Current dose
		Δ BIC = 1.0	Δ BIC = 1.3
Lorazepam (women) (646)	Current dose	Current use	Unweighted cum. use
		Δ BIC = 0.2	Δ BIC = 2.6
Temazepam (165)	Unweighted cum. dur.	Unweighted cum. dose	Current use
		Δ BIC = 1.5	Δ BIC = 1.8
Bromazepam (191)	Unweighted cum. dose	Unweighted cum. dur.	Current use
		Δ BIC = 0.1	Δ BIC = 1.5

Δ BIC indicates the difference in BIC relative to the best model for a given benzodiazepine. The higher the Δ BIC is, the less competitive a given model is.

* statistically significant likelihood ratio tests at $\alpha = 0.05$ for the effect of the variables representing exposure to benzodiazepines.

** statistically significant likelihood ratio tests at $\alpha = 0.01$ for the effect of the variables representing exposure to benzodiazepines.

*** statistically significant likelihood ratio tests at $\alpha = 0.001$ for the effect of the variables representing exposure to benzodiazepines.

Table 7–4: Conventional estimates of the association between benzodiazepines and fall related injuries

Benzodiazepines	**Current exposure†**		**Cumulative exposure‡**	
	HR	**95% CI**	**HR**	**95% CI**
Flurazepam[2,4]	1.67	(1.14-2.46)	1.12	(0.94-1.34)
Chlordiazepoxide[2,4]	1.33	(0.53-3.35)	1.16	(0.75-1.80)
Clonazepam [1,3]	1.19	(0.77-1.83)	1.23	(1.04-1.46)
Nitrazepam[1,3]	4.68	(2.91-7.52)	1.20	(1.04-1.39)
Alprazolam[1,3]	1.46	(1.11-1.92)	1.27	(1.13-1.42)
Lorazepam (men)[1,4]	0.96	(0.68-1.35)	1.14	(0.93-1.43)
Lorazepam (women)[2,3]	0.69	(0.47-1.03)	0.99	(0.85-1.15)
Temazepam[1,3]	1.06	(0.74-1.50)	1.10	(0.96-1.26)
Bromazepam[1,3]	0.93	(0.63-1.39)	1.11	(0.95-1.30)

† HR associated with a 1-day exposure to benzodiazepine at the standard dose compared to a day of non-use, as estimated by the lowest BIC model between the model with current use *Model 1* and the model with current dose *Model 2*. The first superscript beside the name of the benzodiazepine represents the model used for the current exposure.

‡ HR associated with a 30-day exposure to benzodiazepine at the standard dose compared to a 30-day period of non-use as estimated by the lowest BIC model between the model with unweighted cumulative duration (*Model 3*) and the model with unweighted cumulative dose (*Model 4*). The second superscript beside the name of the benzodiazepine represents the model used for the cumulative exposure.

Table 7–5: Weighted cumulative exposure hazard ratio estimates of the association between selected benzodiazepines and fall related injuries (95% CI)

Benzodiazepines	Comparison (i) 1-day exposure	Comparison (ii) 7-day exposure	Comparison (iii) 30-day exposure	Comparison (iv) Timing
Flurazepam[5]	1.07	1.68	2.83	1.37
	(0.70-1.26)	(0.68-3.05)	(1.45-4.34)	(0.43-3.45)
Nitrazepam[6]	1.82	6.35	15.31	4.62
	(1.22-2.22)	(3.25-11.17)	(7.29-34.10)	(2.35-8.03)
Alprazolam[6]	1.01	1.10	1.37	1.03
	(0.98-1.04)	(0.90-1.30)	(0.94-1.93)	(0.87-1.17)
Temazepam[7]	0.42	0.63	1.17	0.52
	(0.16-0.97)	(0.29-1.15)	(0.66-2.01)	(0.22-1.04)

[5] Estimates from the weighted cumulative dose model (*Model 5*).
[6] Estimates from the weighted cumulative duration of treatment model (*Model 6*).
[7] Estimates from the current dose + weighted cumulative duration of treatment model (*Model 7*).
Scenario (i) compares a current user at the recommended dose who has used the benzodiazepine for 1 days and a non-user.
Scenario (ii) compares a current user at the recommended dose who has used the benzodiazepine for 7 days and a non-user.
Scenario (iii) compares a current user at the recommended dose who has used the benzodiazepine for 30 days and a non-user.
Scenario (iv) compares a current user at the recommended dose who has used the benzodiazepine for 7 days and a past user who has used the benzodiazepine for a week, between 14 and 7 days ago, at the recommended dose.

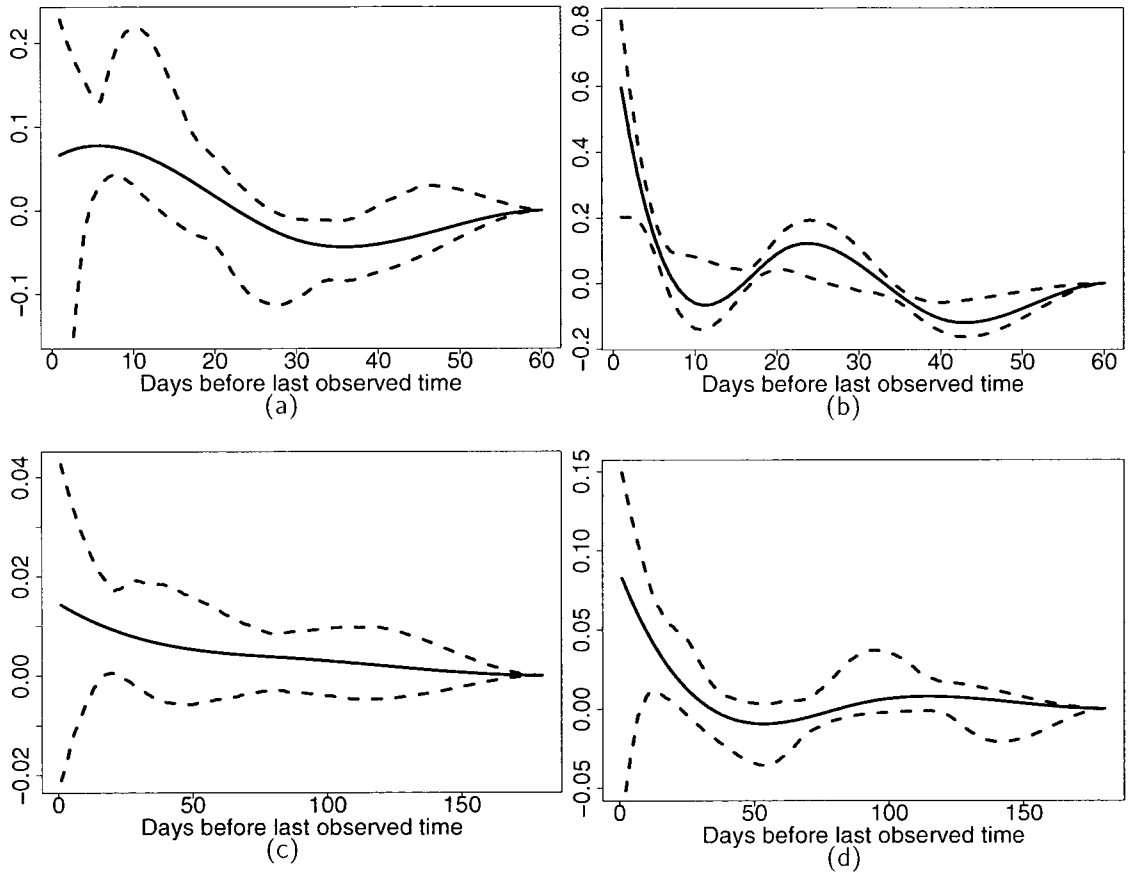

Figure 7–1: Estimated weight function and 95% pointwise bootstrap confidence intervals (dotted curves); (a) *Flurazepam*, weighted cumulative dose, 60 days; (b) *Nitrazepam*, weighted cumulative duration of treatment, 60 days; (d) *Alprazolam*, weighted cumulative duration of treatment, 180 days; (d) *Temazepam*, weighted cumulative duration of treatment and current dose, 180 days.

7.6 Additional material

The results of the models are presented for each benzodiazepine and each time window considered.

Table 7–6: Summary of findings for the association between alprazolam use and fall-related injuries in the elderly - Exposure time window of 60 days

Model and exposure		$\hat{\beta}_{dose}$	LRT p-value (df)	Likelihood	BIC
No exposure		-	-	-1961.46	3939.69
Weighted cumulative dose					
	1 knot	-	0.098 (3)	-1958.31	3950.17
	2 knots	-	0.045 (4)	-1956.58	3952.29
	3 knots	-	0.064 (5)	-1956.25	3957.23
Weighted cumulative duration					
	1 knot	-	0.001 (3)	-1953.31	3940.17
	2 knots	-	< 0.001 (4)	-1950.87	3940.88
	3 knots	-	0.001 (5)	-1950.47	3945.66
Weighted cumulative duration and current dose					
	1 knot	-0.9743	< 0.001 (4)	-1950.65	3940.43
	2 knots	-0.8313	< 0.001 (5)	-1948.94	3942.61
	3 knots	-0.8038	< 0.001 (6)	-1948.69	3947.7
Alternative TD models					
Indicator of current use		0.3774	0.01 (1)	-1958.15	3938.65
Current dose		0.2786	0.226 (1)	-1960.73	3943.82
Unweighted cumulative use		0.008	< 0.001 (1)	-1953.00	3928.37
Unweighted cumulative dose		0.007	0.139 (1)	-1958.434	3939.23

Table 7–7: Summary of findings for the association between alprazolam use and fall-related injuries in the elderly - Exposure time window of 90 days

Model and exposure		$\hat{\beta}_{dose}$	LRT p-value (df)	Likelihood	BIC
No exposure		-	-	-1961.46	3939.69
Weighted cumulative dose					
	1 knot	-	0.118 (3)	-1958.53	3950.6
	2 knots	-	0.135 (4)	-1957.95	3955.04
	3 knots	-	0.103 (5)	-1956.88	3958.48
Weighted cumulative duration					
	1 knot	-	0.001 (3)	-1952.87	3939.29
	2 knots	-	0.001 (4)	-1952.62	3944.37
	3 knots	-	0.001 (5)	-1951.04	3946.82
Weighted cumulative duration and current dose					
	1 knot	-1.01	< 0.001 (4)	-1949.83	3938.79
	2 knots	-0.9815	< 0.001 (5)	-1949.9	3944.52
	3 knots	-0.8657	< 0.001 (6)	-1948.96	3948.23
Alternative TD models					
Indicator of current use		0.3774	0.01 (1)	-1958.15	3938.65
Current dose		0.2786	0.226 (1)	-1960.73	3943.82
Unweighted cumulative use		0.008	< 0.001 (1)	-1953.00	3928.37
Unweighted cumulative dose		0.007	0.139 (1)	-1958.434	3939.23

Table 7–8: Summary of findings for the association between alprazolam use and fall-related injuries in the elderly - Exposure time window of 180 days

Model and exposure		$\hat{\beta}_{dose}$	LRT p-value (df)	Likelihood	BIC
No exposure		-	-	-1961.46	3939.69
Weighted cumulative dose					
	1 knot	-	0.107 (3)	-1958.41	3950.37
	2 knots	-	0.187 (4)	-1958.37	3955.89
	3 knots	-	0.286 (5)	-1958.35	3961.43
Weighted cumulative duration					
	1 knot	-	0.001 (3)	-1952.7	3938.95
	2 knots	-	0.001 (4)	-1952.52	3944.19
	3 knots	-	0.003 (5)	-1952.45	3949.63
Weighted cumulative duration and current dose					
	1 knot	-0.9016	< 0.001 (4)	-1949.82	3938.77
	2 knots	-0.9232	< 0.001 (5)	-1949.74	3944.2
	3 knots	-1.0251	< 0.001 (6)	-1949.31	3948.94
Alternative TD models					
Indicator of current use		0.3774	0.01 (1)	-1958.15	3938.65
Current dose		0.2786	0.226 (1)	-1960.73	3943.82
Unweighted cumulative use		0.008	< 0.001 (1)	-1953.00	3928.37
Unweighted cumulative dose		0.007	0.139 (1)	-1958.434	3939.23

Table 7–9: Summary of findings for the association between bromazepam use and fall-related injuries in the elderly - Exposure time window of 60 days

Model and exposure		$\hat{\beta}_{dose}$	LRT p-value (df)	Likelihood	BIC
No exposure		-	-	-1395.9	2807.56
Weighted cumulative dose					
	1 knot	-	0.239 (3)	-1393.79	2819.1
	2 knots	-	0.269 (4)	-1393.31	2823.39
	3 knots	-	0.229 (5)	-1392.46	2826.93
Weighted cumulative duration					
	1 knot	-	0.136 (3)	-1393.13	2817.78
	2 knots	-	0.177 (4)	-1392.75	2822.26
	3 knots	-	0.038 (5)	-1390.02	2822.05
Weighted cumulative duration and current dose					
	1 knot	-0.246	0.227 (4)	-1393.08	2822.92
	2 knots	-0.1175	0.275 (5)	-1392.73	2827.49
	3 knots	0.1668	0.066 (6)	-1389.99	2827.25
Alternative TD models					
Indicator of current use		-0.07	0.731 (1)	-1395.84	2812.7
Current dose		0.0459	0.91 (1)	-1395.9	2812.8
Unweighted cumulative use		0.003	0.207 (1)	-1395.11	2811.23
Unweighted cumulative dose		0.006	0.304 (1)	-1395.37	2811.76

Table 7–10: Summary of findings for the association between bromazepam use and fall-related injuries in the elderly - Exposure time window of 90 days

Model and exposure		$\hat{\beta}_{dose}$	LRT p-value (df)	Likelihood	BIC
No exposure		-	-	-1395.9	2807.56
Weighted cumulative dose					
	1 knot	-	0.383 (3)	-1394.37	2820.26
	2 knots	-	0.396 (4)	-1393.86	2824.49
	3 knots	-	0.435 (5)	-1393.48	2828.98
Weighted cumulative duration					
	1 knot	-	0.344 (3)	-1394.24	2819.99
	2 knots	-	0.188 (4)	-1392.83	2822.42
	3 knots	-	0.206 (5)	-1392.3	2826.62
Weighted cumulative duration and current dose					
	1 knot	-0.5572	0.413 (4)	-1393.93	2824.62
	2 knots	-0.2316	0.282 (5)	-1392.78	2827.57
	3 knots	-0.2177	0.294 (6)	-1392.26	2831.78
Alternative TD models					
Indicator of current use		-0.07	0.731 (1)	-1395.84	2812.7
Current dose		0.0459	0.91 (1)	-1395.9	2812.8
Unweighted cumulative use		0.003	0.207 (1)	-1395.11	2811.23
Unweighted cumulative dose		0.006	0.304 (1)	-1395.37	2811.76

Table 7–11: Summary of findings for the association between bromazepam use and fall-related injuries in the elderly - Exposure time window of 180 days

Model and exposure		$\hat{\beta}_{dose}$	LRT p-value (df)	Likelihood	BIC
No exposure		-	-	-1395.9	2807.56
Weighted cumulative dose					
	1 knot	-	0.563 (3)	-1394.88	2821.27
	2 knots	-	0.685 (4)	-1394.77	2826.3
	3 knots	-	0.707 (5)	-1394.43	2830.87
Weighted cumulative duration					
	1 knot	-	0.532 (3)	-1394.8	2821.12
	2 knots	-	0.705 (4)	-1394.82	2826.4
	3 knots	-	0.472 (5)	-1393.62	2829.26
Weighted cumulative duration and current dose					
	1 knot	-0.8939	0.39 (4)	-1393.84	2824.45
	2 knots	-0.911	0.562 (5)	-1393.95	2829.91
	3 knots	-0.6015	0.508 (6)	-1393.26	2833.79
Alternative TD models					
Indicator of current use		-0.07	0.731 (1)	-1395.84	2812.7
Current dose		0.0459	0.91 (1)	-1395.9	2812.8
Unweighted cumulative use		0.003	0.207 (1)	-1395.11	2811.23
Unweighted cumulative dose		0.006	0.304 (1)	-1395.37	2811.76

Table 7–12: Summary of findings for the association between flurazepam use and fall-related injuries in the elderly - Exposure time window of 60 days

Model and exposure		$\hat{\beta}_{dose}$	LRT p-value (df)	Likelihood	BIC
No exposure		-	-	-1875.31	3767.2
Weighted cumulative dose					
	1 knot	-	< 0.001 (3)	-1865.17	3763.51
	2 knots	-	< 0.001 (4)	-1864.92	3768.54
	3 knots	-	0.001 (5)	-1864.78	3773.79
Weighted cumulative duration					
	1 knot	-	< 0.001 (3)	-1865.81	3764.8
	2 knots	-	0.001 (4)	-1865.49	3769.69
	3 knots	-	0.001 (5)	-1865.19	3774.62
Weighted cumulative duration and current dose					
	1 knot	0.1303	0.001 (4)	-1865.77	3770.25
	2 knots	0.2293	0.001 (5)	-1865.37	3774.98
	3 knots	0.2724	0.002 (6)	-1865.02	3779.81
Alternative TD models					
Indicator of current use		0.2917	0.089 (1)	-1873.86	3769.85
Current dose		0.5138	0.014 (1)	-1872.27	3766.66
Unweighted cumulative use		0.002	0.468 (1)	-1875.04	3772.21
Unweighted cumulative dose		0.004	0.234 (1)	-1875.60	3771.31

Table 7–13: Summary of findings for the association between flurazepam use and fall-related injuries in the elderly - Exposure time window of 90 days

Model and exposure		$\hat{\beta}_{dose}$	LRT p-value (df)	Likelihood	BIC
No exposure		-	-	-1875.31	3767.2
Weighted cumulative dose					
	1 knot	-	< 0.001 (3)	-1865.4	3763.97
	2 knots	-	< 0.001 (4)	-1865.22	3769.14
	3 knots	-	0.001 (5)	-1864.86	3773.96
Weighted cumulative duration					
	1 knot	-	0.001 (3)	-1866.93	3767.04
	2 knots	-	0.001 (4)	-1865.91	3770.53
	3 knots	-	0.001 (5)	-1865.46	3775.16
Weighted cumulative duration and current dose					
	1 knot	-0.1169	0.002 (4)	-1866.89	3772.49
	2 knots	0.0994	0.002 (5)	-1865.89	3776.01
	3 knots	0.2097	0.003 (6)	-1865.36	3780.48
Alternative TD models					
Indicator of current use		0.2917	0.089 (1)	-1873.86	3769.85
Current dose		0.5138	0.014 (1)	-1872.27	3766.66
Unweighted cumulative use		0.002	0.468 (1)	-1875.04	3772.21
Unweighted cumulative dose		0.004	0.234 (1)	-1875.60	3771.31

Table 7–14: Summary of findings for the association between flurazepam use and fall-related injuries in the elderly - Exposure time window of 180 days

Model and exposure		$\hat{\beta}_{dose}$	LRT p-value (df)	Likelihood	BIC
No exposure		-	-	-1875.31	3767.2
Weighted cumulative dose					
	1 knot	-	0.001 (3)	-1866.58	3766.33
	2 knots	-	0.001 (4)	-1865.31	3769.33
	3 knots	-	0.001 (5)	-1865.33	3774.89
Weighted cumulative duration					
	1 knot	-	0.003 (3)	-1868.23	3769.63
	2 knots	-	0.002 (4)	-1866.8	3772.31
	3 knots	-	0.005 (5)	-1866.96	3778.15
Weighted cumulative duration and current dose					
	1 knot	0.1724	0.006 (4)	-1868.11	3774.93
	2 knots	-0.0708	0.004 (5)	-1866.79	3777.81
	3 knots	-0.1331	0.01 (6)	-1866.91	3783.59
Alternative TD models					
Indicator of current use		0.2917	0.089 (1)	-1873.86	3769.85
Current dose		0.5138	0.014 (1)	-1872.27	3766.66
Unweighted cumulative use		0.002	0.468 (1)	-1875.04	3772.21
Unweighted cumulative dose		0.004	0.234 (1)	-1875.60	3771.31

Table 7–15: Summary of findings for the association between nitrazepam use and fall-related injuries in the elderly - Exposure time window of 60 days

Model and exposure		$\hat{\beta}_{dose}$	LRT p-value (df)	Likelihood	BIC
No exposure		-	-	-563.6	1141.13
Weighted cumulative dose					
	1 knot	-	< 0.001 (3)	-528.61	1085.09
	2 knots	-	< 0.001 (4)	-522.62	1077.75
	3 knots	-	< 0.001 (5)	-523.47	1084.1
Weighted cumulative duration					
	1 knot	-	< 0.001 (3)	-523.34	1074.56
	2 knots	-	< 0.001 (4)	-514.54	1061.59
	3 knots	-	< 0.001 (5)	-515.96	1069.07
Weighted cumulative duration and current dose					
	1 knot	0.4982	< 0.001 (4)	-520.7	1073.9
	2 knots	0.3718	< 0.001 (5)	-513.14	1063.43
	3 knots	0.3682	< 0.001 (6)	-514.63	1071.05
Alternative TD models					
Indicator of current use		1.5427	< 0.001 (1)	-537.41	1093.4
Current dose		0.8527	< 0.001 (1)	-541.25	1101.08
Unweighted cumulative use		0.006	0.031 (1)	-561.26	1141.10
Unweighted cumulative dose		0.004	0.031 (1)	-561.28	1141.15

Table 7–16: Summary of findings for the association between nitrazepam use and fall-related injuries in the elderly - Exposure time window of 90 days

Model and exposure		$\hat{\beta}_{dose}$	LRT p-value (df)	Likelihood	BIC
No exposure		-	-	-563.6	1141.13
Weighted cumulative dose					
	1 knot	-	< 0.001 (3)	-526.12	1080.11
	2 knots	-	< 0.001 (4)	-526.09	1084.68
	3 knots	-	< 0.001 (5)	-525.5	1088.15
Weighted cumulative duration					
	1 knot	-	< 0.001 (3)	-522.72	1073.3
	2 knots	-	< 0.001 (4)	-522.05	1076.61
	3 knots	-	< 0.001 (5)	-520.74	1078.64
Weighted cumulative duration and current dose					
	1 knot	0.4232	< 0.001 (4)	-520.7	1073.91
	2 knots	0.4966	< 0.001 (5)	-519.4	1075.96
	3 knots	0.4235	< 0.001 (6)	-518.9	1079.59
Alternative TD models					
Indicator of current use		1.5427	< 0.001 (1)	-537.41	1093.4
Current dose		0.8527	< 0.001 (1)	-541.25	1101.08
Unweighted cumulative use		0.006	0.031 (1)	-561.26	1141.10
Unweighted cumulative dose		0.004	0.031 (1)	-561.28	1141.15

Table 7–17: Summary of findings for the association between nitrazepam use and fall-related injuries in the elderly - Exposure time window of 180 days

Model and exposure		$\hat{\beta}_{dose}$	LRT p-value (df)	Likelihood	BIC
No exposure		-	-	-563.6	1141.13
Weighted cumulative dose					
	1 knot	-	< 0.001 (3)	-526.11	1080.09
	2 knots	-	< 0.001 (4)	-524.96	1082.43
	3 knots	-	< 0.001 (5)	-524.35	1085.85
Weighted cumulative duration					
	1 knot	-	< 0.001 (3)	-523.72	1075.32
	2 knots	-	< 0.001 (4)	-521.33	1075.17
	3 knots	-	< 0.001 (5)	-521.33	1079.82
Weighted cumulative duration and current dose					
	1 knot	0.434	< 0.001 (4)	-521.14	1074.78
	2 knots	0.3331	< 0.001 (5)	-519.98	1077.12
	3 knots	0.4089	< 0.001 (6)	-519.43	1080.65
Alternative TD models					
Indicator of current use		1.5427	< 0.001 (1)	-537.41	1093.4
Current dose		0.8527	< 0.001 (1)	-541.25	1101.08
Unweighted cumulative use		0.006	0.031 (1)	-561.26	1141.10
Unweighted cumulative dose		0.004	0.031 (1)	-561.28	1141.15

Table 7–18: Summary of findings for the association between clonazepam use and fall-related injuries in the elderly - Exposure time window of 60 days

Model and exposure		$\hat{\beta}_{dose}$	LRT p-value (df)	Likelihood	BIC
No exposure		-	-	-620.64	1255.12
Weighted cumulative dose					
	1 knot	-	0.735 (3)	-620.0	1267.69
	2 knots	-	0.609 (4)	-619.29	1270.88
	3 knots	-	0.711 (5)	-619.17	1275.27
Weighted cumulative duration					
	1 knot	-	0.225 (3)	-618.46	1264.61
	2 knots	-	0.077 (4)	-616.41	1265.14
	3 knots	-	0.114 (5)	-616.2	1269.32
Weighted cumulative duration and current dose					
	1 knot	-0.7935	0.336 (4)	-618.36	1269.03
	2 knots	-0.4212	0.131 (5)	-616.38	1269.69
	3 knots	-0.3215	0.179 (6)	-616.18	1273.9
Alternative TD models					
Indicator of current use		0.1709	0.447 (1)	-620.35	1259.16
Current dose		0.6812	0.564 (1)	-620.47	1259.4
Unweighted cumulative use		0.007	0.018 (1)	-617.83	1254.12
Unweighted cumulative dose		0.017	0.194 (1)	-619.79	1258.05

Table 7–19: Summary of findings for the association between clonazepam use and fall-related injuries in the elderly - Exposure time window of 90 days

Model and exposure		$\hat{\beta}_{dose}$	LRT p-value (df)	Likelihood	BIC
No exposure		-	-	-620.64	1255.12
Weighted cumulative dose					
	1 knot	-	0.574 (3)	-619.64	1266.97
	2 knots	-	0.676 (4)	-619.47	1271.25
	3 knots	-	0.718 (5)	-619.2	1275.31
Weighted cumulative duration					
	1 knot	-	0.124 (3)	-617.76	1263.21
	2 knots	-	0.15 (4)	-617.26	1266.83
	3 knots	-	0.145 (5)	-616.53	1269.98
Weighted cumulative duration and current dose					
	1 knot	-1.0787	0.191 (4)	-617.58	1267.47
	2 knots	-0.7793	0.225 (5)	-617.17	1271.25
	3 knots	-0.5333	0.217 (6)	-616.48	1274.5
Alternative TD models					
Indicator of current use		0.1709	0.447 (1)	-620.35	1259.16
Current dose		0.6812	0.564 (1)	-620.47	1259.4
Unweighted cumulative use		0.007	0.018 (1)	-617.83	1254.12
Unweighted cumulative dose		0.017	0.194 (1)	-619.79	1258.05

Table 7–20: Summary of findings for the association between clonazepam use and fall-related injuries in the elderly - Exposure time window of 180 days

Model and exposure		$\hat{\beta}_{dose}$	LRT p-value (df)	Likelihood	BIC
No exposure		-	-	-620.64	1255.12
Weighted cumulative dose					
	1 knot	-	0.423 (3)	-619.23	1266.16
	2 knots	-	0.399 (4)	-618.61	1269.53
	3 knots	-	0.536 (5)	-618.59	1274.1
Weighted cumulative duration					
	1 knot	-	0.078 (3)	-617.23	1262.16
	2 knots	-	0.073 (4)	-616.35	1265.0
	3 knots	-	0.097 (5)	-615.97	1268.87
Weighted cumulative duration and current dose					
	1 knot	-0.6818	0.138 (4)	-617.15	1266.61
	2 knots	-1.0762	0.112 (5)	-616.18	1269.27
	3 knots	-0.9087	0.144 (6)	-615.85	1273.24
Alternative TD models					
Indicator of current use		0.1709	0.447 (1)	-620.35	1259.16
Current dose		0.6812	0.564 (1)	-620.47	1259.4
Unweighted cumulative use		0.007	0.018 (1)	-617.83	1254.12
Unweighted cumulative dose		0.017	0.194 (1)	-619.79	1258.05

Table 7–21: Summary of findings for the association between Chlordiazepoxide use and fall-related injuries in the elderly - Exposure time window of 60 days

Model and exposure		$\hat{\beta}_{dose}$	LRT p-value (df)	Likelihood	BIC
No exposure		-	-	-292.17	596.08
Weighted cumulative dose					
	1 knot	-	0.823 (3)	-291.71	606.9
	2 knots	-	0.899 (4)	-291.64	610.66
	3 knots	-	0.952 (5)	-291.61	614.51
Weighted cumulative duration					
	1 knot	-	0.996 (3)	-292.14	607.75
	2 knots	-	0.985 (4)	-291.98	611.35
	3 knots	-	0.938 (5)	-291.54	614.37
Weighted cumulative duration and current dose					
	1 knot	0.5547	0.965 (4)	-291.88	611.15
	2 knots	0.5139	0.978 (5)	-291.77	614.84
	3 knots	0.599	0.934 (6)	-291.25	617.71
Alternative TD models					
Indicator of current use		-0.069	0.883 (1)	-292.16	599.97
Current dose		0.2833	0.592 (1)	-292.03	599.7
Unweighted cumulative use		0.002	0.770 (1)	-292.13	592.25
Unweighted cumulative dose		0.005	0.524 (1)	-292.17	591.93

Table 7–22: Summary of findings for the association between Chlordiazepoxide use and fall-related injuries in the elderly - Exposure time window of 90 days

Model and exposure		$\hat{\beta}_{dose}$	LRT p-value (df)	Likelihood	BIC
No exposure		-	-	-292.17	596.08
Weighted cumulative dose					
	1 knot	-	0.823 (3)	-291.72	606.9
	2 knots	-	0.91 (4)	-291.67	610.73
	3 knots	-	0.936 (5)	-291.52	614.35
Weighted cumulative duration					
	1 knot	-	0.998 (3)	-292.15	607.77
	2 knots	-	0.999 (4)	-292.16	611.7
	3 knots	-	0.912 (5)	-291.42	614.13
Weighted cumulative duration and current dose					
	1 knot	0.5709	0.959 (4)	-291.85	611.08
	2 knots	0.5803	0.988 (5)	-291.87	615.04
	3 knots	0.4862	0.93 (6)	-291.23	617.67
Alternative TD models					
Indicator of current use		-0.069	0.883 (1)	-292.16	599.97
Current dose		0.2833	0.592 (1)	-292.03	599.7
Unweighted cumulative use		0.002	0.770 (1)	-292.13	592.25
Unweighted cumulative dose		0.005	0.524 (1)	-292.17	591.93

Table 7–23: Summary of findings for the association between Chlordiazepoxide use and fall-related injuries in the elderly - Exposure time window of 180 days

Model and exposure		$\hat{\beta}_{dose}$	LRT p-value (df)	Likelihood	BIC
No exposure		-	-	-292.17	596.08
Weighted cumulative dose					
	1 knot	-	0.807 (3)	-291.68	606.84
	2 knots	-	0.751 (4)	-291.21	609.81
	3 knots	-	0.888 (5)	-291.32	613.93
Weighted cumulative duration					
	1 knot	-	0.996 (3)	-292.14	607.75
	2 knots	-	0.991 (4)	-292.03	611.45
	3 knots	-	0.999 (5)	-292.11	615.52
Weighted cumulative duration and current dose					
	1 knot	0.4796	0.969 (4)	-291.9	611.18
	2 knots	0.447	0.985 (5)	-291.84	614.97
	3 knots	0.5306	0.996 (6)	-291.85	618.92
Alternative TD models					
Indicator of current use		-0.069	0.883 (1)	-292.16	599.97
Current dose		0.2833	0.592 (1)	-292.03	599.7
Unweighted cumulative use		0.002	0.770 (1)	-292.13	592.25
Unweighted cumulative dose		0.005	0.524 (1)	-292.17	591.93

Table 7–24: Summary of findings for the association between temazepam use and fall-related injuries in the elderly - Exposure time window of 60 days

Model and exposure		$\hat{\beta}_{dose}$	LRT p-value (df)	Likelihood	BIC
No exposure		-	-	-1156.47	2328.26
Weighted cumulative dose					
	1 knot	-	0.593 (3)	-1155.52	2341.68
	2 knots	-	0.62 (4)	-1155.15	2346.05
	3 knots	-	0.664 (5)	-1154.85	2350.56
Weighted cumulative duration					
	1 knot	-	0.22 (3)	-1154.26	2339.16
	2 knots	-	0.332 (4)	-1154.18	2344.1
	3 knots	-	0.345 (5)	-1153.66	2348.17
Weighted cumulative duration and current dose					
	1 knot	-0.9371	0.04 (4)	-1151.46	2338.67
	2 knots	-0.9551	0.074 (5)	-1151.44	2343.74
	3 knots	-0.8938	0.112 (6)	-1151.32	2348.59
Alternative TD models					
Indicator of current use		0.0548	0.76 (1)	-1156.42	2333.27
Current dose		-0.0041	0.98 (1)	-1156.47	2333.37
Unweighted cumulative use		0.003	0.170 (1)	-1155.53	2331.49
Unweighted cumulative dose		0.001	0.523 (1)	-1156.27	2332.97

Table 7–25: Summary of findings for the association between temazepam use and fall-related injuries in the elderly - Exposure time window of 90 days

Model and exposure		$\hat{\beta}_{dose}$	LRT p-value (df)	Likelihood	BIC
No exposure		-	-	-1156.47	2328.26
Weighted cumulative dose					
	1 knot	-	0.318 (3)	-1154.71	2340.05
	2 knots	-	0.471 (4)	-1154.7	2345.14
	3 knots	-	0.579 (5)	-1154.57	2349.99
Weighted cumulative duration					
	1 knot	-	0.209 (3)	-1154.21	2339.05
	2 knots	-	0.313 (4)	-1154.09	2343.93
	3 knots	-	0.429 (5)	-1154.02	2348.89
Weighted cumulative duration and current dose					
	1 knot	-0.8861	0.036 (4)	-1151.33	2338.4
	2 knots	-0.9326	0.065 (5)	-1151.28	2343.41
	3 knots	-0.9676	0.103 (6)	-1151.2	2348.35
Alternative TD models					
Indicator of current use		0.0548	0.76 (1)	-1156.42	2333.27
Current dose		-0.0041	0.98 (1)	-1156.47	2333.37
Unweighted cumulative use		0.003	0.170 (1)	-1155.53	2331.49
Unweighted cumulative dose		0.001	0.523 (1)	-1156.27	2332.97

Table 7–26: Summary of findings for the association between temazepam use and fall-related injuries in the elderly - Exposure time window of 180 days

Model and exposure		$\hat{\beta}_{dose}$	LRT p-value (df)	Likelihood	BIC
No exposure		-	-	-1156.47	2328.26
Weighted cumulative dose					
	1 knot	-	0.705 (3)	-1155.77	2342.18
	2 knots	-	0.845 (4)	-1155.77	2347.29
	3 knots	-	0.289 (5)	-1153.38	2347.61
Weighted cumulative duration					
	1 knot	-	0.316 (3)	-1154.7	2340.04
	2 knots	-	0.515 (4)	-1154.84	2345.42
	3 knots	-	0.08 (5)	-1151.55	2343.95
Weighted cumulative duration and current dose					
	1 knot	-0.9547	0.017 (4)	-1150.48	2336.7
	2 knots	-1.0192	0.041 (5)	-1150.68	2342.21
	3 knots	-0.8338	0.02 (6)	-1148.96	2343.88
Alternative TD models					
Indicator of current use		0.0548	0.76 (1)	-1156.42	2333.27
Current dose		-0.0041	0.98 (1)	-1156.47	2333.37
Unweighted cumulative use		0.003	0.170 (1)	-1155.53	2331.49
Unweighted cumulative dose		0.001	0.523 (1)	-1156.27	2332.97

Table 7–27: Summary of findings for the association between lorazepam use and fall-related injuries in elderly men - Exposure time window of 60 days

	Model	Coefficient	LRT p-value (df)	Likelihood	BIC
No exposure		-	-	-1497.89	3006.41
Weighted cumulative dose					
	1 knot	-	0.425 (3)	-1496.49	3019.58
	2 knots	-	0.161 (4)	-1494.61	3021.13
	3 knots	-	0.152 (5)	-1493.85	3024.93
Weighted cumulative duration					
	1 knot	-	0.24 (3)	-1495.79	3018.16
	2 knots	-	0.078 (4)	-1493.69	3019.3
	3 knots	-	0.065 (5)	-1492.69	3022.6
Weighted cumulative duration and current dose					
	1 knot	-0.5712	0.257 (4)	-1495.23	3022.38
	2 knots	-0.36	0.116 (5)	-1493.47	3024.18
	3 knots	-0.2419	0.101 (6)	-1492.59	3027.72
Alternative TD models					
Indicator of current use		-0.0465	0.787 (1)	-1497.85	3011.66
Current dose		0.0292	0.919 (1)	-1497.88	3011.72
Unweighted cumulative use		0.001	0.676 (1)	-1497.8	3011.56
Unweighted cumulative dose		0.0046	0.229 (1)	-1497.16	3010.28

Table 7–28: Summary of findings for the association between lorazepam use and fall-related injuries in elderly men - Exposure time window of 90 days

	Model	Coefficient	LRT p-value (df)	Likelihood	BIC
No exposure		-	-	-1497.89	3006.41
Weighted cumulative dose					
	1 knot	-	0.494 (3)	-1496.69	3019.97
	2 knots	-	0.256 (4)	-1495.23	3022.37
	3 knots	-	0.229 (5)	-1494.44	3026.12
Weighted cumulative duration					
	1 knot	-	0.113 (3)	-1494.9	3016.4
	2 knots	-	0.041 (4)	-1492.9	3017.7
	3 knots	-	0.052 (5)	-1492.4	3022.03
Weighted cumulative duration and current dose					
	1 knot	-0.7842	0.087 (4)	-1493.82	3019.55
	2 knots	-0.5419	0.052 (5)	-1492.4	3022.02
	3 knots	-0.4507	0.07 (6)	-1492.06	3026.67
Alternative TD models					
Indicator of current use		-0.0465	0.787 (1)	-1497.85	3011.66
Current dose		0.0292	0.919 (1)	-1497.88	3011.72
Unweighted cumulative use		0.001	0.676 (1)	-1497.8	3011.56
Unweighted cumulative dose		0.0046	0.229 (1)	-1497.16	3010.28

Table 7–29: Summary of findings for the association between lorazepam use and fall-related injuries in elderly men - Exposure time window of 180 days

	Model	Coefficient	LRT p-value (df)	Likelihood	BIC
No exposure		-	-	-1497.89	3006.32
Weighted cumulative dose					
	1 knot	-	0.419 (3)	-1496.47	3019.31
	2 knots	-	0.53 (4)	-1496.3	3024.25
	3 knots	-	0.529 (5)	-1495.82	3028.55
Weighted cumulative duration					
	1 knot	-	0.169 (3)	-1495.37	3017.1
	2 knots	-	0.155 (4)	-1494.56	3020.76
	3 knots	-	0.062 (5)	-1492.63	3022.17
Weighted cumulative duration and current dose					
	1 knot	-0.2759	0.248 (4)	-1495.19	3022.01
	2 knots	-0.5115	0.172 (5)	-1494.03	3024.97
	3 knots	-0.8349	0.044 (6)	-1491.41	3025.01
Alternative TD models					
Indicator of current use		-0.0465	0.787 (1)	-1497.85	3011.52
Current dose		0.0292	0.919 (1)	-1497.88	3011.59
Unweighted cumulative use		0.001	0.676 (1)	-1497.8	3011.42
Unweighted cumulative dose		0.0046	0.229 (1)	-1497.16	3010.15

Table 7–30: Summary of findings for the association between lorazepam use and fall-related injuries in elderly women- Exposure time window of 60 days

	Model	Coefficient	LRT p-value (df)	Likelihood	BIC
No exposure		-	-	-5307.75	10628.45
Weighted cumulative dose					
	1 knot	-	0.264 (3)	-5305.77	10643.88
	2 knots	-	0.35 (4)	-5305.54	10649.89
	3 knots	-	0.118 (5)	-5303.37	10652.03
Weighted cumulative duration					
	1 knot	-	0.532 (3)	-5306.66	10645.67
	2 knots	-	0.413 (4)	-5305.78	10650.38
	3 knots	-	0.062 (5)	-5302.5	10650.29
Weighted cumulative duration and current dose					
	1 knot	-1.1275	0.03 (4)	-5302.41	10643.65
	2 knots	-1.0546	0.05 (5)	-5302.21	10649.72
	3 knots	-0.8739	0.017 (6)	-5300.02	10651.81
Alternative TD models					
Indicator of current use		-0.1837	0.067 (1)	-5306.08	10631.57
Current dose		-0.3651	0.059 (1)	-5305.97	10631.34
Unweighted cumulative use		-2e-04	0.851 (1)	-5307.74	10634.89
Unweighted cumulative dose		-4e-04	0.871 (1)	-5307.74	10634.9

Table 7–31: Summary of findings for the association between lorazepam use and fall-related injuries in elderly women - Exposure time window of 90 days

	Model	Coefficient	LRT p-value (df)	Likelihood	BIC
No exposure		-	-	-5307.75	10628.45
Weighted cumulative dose					
	1 knot	-	0.941 (3)	-5307.56	10647.47
	2 knots	-	0.2 (4)	-5304.76	10648.35
	3 knots	-	0.298(5)	-5304.71	10654.72
Weighted cumulative duration					
	1 knot	-	0.95 (3)	-5307.58	10647.51
	2 knots	-	0.367 (4)	-5305.61	10650.04
	3 knots	-	0.431 (5)	-5305.32	10655.93
Weighted cumulative duration and current dose					
	1 knot	-1.2339	0.022 (4)	-5302.02	10642.87
	2 knots	-1.1137	0.027 (5)	-5301.43	10648.16
	3 knots	-1.0964	0.05 (6)	-5301.45	10654.67
Alternative TD models					
Indicator of current use		-0.1837	0.067 (1)	-5306.08	10631.57
Current dose		-0.3651	0.059 (1)	-5305.97	10631.34
Unweighted cumulative use		-2e-04	0.851 (1)	-5307.74	10634.89
Unweighted cumulative dose		-4e-04	0.871 (1)	-5307.74	10634.9

Table 7–32: Summary of findings for the association between lorazepam use and fall-related injuries in elderly women - Exposure time window of 180 days

	Model	Coefficient	LRT p-value (df)	Likelihood	BIC
No exposure		-	-	-5307.75	10628.45
Weighted cumulative dose					
	1 knot	-	0.992 (3)	-5307.71	10647.77
	2 knots	-	0.998 (4)	-5307.69	10654.21
	3 knots	-	0.993 (5)	-5307.52	10660.33
Weighted cumulative duration					
	1 knot	-	0.523 (3)	-5306.63	10645.62
	2 knots	-	0.68 (4)	-5306.6	10652.03
	3 knots	-	0.814 (5)	-5306.63	10658.56
Weighted cumulative duration and current dose					
	1 knot	-0.958	0.024 (4)	-5302.15	10643.12
	2 knots	-1.1297	0.024 (1)	-5301.27	10647.83
	3 knots	-1.2345	0.036 (1)	-5301.03	10653.82
Alternative TD models					
Indicator of current use		-0.1837	0.067 (1)	-5306.08	10631.57
Current dose		-0.3651	0.059 (1)	-5305.97	10631.34
Unweighted cumulative use		-2e-04	0.851 (1)	-5307.74	10634.89
Unweighted cumulative dose		-4e-04	0.871 (1)	-5307.74	10634.9

CHAPTER 8
Discussion

Exposures that vary over time, both in terms of status and intensity, are frequently encountered in clinical and epidemiological research. While ignoring the time-varying nature of the exposure may lead to biased estimates of the association between the exposure and an outcome [7, 8, 9], modelling complex patterns of exposure is a challenging task, partly because the etiological relevance of past exposures is often unclear [10, 11, 12, 13]. The overall objective of this thesis was to develop a flexible method to combine the information about the duration, intensity and timing of exposure into a time-varying summary measure, the weighted cumulative exposure, in the Cox proportional hazards (PH) model [18, 19, 12]. In the WCE method, a weight function assigns each exposure in the past a weight that represented the importance of that exposure in explaining the current risk, and the current WCE is obtained by summing the weighted past exposures up to the current time. I proposed a novel parametrization of the Cox proportional hazards model with time-dependent covariates, which allows for a convenient estimation of the weight function using regression cubic B-splines. The flexibility of the cubic regression splines allowed me to avoid the restrictive assumptions about the functional form of the weight function.

The development of the weighted cumulative dose method presented in manuscript 2 involved several methodological challenges, and some of the proposed solutions, which may be useful in other flexible modelling applications. First, the proposed parametrization of the initially non-linear model into a linear model, illustrated how nonlinear functions of time-dependent covariates, or time-dependent effects [49],

can be represented by artificial time-dependent variables and estimated with standard software. Second, manuscript 2 offered a pragmatic solution, adapted from a different context [159], to perform hypothesis testing conditional on models that have been selected *a posteriori*, based on goodness of fit criteria. This addresses a major problem related to inference about flexible models, where *a posteriori* selection of the model complexity, or degree of smoothness, improves the accuracy of the estimates, but, at the same time, invalidates conventional statistical inference [47, 49]. Third, the bootstrap method used to calculate pointwise confidence bands around the weight function incorporated the uncertainty at the model selection stage, in addition to the sampling variation of the regression coefficients.

Conceptually speaking, the idea of a time-weighted cumulative exposure metric is related to that of time-varying coefficients in the PH model, where the constant log HR β is replaced by $\beta(t)$ [11]. One common application of the general varying-coefficient models proposed by Hastie and Tibshirani is the Cox PH model, in which the coefficients of baseline or fixed-in-time covariates are allowed to changed smoothly over the follow-up time [170]. This relaxes the assumption of proportional hazards and estimates how the hazard ratios associated with a given covariate change over time [31].

In comparison, while regression the coefficient associated with the WCE variable does not depend on time, the estimated weight function provides an indication of how the risk associated with an exposure changes over time. However, in the time-varying coefficient model, $\beta(t)$ is generally multiplied by a baseline or fixed-in-time exposure, and the model does not incorporate potential cumulative effects. In contrast, the WCE framework allows to investigate how the effect of past doses cumulate over time to produce the current risk on a given day, and allows assessing different importance of past exposures. This is reflected in the calculation of hazard

ratios associated with specific patterns of exposure, which vary according to both timing and intensity of past exposures. Extensions of the coefficient-varying Cox PH model have been suggested to incorporate time-dependant variables but they are restricted to indicators of one-time change in exposure status [171, 172]. Consequently, in comparison to the models with time-varying coefficients, the proposed WCE model offers a richer representation of past exposure history, and allows for both cumulative and time-dependent effects of current and past intensity of exposure on the hazard.

In manuscript 3, the WCE method was applied to re-assess the association between exposure to benzodiazepines and fall-related injuries. It provided substantive evidence that different benzodiazepines had different mechanisms underlying their association with the risk of fall-related injuries, and supported to the conjecture that the effects of some benzodiazepines cumulated over time. This application provided an illustration of potential advantages due to the use of a more precise representation of exposure than conventional exposure metrics based on current use, current dose, or indicators of use during specific time windows.

Furthermore, the application of the WCE for the benzodiazepine and fall-related injuries association also highlighted several features of the WCE model. First, in manuscript 3, it was showed how the WCE model could be adapted to model cumulative duration of exposure, with or without an additional time-dependent variable representing the current dose [14]. This proved useful as the best WCE model varied for different benzodiazepines. In addition, the use of several time windows provided a way to test the robustness of the estimated weight function. However, the example for Nitrazepam also illustrated that, in real-life applications with a limited number of events, it could be difficult to assess whether a more bumpy weight function were

representing the true underlying, complex mechanism or whether it simply reflected the overfitting bias.

The application of the WCE method to re-assess the associations between benzodiazepine use and the risk of fall-related injuries also generated programming challenges, whose solutions might prove useful in future analyses of large datasets. The database, which spanned over five years of daily data, had to be restructured in a counting process format where each individual day of follow-up was represented by a row in the data matrix. Careful programming was required to restrict the computational burden on the computer's memory. Accordingly, generic programs were created to partition the data in manageable subsets, in which WCE-related variables were created, before being subsequently merged together to create a data matrix. To optimize the estimation of the WCE models, the rows of the data matrix that corresponded to days when events occurred were extracted to form a smaller data matrix, on which the models were estimated. This reduced the size of the dataset considerably, without impacting on the accuracy of the estimation, since the lines that corresponded to a day on which no event did occur would not appear in any of the risk sets used to estimate the Cox PH model. While, alternatively, the WCE-related variables could have been created dynamically at the estimation stage, this would have required keeping excessively large data matrices in memory. With these automated approaches, the WCE method ended up being a computationally efficient alternative approach to nested case control for the analyses of cohort studies.

The WCE model developed in manuscript 2 was validated using simulations. Since the WCE method was computer-intensive, efficient methods were required to accurately generate cohorts in which the event times were conditional on complex time-dependent covariates. This motivated the use of the permutational algorithm and the development of its extension to include a rejection sample, which significantly

reduced the computational time. In addition to its ability to generate datasets that, once analyzed, provided virtually unbiased estimates with small variances, the class of permutational algorithms allows the user to easily select the marginal distribution of the event and/or censoring times.

It is important that researchers facilitate the replication of their findings by other researchers in order to accumulate scientific evidence [173]. One step towards that is to make the computer code or instructions for the analysis available publicly [173]. In that sense, the commented code for the proposed permutational algorithm and the code associated with the permutational algorithm and the WCE method will be publicly available on request and are included in Appendix A and B. Ideally, integrated, dynamic documents that contain text, code, data, and any auxiliary content needed to recreate the computations would be available [174]. Accordingly, I will also consider writing a R package for the class of permutational algorithm and for the WCE models [65].

The validity of the estimates from the WCE model depends on three underlying assumptions that warrant some discussion, especially in order to guide its use in future applications. First, similar to standard Cox proportional models, the proposed WCE model relies on the assumption of proportionality of hazards (PH) [30]. In our context, the PH assumption would be violated if two identical patterns of exposure that occurred at different times were leading to different effects on the risk. For example, in cohorts with long follow-up, early versus late effects of the same treatment may have different effects because of a change in risk over time, for example, due to the underlying aging process or disease progression. In the context of our application, this could occur if the prescribing of benzodiazepines changed over time, for example, if the tendency to prescribe a given benzodiazepine to individuals who were suspected to be at a greater risk of falls would become weaker over time.

Several methods have been proposed to check the PH assumption, ranging from a visual inspection of the Schoenfeld residuals to many formal tests [175]. All these methods are either performed on the complete model, or on each of the variables in the model. This becomes problematic in the case of the WCE model, because the hazard ratio for the weighted cumulative exposure is not directly estimated, but constructed from each of the coefficients of the artificial time-dependent covariates used to represent the exposure. In order to use the available methods to check the proportionality of hazards assumption I would either need to check each of the coefficients of the artificial time-dependent covariates, or use a global test of the proportionality of hazards for the entire model. It remains unclear how the violation of the proportional hazards assumption by one of the artificial time-dependent variables used in the WCE model would affect the accuracy of the entire WCE model. Neither testing each artificial time-dependent covariates coefficients nor the global model is a completely satisfying approach to test the proportionality of hazards and this issue needs to be investigated further. This does not affect the results reported in manuscript 2 since the simulations conducted in manuscript 2 were designed so that the proportionality of hazards assumptions would hold. If the assumption is violated, in some cases, an alternative could be to use an accelerated failure time model [176] or flexible extensions of the PH model that account for time-dependent effects [49].

Second, the WCE model assumes a linear effect of the weighted cumulative dose on the log hazard for the event. In the case of a non-linear dose-response relationship, the WCE model may provide biased estimates of the effect and even fail to detect existing associations. It is unlikely that the results of the use of the WCE model to re-assess the association between benzodiazepine exposure and fall-related injuries would be significantly affected by a violation of the linearity assumption. Indeed, the empirical range of the daily doses of benzodiazepine was restricted to a very few

values, in most cases corresponding to 0.5, 1 or 2 times the recommended adult daily dose. However, the linearity assumption may not be plausible in other applications of the WCE model. As Vacek suggested [12] the weighted cumulative metric may accommodate the assumption of nonlinearity of the effect of the exposure by replacing the dose $X(t)$ by a smooth dose-response function of the dose $g(X(t))$. The dose-response function can be estimated with a flexbile method such as regression splines but the resulting WCE model is no longer linear in the coefficients to estimate, so the conventional estimation techniques used in this thesis cannot be used [12, 140]. Still, in future, it may be possible to simultaneously estimate the weight function and the dose-response effect by using more sophisticated estimation techniques such as alternative conditional estimation, as described in [177].

Finally, in our analyses, I assumed that there were no time-dependent covariates that confounded the association between the exposure and the risk of an event. If the time-dependent exposure is both affected by and affecting a time-dependent covariate that is also related to the event, then the time-dependent covariate is both a confounder and an intermediate variable in the pathway between the exposure and the outcome [178]. Standard adjustment methods will give biased results for the estimates of the exposure on the hazard because they will also adjust for the effect of the exposure on the confounder [179]. If a time-dependent predictor of the risk of an event also predicts subsequent treatments, specialized methods such as structural equation modelling, estimated with g-estimation can be used [180, 181]. In depth discussions of the problem of time-dependent confounding include Hernan *et al.* [182], Robins and Greenland [183] and Robins [184].

Depending on the specific application, it remains unclear to what extent the WCE model is affected by violations of the assumptions described below. Since the simulations in manuscripts 1 and 2 were designed to meet these assumptions,

additional simulations may be needed to check whether the WCE will (or not) be robust to mild and more severe violations of assumptions.

The use of the WCE model was validated using simulations based on clinically plausible assumptions that resembled general features of the data analyzed in manuscript 3. However, additional simulations may be required to evaluate the effect of the following parameters: (i) how the estimates and statistical power would be affected by the use of the WCE method on a dataset with a markedly smaller number of events (e.g. < 100); (ii) how the ability of the WCE method to capture the shape of the weight function would be affected weakening of the exposure effect (e.g. log hazard for the WCE < 2); (iii) how the WCE method would perform in a case where the measure of exposure are sparse in time, for example if the method was used on the biannual assessments of the cardiovascular risk factors in the Framingham cohort [178].

Furthermore, the interpretation of the results of manuscript 3 must account for the limitations related with the use of administrative datasets for pharmacoepidemiological studies, such as the potential exposure misclassification due to using prescriptions as a proxy for the actual medication use [163, 169]. In addition, although our analyses controlled for age, sex, and previous falls, they did not account for other factors that could have partly confounded the association between benzodiazepine exposure and falls-related injuries, such as other medication use or co-morbidity [123].

In conclusion, with the underlying assumptions and limitations of the WCE method in mind, I see various potential applications where it could be used instead of more conventional models to possibly gain additional insights regarding the effect of the intensity, duration and timing of exposure on an outcome. Pharmacoepidemiological studies of both therapeutic or adverse events of drugs whose patterns of

use change over time would likely benefit from using the WCE methods. Alternatively, the WCE method could be used in environmental or occupational epidemiology studies of the health effects of long-term exposure to pollutants.

Furthermore, the method can be employed to assess the etiological relevance of risk factor values measured at different times or ages. For example, in cardiovascular epidemiology there is an ongoing controversy regarding the relative importance of risk factor values one had in middle life versus in older age [185, 186]. Similarly, the latency or lag of exposures such as smoking may vary considerably depending on the outcome [13]. The ability of the proposed method to estimate differential weights assigned to exposures that occurred at different periods in the past, while avoiding *a priori* assumptions about the shape of the weight function, makes it a promissing tool to address such complex issues.

Additionally, it will be interesting to develop an extension of the WCE model that allows for non-linear dose-response relationships and to validate this more complex version of the proposed method with simulations. The extended WCE method could then be applied to investigate the effect of lifetime patterns of cardiovascular risk factors, such as blood pressure, on cardiovascular risk, from data sources like the Framingham study where such variables are measured biannually. Indeed, several cardiovascular risk factors have been shown to have non-linear effects on the risk of myocardial infarction [187, 188] or cardiovascular mortality [189]. This application would warrant additional simulations on the effect of using the WCE on a more sparse matrix of exposure.

In conclusion, I hope that the implementation of the flexible modelling of the weighted cumulative dose in the familiar Cox proportional hazards model will motivate a more widespread use of the recency-weighted cumulative dose metric, provide useful

insights regarding the mechanisms linking the history of time-dependent exposure with the risk of events investigated in clinical and epidemiological studies.

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CHAPTER 9
Additional material

Appendix A - R code for the permutational algorithm

This Appendix contains the code for the permutational algorithm with and without rejection sampling. It is written for a model that uses three fixed-in-time variables, age, sex, comorbidity, and one TD covariate, bin.exp. It is also written assuming that the coefficient of the sex variable is negative but that can obviously be easily changed.

```
#############################################################################
#
#  Code for the permutational algorithm and its extension
#  Goal is to generate event times conditional on time-dependent covariates
#
#############################################################################
#
#  Author: Marie-Pierre Sylvestre
#          Department of Epidemiology, Biostatistics and Occupational Health,
#          McGill University, Montreal, Quebec, Canada.
#
#############################################################################
#
#  This program is meant to be used for non-commercial purposes only.
#  Please report any problems/ suggestions to Marie-Pierre Sylvestre at:
#  marie-pierre.sylvestre@mail.mcgill.ca
#
#############################################################################
#
#  Please reference the manuscript below if the results of this program are
#  used in any published material.
#
#  Sylvestre, MP and Abrahamowicz, M. Comparison of algorithms to generate event
#  times conditional on time-dependent covariates. Statistics in
#  Medicine, 2008 (e-print).
#
#############################################################################
#
# This file contains two algorithms, PA and PARS for the two models in the
# paper.
#

library(survival)

#############################################################################
###
### Functions
###
#############################################################################

# need to evaluate partial hazard from a given risk set and with given
#parameters AT A GIVEN time t
# covlist is the list of covariates as index in mylist (listed by individual
#then time*var)
# returns a vector of lengh(ID) with partial.hazard at that time.
```

```
# model 1
partial.hazard.t.matrix <- function(betas,covmatrix,t, idlist,m){
  PH <- vector(length=length(idlist)) # storage vector
  for (i in 1:length(idlist)){
    id=idlist[i]
    ind.data=covmatrix[((id-1)*m+1):(id*m),]
    bin.at.t=ind.data[t,4]
    age=ind.data[t,1]
    sex=ind.data[t,2]
    comorb=ind.data[t,3]
    PH[i]=exp(betas[1]*age + betas[2]*sex + betas[3]*comorb +
betas[4]*bin.at.t)
  }
  return(PH)
}

# generates a vector according to a given marginal dist'n and round if necessary
# dist is the distribution, par are the parameters, round is the number of
#decimal places when rounding
# returns a vector of simulated values
gen <- function(dist,n,par1,par2,round){
  vec=round(dist(n,par1,par2),round)
  return(vec)}

# choose.min
# choosing the minimum of two items in two columns (to put in an apply)
chose.min <- function(vec){
  min=min(vec[1], vec[2])
  return(min)}

##############################################################################
###
### PA Algorithm without Rejection sampling
###
##############################################################################

# IMPORTANT! In the perm algo with RS, the min max have to be changed according
#to the signs of the true betas!!!!
# parameters are passed through parms.v
# n is number of subjects, m is the length of follow-up
# H calibrate the random censoring function
# mymatrix is a (n*m) x 5 matrix of predictors of the form  cbind(age, sex,
#comorb, bin.exp, time)) where time indexes the follow-up time.

perm.algo <- function(n, m, T.dist, parms.v , H, betas, mymatrix){

### Step 1: Survival times

T.star <- gen(T.dist, n, parms.v[1,6], parms.v[2,6], 0)

### Step 2: Censoring times

  C <- round(runif(n,1,H),0) # I have assume uniform censoring but any other
        #distribution can be used.

### Step 3 Sorting

# observed time is the minimum between event time and censoring time
obs.t=apply(cbind(T.star,C),1,chose.min)
# d is a non-censoring indicator that takes value of 1 when C>T.star
d=rep(1,n)
d[C<T.star]=0
```

```
# id.tuples keeps track of tuples as they were created and before they were
sorted by event time
id.tuples=seq(1,n)
tuples=cbind(obs.t,d,id.tuples)
tuples[,2][tuples[,1]>m & tuples[,2]==1]=0 # if event after m then censored
tuples[,1][tuples[,1]>m]=m # if obs after m then admin censoring
T.star[T.star>m]=m
obs.t[obs.t>m]=m
sorted.tuples=tuples[order(tuples[,1]),]
sorted.tuples=data.frame(sorted.tuples)

### Step 4 Pairing

# k is the number of distinct outcome events
# number of similar T.star
#  'unique' returns a vector, data frame or array like 'x' but with duplicate
elements removed.
distint.Tstar=sort(unique(T.star))
k=length(distint.Tstar)
# remaining id will be a list of id updates so that people are not chosen twice

# starting at earliest observed time... (will put that in a loop)
distinct.obs.t=sort(unique(obs.t))
# how many distinct observed times???
kk=length(distinct.obs.t)

# these are two elements to keep track of who is matched and who is moving in
#and out of risksets or availability
matched.id=c(0,0)
idlist=seq(1,n) # at first, everybody is in

# we will pair the event with an individual at time 'current time'
# we will have to repeat this step kk times BUT the indexing is done over the
#observed times
for (i in 1:kk){
# what is current time
  current.time=distinct.obs.t[i]
  current.tuples <- subset(sorted.tuples, sorted.tuples$obs.t==current.time)
# who is in the risk set ? People still alive and not censored at current time
# still alive
  current.risk.set <- subset(sorted.tuples, sorted.tuples$obs.t>current.time)
#### this is people at risk + current events
  number.tuples=dim(current.tuples)[1]
# to record the selected
  selected=vector(length=number.tuples)
  for (h in 1:number.tuples) { # we matched every individual who has an event
#now
    if (current.tuples$d[h]==1) { # so the person is not censored
    # select individual who has a failure at current time from corresponding
#risk set with prob proportional to HR at current time
      if (length(idlist)==1) {current.ind=idlist[1]} # if reached end of list
      if (length(idlist)!=1) {
        current.PH <- partial.hazard.t.matrix(betas,mymatrix,current.time,
idlist,m) # NEED NOT SUM TO 1
        current.ind <- sample(idlist,1,replace=FALSE, prob=current.PH)
      }
    # someone has been chosen so update idlist
      idlist=idlist[idlist!=current.ind]
      selected[h]=current.ind
     }
    if (current.tuples$d[h]==0) {
      if (length(idlist)==1) {current.ind=idlist[1]} # if reached end of list
      if (length(idlist)!=1) {
```

```
    # select individual who is censored at current time by SRS from
#corresponding risk set (since censoring ind of cov)
    # so sample from the list
    # so I select out of cov (list.id) who have not been matched to tuples yet
#and I do that at current.time
      current.ind=sample(idlist,1, replace=FALSE, prob=NULL)}  # current.ind is
#then the id from mylist
    # someone has been chosen so update idlist
      idlist=idlist[idlist!=current.ind]
      selected[h]=current.ind
    }
  }
### so here we have tuples matched with cov.id so we can update the dataset
  matched.id=rbind(matched.id,cbind(current.tuples$id.tuples,selected))
}

matched.id=data.frame(matched.id)
matched.id=matched.id[-1,] # remove the bogus column
names(matched.id)[1] <- 'tuples.id'
names(matched.id)[2] <- 'cov.id'
ordered.matched.id=matched.id[order(matched.id$tuples.id),]

### Construct the data set

data=matrix(nrow=m*n, ncol=13)

info=data.frame(cbind(tuples,cov.id=ordered.matched.id$cov.id))
ordered.info=info[order(info$cov.id),]


data[,1]=RepSeqfun(n,m)                          # ID
data[,2]=RepVeqfun(ordered.info$d,m)             # event  redundant
data[,3]=RepVeqfun((1-ordered.info$d),m)         # censored
data[,4]=mymatrix[,1]                            # age
data[,5]=mymatrix[,2]                            # sex
data[,6]=mymatrix[,3]                            # comorbid
data[,7]=mymatrix[,5]                            # time
data[,8]=RepVeqfun(ordered.info$obs.t,m)         # obs.time
data[,8][data[,7]>data[,8]]=NA                  # data[,6][data[,6]>0]=1
          # Change it to 1
data[,8][data[,8]!=data[,7]]=0
data[,8][data[,8]>1]=1
data[,9]=data[,8]                                # event.time
data[,9][data[,3]==1]=0
data[,10]=RepVeqfun(ordered.info$obs.t,m)
data[,11]=mymatrix[,4]                            # bin
data[,12]=data[,7]-1                          #
data[,13]=data[,7]
data=data.frame(data)
data=subset(data,is.na(data[,8])==FALSE)  # delete what happens after censoring
or event time

names(data) <- c('id', 'event', 'censored', 'age', 'sex', 'comorb',
'time',  'obs.time', 'event.time', 'fu.time', 'bin.exp', 'start' 'stop')

dd <- subset(data, data$time==1)
ne <- sum(dd$event)
nc <- sum(dd$censored)

# returns a list with the data set, the number of events and the number of
subjects censored.
return(list(data = data, ne=ne, nc=nc))}
```

```
##############################################################################
###
### Algorithm with Rejection sampling
###
##############################################################################

# Replace Step 4 in the previous function by the following:

### Step 4 Pairing with rejection sampling

elements removed.
distint.Tstar=sort(unique(T.star))
k=length(distint.Tstar)
distinct.obs.t=sort(unique(obs.t))
kk=length(distinct.obs.t)
matched.id=c(0,0)
idlist=seq(1,n) # at first, everybody is in

# we will pair the event with an individual at time 'current time'
# we will have to repeat this step kk times BUT the indexing is done over the
# observed times!!!

count <- 0
 # theoritical max is for someone who would have been exposed all the time but
#this is WAY too high!
#max.h <-
exp(betas[1]*max(mymatrix[,1])+betas[2]+betas[3]*max(mymatrix[,3])+betas[4] +
betas[5]*seq(1,m))
  fixed <- subset(mymatrix, mymatrix[,5]==1)
  max1 <- max(fixed[,1])
  max2 <- min(fixed[,2])########## because beta2 is negative!
  max3 <- max(fixed[,3])
  which.max1 <- which.max(fixed[,1])
  which.max2 <- which.min(fixed[,2])########## because beta2 is negative!
  which.max3 <- which.max(fixed[,3])

  if (betas[4]>0) current.max.h <-
exp(betas[1]*max1+betas[2]*max2+betas[3]*max3+betas[4]*(1)) else current.max.h
<- exp(betas[1]*max1+betas[2]*max2+betas[3]*max3+betas[4]*(0))


for (i in 1:kk){
# what is current time
  current.time=distinct.obs.t[i]

  current.tuples <- subset(sorted.tuples, sorted.tuples$obs.t==current.time)
# who is in the risk set ? People still alive and not censored at current time
# still alive
  current.risk.set <- subset(sorted.tuples, sorted.tuples$obs.t>current.time)
#### this is people at risk + current events
  number.tuples=dim(current.tuples)[1]
# to record the selected
  selected=vector(length=number.tuples)
  for (h in 1:number.tuples) { # we matched every individual who has an event
#now
    if (current.tuples$d[h]==1) { # so the person is not censored
    # select individual who has a failure at current time from corresponding
risk set with prob proportional to HR at current time
      if (length(idlist)==1) {current.ind=idlist[1]} # if reached end of list
      flag <- 0
      if (length(idlist)!=1) {
        while(flag<1){
          U <- runif(1)
```

```
          X <- sample(idlist,1)
          if (U <=  exp(betas[1]*(mymatrix[(m*(X-1)+current.time),1]) +
                betas[2]*(mymatrix[(m*(X-1)+current.time),2]) +
                betas[3]*(mymatrix[(m*(X-1)+current.time),3]) +
                betas[4]*(mymatrix[(m*(X-1)+current.time),4])) / current.max.h)
{
            current.ind <- X
            flag <- 1 }

          if (U >  exp(betas[1]*(mymatrix[(m*(X-1)+current.time),1]) +
                       betas[2]*(mymatrix[(m*(X-1)+current.time),2]) +
                       betas[3]*(mymatrix[(m*(X-1)+current.time),3]) +
                       betas[4]*(mymatrix[(m*(X-1)+current.time),4])) /
current.max.h){
              count <- count+1}
        }
      }
    # someone has been chosen so update idlist
      idlist=idlist[idlist!=current.ind]
      selected[h]=current.ind
      # IF necessary, modify max
      if (current.ind == which.max1) {
        # choisir dans ce qui reste
        max1 <- max(fixed[idlist,1])
        which.max1 <- which.max(fixed[idlist,1])
         if (betas[4]>0) current.max.h <-
exp(betas[1]*max1+betas[2]*max2+betas[3]*max3+betas[4]*(1)) else current.max.h
<- exp(betas[1]*max1+betas[2]*max2+betas[3]*max3+betas[4]*(0))}
      if (current.ind == which.max2) {
        # choisir dans ce qui reste
        max2 <- min(fixed[idlist,2])  ################ because beta2 is
#negative!!!
        which.max2 <- which.min(fixed[idlist,2])
        if (betas[4]>0) current.max.h <-
exp(betas[1]*max1+betas[2]*max2+betas[3]*max3+betas[4]*(1)) else current.max.h
<- exp(betas[1]*max1+betas[2]*max2+betas[3]*max3+betas[4]*(0))}
      if (current.ind == max1) {
        # choisir dans ce qui reste
        max3 <- max(fixed[idlist,3])
        which.max3 <- which.max(fixed[idlist,3])
        if (betas[4]>0) current.max.h <-
exp(betas[1]*max1+betas[2]*max2+betas[3]*max3+betas[4]*(1)) else current.max.h
<- exp(betas[1]*max1+betas[2]*max2+betas[3]*max3+betas[4]*(0))

    }
    } #END OF IF NOT CENSORED

    if (current.tuples$d[h]==0) {
      if (length(idlist)==1) {current.ind=idlist[1]} # if reached end of list
      if (length(idlist)!=1) {
    # select individual who is censored at current time by SRS from
#corresponding risk set (since censoring ind of cov)
    # so sample from the list
    # so I select out of cov (list.id) who have not been matched to tuples yet
#and I do that at current.time
      current.ind=sample(idlist,1, replace=FALSE, prob=NULL)}  # current.ind is
#then the id from mylist
    # someone has been chosen so update idlist
      idlist=idlist[idlist!=current.ind]
      selected[h]=current.ind
          # IF necessary, modify max
      if (current.ind == which.max1) {
        # choisir dans ce qui reste
```

```
        max1 <- max(fixed[idlist,1])
        which.max1 <- which.max(fixed[idlist,1])
        if (betas[4]>0) current.max.h <-
exp(betas[1]*max1+betas[2]*max2+betas[3]*max3+betas[4]*(1)) else current.max.h
<- exp(betas[1]*max1+betas[2]*max2+betas[3]*max3+betas[4]*(0))}
      if (current.ind == which.max2) {
        # choisir dans ce qui reste
        max2 <- min(fixed[idlist,2]) ############### because beta2 is
#negative!!!
        which.max2 <- which.min(fixed[idlist,2]) ############### because beta2
#is negative!!!
        if (betas[4]>0) current.max.h <-
exp(betas[1]*max1+betas[2]*max2+betas[3]*max3+betas[4]*(1)) else current.max.h
<- exp(betas[1]*max1+betas[2]*max2+betas[3]*max3+betas[4]*(0))}
      if (current.ind == max1) {
        # choisir dans ce qui reste
        max3 <- max(fixed[idlist,3])
        which.max3 <- which.max(fixed[idlist,3])
        if (betas[4]>0) current.max.h <-
exp(betas[1]*max1+betas[2]*max2+betas[3]*max3+betas[4]*(1)) else current.max.h
<- exp(betas[1]*max1+betas[2]*max2+betas[3]*max3+betas[4]*(0))}

    }
  }
### so here we have tuples matched with cov.id so we can update the dataset
  matched.id=rbind(matched.id,cbind(current.tuples$id.tuples,selected))
}

matched.id=data.frame(matched.id)
matched.id=matched.id[-1,] # remove the bogus column
names(matched.id)[1] <- 'tuples.id'
names(matched.id)[2] <- 'cov.id'
ordered.matched.id=matched.id[order(matched.id$tuples.id),]
```

Appendix B - R code for the WCE model

This Appendix contains the code for the WCE model for the manuscript 3. Its input is a dataset in the counting process format that contains the variables: id, sex, age, injury at baseline (labelled as comorb), dose, fu.time, event.time, start, stop. If individual *i* had an event, then for this individual, event.time=1 on the day of the event and event.time = 0 otherwise.

```
#################################################################################
#
#  Code for the WCE models
#
#################################################################################
#
#  Author: Marie-Pierre Sylvestre
#          Department of Epidemiology, Biostatistics and Occupational Health,
#          McGill University, Montreal, Quebec, Canada.
#
#################################################################################
#
#  This program is meant to be used for non-commercial purposes only.
#  Please report any problems/ suggestions to Marie-Pierre Sylvestre at:
#  marie-pierre.sylvestre@mail.mcgill.ca
#
#################################################################################
#
#  Please reference the manuscript below if the results of this program are
#  used in any published material.
#
#  Sylvestre, MP and Abrahamowicz, Flexible modelling of the cumulative effects
#  of time-dependent exposures on the hazard (unpublished)
#
#################################################################################

library(splines)
library(survey)

# functions required:

# equidistant interior knots
period.
knots.equi <- function(n.knots, m){
  if (n.knots==1){   f <- round(quantile(seq(1,m),seq(0,1,
by=1/(n.knots+1))),0)[2]}
  if (n.knots>1){
    f <- round(quantile(seq(1,m),seq(0,1, by=1/(n.knots+1))),0)[-1]}
  return(f[1:(length(f)-1)])}

# adding the outter knots
augm.knots <- function(inner, f.up){
  return(c(-3,-2,-1,0, inner, f.up,(f.up+1), (f.up+2), (f.up+3)))}

# Functions for spline modelling
```

```
# start by calculating Dj(t) for 1 j for 1 individual and for 1 t
DFor1For1t <- function(vec, ColBmatrix,t){
elt <- sum(ColBmatrix[1:t]*rev(vec[1:t]))# this parts
return(elt)}

# repeat for all t
# need to apply this to all t of a vec
DFor1 <- function(vec, ColBmatrix){
u <- length(vec)
whatever <- unlist(lapply(1:u, function(i) DFor1For1t(vec, ColBmatrix, i)))
return(whatever)}

# repeat for all D's
AllD <- function(vec, Bmatrix){
return(matrix(unlist(lapply(1:dim(Bmatrix)[2], function(i) DFor1(vec,
Bmatrix[,i]))), ncol=dim(Bmatrix)[2], byrow=FALSE))}

# repeat for all individuals
BuildD <- function(n, Bmatrix, data){
beg <- index.beg(data)
end <- index.end(data)
return(do.call("rbind", lapply(1:n, function(i) AllD(data$dose[beg[i]:end[i]],
Bmatrix))))}

# have the list of lengths
uGet <- function(data){
return(subset(data, data$start==0)$fu.time)}

# have the list of indexes
index.beg <- function(data){
u <- c(0, uGet(data)[1:(length(uGet(data))-1)])
beg <- cumsum(u)+1
return(beg)}

index.end <- function(data){
end <- index.beg(data)+ uGet(data)-1
return(end)}
# BIC
my.bic <- function(mod, n.events){
bic <- -2*(mod$loglik[2]) + length(coef(mod)) * log(n.events)
return(bic)}
# LRT
LRT.exp <- function(model,null ){
  LRT <- -2*null$loglik[2] + 2*model$loglik[2]
  df <- length(model$coefficients)-length(null$coefficients)
  cat("\n","LRT: ", LRT, " with ", df,  " p-val ", (1-pchisq(LRT, df)),"\n")
}

##############################################################################
# input data

# benzo name
b.name <- "Alpra"
cutoff <- 60

dir.create(paste("/home/mariepierre/PhD/Thesis/Splines/Benzo", b.name,
"Results", sep="/"), showWarnings = TRUE, recursive = FALSE)
dir.create(paste("/home/mariepierre/PhD/Thesis/Splines/Benzo", b.name,
"Results", paste("Cutoff", cutoff, sep=""), sep="/"), showWarnings = TRUE,
recursive = FALSE)

# dir
```

```
input.dir <- paste("/home/mariepierre/PhD/Thesis/Splines/Benzo", b.name,
sep="/")
output.dir <- paste("/home/mariepierre/PhD/Thesis/Splines/Benzo", b.name,
"Results", paste("Cutoff", cutoff, sep=""), sep="/")

# input data set in the counting process format
load(paste(input.dir, "data.RData", sep="/"))
n <- length(unique(data$id))
n.event <- sum(subset(data, data$event.time==1)$event)
m <- max(data$fu.time)

################################################################################
# calculate the b-spline basis

kev1 <- augm.knots(knots.equi(1, cutoff), cutoff)
Bbasis <- splineDesign(knots = kev1, x = 1:cutoff, ord=4)
Bmatrix1 <- rbind(Bbasis, matrix(0, ncol=dim(Bbasis)[2], nrow=m-dim(Bbasis)[1]))

kev2 <- augm.knots(knots.equi(2, cutoff), cutoff)
Bbasis <- splineDesign(knots = kev2, x = 1:cutoff, ord=4)
Bmatrix2 <- rbind(Bbasis, matrix(0, ncol=dim(Bbasis)[2], nrow=m-dim(Bbasis)[1]))

kev3 <- augm.knots(knots.equi(3, cutoff), cutoff)
Bbasis <- splineDesign(knots = kev3, x = 1:cutoff, ord=4)
Bmatrix3 <- rbind(Bbasis, matrix(0, ncol=dim(Bbasis)[2], nrow=m-dim(Bbasis)[1]))

#split data in manageable chunks

last.id <- data$id[dim(data)[1]]
max.size <- round(last.id/12)
iter <- 12

i.beg <- rep(0,iter)
i.end <- rep(0,iter)

block <- rep(0, dim(data)[1])

for (i in 1:iter) {
  i.beg[i] <- (i-1)*max.size + 1
  i.end[i] <- i.beg[i] + max.size
  if (i.end[i] > last.id) i.end[i] <- last.id
  first <- which(data$id==i.beg[i])[1]
  lala <- which(data$id==i.end[i])
  last <- lala[length(lala)]
  block[first:last] <- i}


block[block==0] <- iter
data$block <- block

split.data <- split(data, data$block)
rm(data)
save(split.data, file = paste(input.dir, "splitdata.RData", sep="/"))
rm(split.data)

# evaluate the D variables on each chunk and save
partD1 <- function(i, output.dir, Bmatrix){
  load(paste(input.dir, "splitdata.RData", sep="/"))
  data <- split.data[[i]]
  rm(split.data)
  n <- length(unique(data$id))
  gc()
  assign(paste("D1", i,sep=""), data.frame(BuildD(n, Bmatrix, data)))
```

```
  save(list=paste("D1", i,sep=""), file=paste(output.dir, "/","D1", i,".RData",
sep=""))
  rm(list=paste("D1", i,sep=""))
  gc()
  }
partD2 <- function(i, output.dir, Bmatrix){
  load(paste(input.dir, "splitdata.RData", sep="/"))
  data <- split.data[[i]]
  rm(split.data)
  n <- length(unique(data$id))
  gc()
  assign(paste("D2", i,sep=""), data.frame(BuildD(n, Bmatrix, data)))
  save(list=paste("D2", i,sep=""), file=paste(output.dir, "/","D2", i,".RData",
sep=""))
  rm(list=paste("D2", i,sep=""))
  gc()
  }
partD3 <- function(i, output.dir, Bmatrix){
  load(paste(input.dir, "splitdata.RData", sep="/"))
  data <- split.data[[i]]
  rm(split.data)
  n <- length(unique(data$id))
  gc()
  assign(paste("D3", i,sep=""), data.frame(BuildD(n, Bmatrix, data)))
  save(list=paste("D3", i,sep=""), file=paste(output.dir, "/","D3", i,".RData",
sep=""))
  rm(list=paste("D3", i,sep=""))
  gc()
  }

for (i in 1:iter){
gc()
partD1(i, output.dir, Bmatrix1)
partD2(i, output.dir, Bmatrix2)
partD3(i, output.dir, Bmatrix3)
#partD4(i, output.dir, Bmatrix4)
gc()
}

# put it all together now
load(paste(output.dir, "/","D1", 1,".RData", sep=""))
D1 <- D11
for (i in 2:iter){
load(paste(output.dir, "/","D1", i,".RData", sep=""))
D1 <- rbind(D1,get(paste("D1", i, sep="")))
rm(list=paste("D1", i, sep=""))
gc()
}
save(D1, file=paste(output.dir, "/","D1.RData", sep=""))
rm(D1)

load(paste(output.dir, "/","D2", 1,".RData", sep=""))
D2 <- D21
for (i in 2:iter){
load(paste(output.dir, "/","D2", i,".RData", sep=""))
D2 <- rbind(D2,get(paste("D2", i, sep="")))
rm(list=paste("D2", i, sep=""))
gc()
}
save(D2, file=paste(output.dir, "/","D2.RData", sep=""))
rm(D2)

load(paste(output.dir, "/","D3", 1,".RData", sep=""))
```

```
D3 <- D31
for (i in 2:iter){
load(paste(output.dir, "/","D3", i,".RData", sep=""))
D3 <- rbind(D3,get(paste("D3", i, sep="")))
rm(list=paste("D3", i, sep=""))
gc()
}
save(D3, file=paste(output.dir, "/","D3.RData", sep=""))
rm(D3)

load(paste(input.dir, "data.RData", sep="/"))

# deal with hospitalization (Benzo-relate issue - not required for other WCE
# applications
# When people are hospitalized, and 15 dats after their hospitalizations, they
# are not considered at risk, so they
# should *not* be in any risk set. Now that the variables have all been
# computed, I will simply remove the lines.

AddNA <- function(vec){
  if (length(vec)>14){
    for (i in (length(vec)-14):1 ){
      if (is.na(vec[i])== TRUE){ vec[i:(i+14)] <- NA}
    }}
  return(vec)}

data$hosp <- unlist(sapply(split(data$old.dose,data$id),AddNA))
save(data, file= paste(input.dir, "dataNA.RData", sep="/"))

# Now back to WCE
# Remove lines that do not enter any risk set


load(paste(input.dir, "dataNA.RData", sep="/"))
# event times
e.time <- sort(unique(data$fu.time[data$event.time==1]))

# remove from dataset
flag <- rep(0, dim(data)[1])
flag[data$stop %in% e.time]=1
NEWDATA <- data[flag==1,]
save(NEWDATA, file = paste(output.dir, "NEWDATA.RData", sep="/"))
rm(NEWDATA)
rm(data)
gc()

# remove from D
load(paste(output.dir, "D1.RData", sep="/"))
names(D1) <- paste("D1", 1:dim(D1)[2], sep="")
sumD <- apply(D1,2,sum, na.rm=TRUE)
D1 <- D1[, which(sumD>0)[1]: which(sumD>0)[length(sumD[sumD>0])]]
NEWD <- D1[flag==1,]

# merge data and D
load(paste(output.dir, "NEWDATA.RData", sep="/"))
newdata1 <- cbind(NEWDATA, NEWD)
rm(NEWDATA)
rm(NEWD)
gc()
newdata1 <- subset(newdata1,is.na(newdata1$hosp)==FALSE)
save(newdata1, file = paste(output.dir, "newdata1.RData", sep="/"))
rm(newdata1)
rm(D1)
```

```
gc()

load(paste(output.dir, "D2.RData", sep="/"))
names(D2) <- paste("D2", 1:dim(D2)[2], sep="")
sumD <- apply(D2,2,sum, na.rm=TRUE)
D2 <- D2[, which(sumD>0)[1]: which(sumD>0)[length(sumD[sumD>0])]]
NEWD <- D2[flag==1,]

load(paste(output.dir, "NEWDATA.RData", sep="/"))
newdata2 <- cbind(NEWDATA, NEWD)
rm(NEWDATA)
rm(NEWD)
gc()
newdata2 <- subset(newdata2,is.na(newdata2$hosp)==FALSE)
save(newdata2, file = paste(output.dir, "newdata2.RData", sep="/"))
rm(newdata2)
rm(D2)
gc()

load(paste(output.dir, "D3.RData", sep="/"))
names(D3) <- paste("D3", 1:dim(D3)[2], sep="")
sumD <- apply(D3,2,sum, na.rm=TRUE)
D3 <- D3[, which(sumD>0)[1]: which(sumD>0)[length(sumD[sumD>0])]]
NEWD <- D3[flag==1,]

load(paste(output.dir, "NEWDATA.RData", sep="/"))
newdata3 <- cbind(NEWDATA, NEWD)
rm(NEWDATA)
rm(NEWD)
gc()
newdata3 <- subset(newdata3,is.na(newdata3$hosp)==FALSE)
save(newdata3, file = paste(output.dir, "newdata3.RData", sep="/"))
rm(newdata3)
rm(D3)
gc()

# Estimation

load(paste(output.dir, "newdata1.RData", sep="/"))
load(paste(output.dir, "newdata2.RData", sep="/"))
load(paste(output.dir, "newdata3.RData", sep="/"))

DVAR1 <- c("D11","D12", "D13")
DVAR2 <- c("D21","D22","D23", "D24")
DVAR3 <- c("D31","D32","D33","D34", "D35")

newdata <- cbind(newdata1, newdata2[,DVAR2], newdata3[,DVAR3])

rm(newdata1)
rm(newdata2)
rm(newdata3)
gc()

# Formulas
formula1<- as.formula(paste("Surv(start, stop, event.time) ~ sex + age + comorb
+ cluster(id)+", paste(DVAR1, collapse= "+")))
formula2<- as.formula(paste("Surv(start, stop, event.time) ~ sex + age + comorb
+ cluster(id)+", paste(DVAR2, collapse= "+")))
formula3<- as.formula(paste("Surv(start, stop, event.time) ~ sex + age + comorb
+ cluster(id)+", paste(DVAR3, collapse= "+")))
formula5<- as.formula("Surv(start, stop, event.time) ~ sex + age + comorb +
cluster(id)+ bin")
formula6<- as.formula("Surv(start, stop, event.time) ~ sex + age + comorb +
```

```
cluster(id)+ dose")
formula7<- as.formula("Surv(start, stop, event.time) ~ sex + age + comorb +
cluster(id)+ cum")
formula9<- as.formula("Surv(start, stop, event.time) ~ sex + age + comorb +
cluster(id)+ cum.dose")


# Cox models
cox1 <- coxph(formula1, data=newdata, method="efron", singular.ok=TRUE,
robust=TRUE, model=FALSE, x=FALSE, y=TRUE, iter.max =20, eps=1e-04)
cox2 <- coxph(formula2, data=newdata, method="efron", singular.ok=TRUE,
robust=TRUE, model=FALSE, x=FALSE, y=TRUE, iter.max =20, eps=1e-04)
cox3 <- coxph(formula3, data=newdata, method="efron", singular.ok=TRUE,
robust=TRUE, model=FALSE, x=FALSE, y=TRUE, iter.max =20, eps=1e-04)
cox5 <- coxph(formula5, data=newdata, method="efron", singular.ok=TRUE,
robust=TRUE, model=FALSE, x=FALSE, y=TRUE, iter.max =20, eps=1e-04)
cox6 <- coxph(formula6, data=newdata, method="efron", singular.ok=TRUE,
robust=TRUE, model=FALSE, x=FALSE, y=TRUE, iter.max =20, eps=1e-04)
cox7 <- coxph(formula7, data=newdata, method="efron", singular.ok=TRUE,
robust=TRUE, model=FALSE, x=FALSE, y=TRUE, iter.max =20, eps=1e-04)
cox9 <- coxph(formula9, data=newdata, method="efron", singular.ok=TRUE,
robust=TRUE, model=FALSE, x=FALSE, y=TRUE, iter.max =20, eps=1e-04)

null.mod <- coxph(Surv(start, stop, event.time) ~ sex + age + comorb +
cluster(id), data=newdata, method="efron", singular.ok=TRUE, robust=TRUE,
model=FALSE, x=FALSE, y=TRUE, iter.max =20, eps=1e-04)
```

Appendix C - Letter of acceptance for the manuscript 1 from Statistics in Medicine

Date: 30-Aug-2007

Manuscript Number: SIM-07-0110.R1

Title: "Comparison of algorithms to generate event times conditional on time-dependent covariates"

Dear Ms. Sylvestre:

I am pleased to inform you that your Paper has been accepted for publication in Statistics in Medicine.

The publisher is able to access the final version of your Paper online.

To enable the publisher to disseminate the author's work to the fullest extent, the author must sign a Copyright Transfer Agreement, transferring the copyright of the article from the author to the publisher. Please note that this does not take away your rights to reuse your own article after publication, and that if the copyright belongs to your employing institution, they should sign the form instead of you.

If you have already provided us with the signed form, you do not need to do anything at this stage. You will be contacted by our typesetters/copyeditors shortly.

If you need to submit the copyright form a copy is attached for your convenience. Please write the manuscript reference number at the top of the form, scan the signed form, and send it as an e-mail attachment to stompson@bu.edu. Or, if you prefer, you may fax the form to Wiley's Production Department at +44 (0) 1243 770450.

Should you have any questions about this process please contact the Journal Administrator, Suzanne Thompson (stompson@bu.edu).

Thank you for your support of Statistics in Medicine. We look forward to seeing more of your work in the future.

Sincerely,

Dr. Ralph D'Agostino
Editor
Statistics in Medicine

Appendix E - Waiver from Wiley and Sons for manuscript 1

I have been authorized by Wiley and Sons, the publisher of Statistics in Medicine where manuscript 1 was published, to include the manuscript in the thesis. However, Wiley and Sons did not grant permission to reproduce the manuscript in the copy of the thesis that is going to the Library of Canada.

As approved by Associate Dean Dr. Heather Durham, the copy of the manuscript 1 will be removed from the copy of the thesis that will be available at the Library of Canada. Instead, a full reference to the journal is provided.

The documents from Wiley and Sons and the confirmation letter from Associate Dean Dr. Heather Durham are copied here.