STATISTICAL MODELING OF LONGITUDINAL SURVEY DATA WITH BINARY OUTCOMES

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ABSTRACT

Data obtained from longitudinal surveys using complex multi-stage sampling designs contain cross-sectional dependencies among units caused by inherent hierarchies in the data, and within subject correlation arising due to repeated measurements. The statistical methods used for analyzing such data should account for stratification, clustering and unequal probability of selection as well as within-subject correlations due to repeated measurements.

The complex multi-stage design approach has been used in the longitudinal National Population Health Survey (NPHS). This on-going survey collects information on health determinants and outcomes in a sample of the general Canadian population.

This dissertation compares the model-based and design-based approaches used to determine the risk factors of asthma prevalence in the Canadian female population of the NPHS (marginal model). Weighted, unweighted and robust statistical methods were used to examine the risk factors of the incidence of asthma (event history analysis) and of recurrent asthma episodes (recurrent survival analysis). Missing data analysis was used to study the bias associated with incomplete data. To determine the risk factors of asthma prevalence, the Generalized Estimating Equations (GEE) approach was used for marginal modeling (model-based approach) followed by Taylor Linearization and bootstrap estimation of standard errors (design-based approach). The incidence of asthma (event history analysis) was estimated using weighted, unweighted and robust methods. Recurrent event history analysis was conducted using Anderson and Gill, Wei, Lin and Weissfeld (WLW) and Prentice, Williams and Peterson (PWP) approaches. To assess the presence of bias associated with missing data, the weighted GEE and pattern-mixture models were used.

The prevalence of asthma in the Canadian female population was 6.9% (6.1-7.7) at the end of Cycle 5. When comparing model-based and design- based approaches for asthma prevalence, design-based method provided unbiased estimates of standard errors. The overall incidence of asthma in this population, excluding those with asthma at baseline, was 10.5/1000/year (9.2-12.1). For the event history analysis, the robust method provided the most stable estimates and standard errors.

For recurrent event history, the WLW method provided stable standard error estimates. Finally, for the missing data approach, the pattern-mixture model produced the most stable standard errors

To conclude, design-based approaches should be preferred over model-based approaches for analyzing complex survey data, as the former provides the most unbiased parameter estimates and standard errors.

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DEDICATION

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LIST OF ABBREVIATIONS

AFT	Accelerated failure time
AG	Anderson and Gill Model
BHR	Bronchial hyper responsiveness
BMI	Body mass index
BRFSS	Behavioral Risk Factor Surveillance System
BRR	Balanced repeated replication
CC	Complete case analysis
COPD	Chronic Obstructive Pulmonary Disease
EB	Empirical Bayes
ECRHS	European Community Respiratory Health Survey
EM	Expectation-maximization
ESS	Enquete sociale et de Sante
GEE	Generalized Estimating Equation
GINA	Global Initiative for Asthma
GLM	Generalized Linear Models
GLMM	Generalized linear mixed model
GT-UR	Gap time- unrestricted
IID	Identically Independently Distributed
IUTALD	International Union Against Tuberculosis and Lung Disease
LOCF	Last observation carried forward
LWA	Lee, Wei and Amato

MAR	Missing at random
MCAR	Missing completely at random
MI	Multiple imputation
ML	Maximum likelihood
MNAR	Missingness not at random
MQL	Marginalized Quasi Likelihood
NPHS	National Population Health Survey
PPS	Probability proportional to size
PQL	Penalized Quasi Likelihood
PSU	Primary Sampling Units
PWP	Prentice, William and Peterson
REML	Restricted maximum likelihood
SRS	Simple random sample
TT-R	Total Time –Restricted
WGEE	Weighted generalized estimating equations
WLW	Wei, Lin and Weissfeld

CHAPTER 1 - INTRODUCTION

1.1 Rationale

Large national health surveys are an invaluable source of information on the incidence and prevalence of disease and associated risk factors. Such surveys require the use of multi-stage sampling designs to collect information. Multi-stage sampling procedures involve a number of steps including stratification, clustering, random sampling of households within clusters with unequal inclusion probabilities, and selecting individuals within responding households. Hence, the three features of multi-stage design are: stratification, clustering and unequal inclusion probabilities. To obtain consistent estimates of parameters and their variances, the analysis of survey data should account for the sampling design.

The first feature of multi-stage sampling, stratification, is achieved by creating homogeneous subgroups or strata. These homogeneous subgroups created by stratifying the probability samples assist in minimizing sampling error [4], reducing the variance of parameter estimates, and making the population subgroups more adequately representative of the overall population [5]. Stratification also aids in increasing statistical efficiency [4].

The second feature of multi-stage design is clustering. Compared to data collected using a simple random sampling approach, data collected by a multi-stage design incorporating a clustering effect produces more stable parameter estimates [5]. However, due to a clustering effect, the multi-stage method of data collection results in larger standard errors and variances. [5] Hence, clustering underestimates the true population variance and results in loss of statistical efficiency [5].

The third feature, weighting, accounts for unequal inclusion probabilities and non-response. The sampling weights assists in reducing bias in the parameter estimates, and can result in large standard errors if the variance of the weights is large [4].

Statistical methods for cross-sectional survey designs are well developed and can be easily applied through commercial software such as SAS[1], SUDAAN[2], STATA[3] and WESVAR[4]. The software can handle the complexities of both design-based and model-based statistical approaches used with data from cross-sectional surveys. Contrary to the analysis of data from cross-sectional survey designs, the analysis of data from longitudinal survey designs can be more complicated. The analysis of longitudinal survey data should not only account for stratification, clustering and an unequal inclusion probability, but must also take into account the within-subject correlation arising from repeated observations or missing data on the same individual over time. Ignoring the sampling design may result in severely biased estimates, leading to false inferences, especially when the outcome variable is correlated with design variables not included in the model [6].

[1] SAS Institute, Inc. Cary, NC, version 9.1.3 (http://www.sas.com/)
[2] SUDAAN, Research Triangle Institute, 2005 (http://www.rti.org/)
[3] STATA, Stata Corp LP, 1996-2006 (http://www.stata.com)
[4] WESVAR, Westat Inc., 2006 (http://www.westat.com/)

There is limited work conducted with complex survey data sets that are longitudinal in nature and with binary outcomes. Some recent work in the area of longitudinal survey data analysis has been conducted by Skinner and Holmes [7] and Feder et al. [6], who have used the random effects modeling approach for continuous outcomes. Rao [3] proposed the use of a marginal modeling approach with binary outcomes, while Lawless [8] proposed the use of event history analysis for binary outcomes. These methods focused on design-based approaches. Model-based methods have also been used and have been compared to design-based methods for cross-sectional survey data [9], but their use is limited with longitudinal survey data. There is ongoing debate as to which of these approaches is best for the analysis of survey data [10].

Results from complex survey analyses that have used the appropriate statistical methods can be generalized to the specific target population of interest. In this thesis, the National Population Health Survey (NPHS), a multi-stage complex longitudinal survey dataset, was used. The primary purpose of this study was to examine the prevalence and incidence of asthma and associated risk factors among adult women using different statistical approaches, ultimately evaluating the statistical efficiency of these different approaches. Asthma is a chronic respiratory disease and its symptoms include wheezing, shortness of breath, tightness of chest and coughing [11]. Research conducted in Canada and other countries has shown that asthma prevalence among the adult population is rising and is more predominant in western and developed countries [12]. During adulthood, asthma prevalence appears to decrease with age, however, there is a change in the gender distribution of asthma from childhood to adulthood with more

[12] females affected than males during adulthood [11]. These finding are supported by several studies of adult populations which clearly show the higher prevalence and incidence of asthma among females compared to males [13-19]. Research has focused on rural/urban differences in the prevalence and incidence of asthma among adults [20-22]. While researchers have reported results adjusted for gender, they have not specifically examined the role of gender by location.

In Canada, cross-sectional studies of asthma prevalence show that between 1994 and 2003, the overall prevalence of asthma among persons aged 12 years and over increased and then plateaus. Asthma prevalence is consistently higher among females than males, indicating that the increase in overall prevalence of asthma is primarily due to an increase in prevalence among females. To date, most of the research on the prevalence and incidence of asthma in adult populations has focused on gender differences [13, 15, 17, 18]. Further research is needed using longitudinal study designs to explore the reasons behind the higher prevalence and incidence of asthma among the female population in Canada.

Beginning in 1994, the NPHS longitudinal survey has collected health and other information of the Canadian population every two years using a multi-stage sampling design[5]. This dataset is unique in that the results obtained can be generalized to the Canadian population. To date, the NPHS dataset has not been analyzed longitudinally using all five cycles for a comparative study of model-based and design-based approaches. As well, the dataset has not been used to study the prevalence and incidence of asthma and associated risk factors using appropriate statistical technique to account for the complex survey design.

[5] Refer to Chapter 4 for a detailed description of the NPHS data set

This thesis compares the design-based and model-based methods for longitudinal survey data with a binary asthma outcome. Although these methods have been discussed separately in literature, there has been no comparison between them using the NPHS dataset with asthma as the outcome. The uniqueness of the thesis is that it compares the model-based and design-based approaches for marginal modeling, survival analysis techniques, and variance corrected estimation methods for recurrent events. In addition, this thesis explores the effectiveness of various statistical methods for handling missing data commonly occurring in longitudinal surveys.

1.2. Study objectives

The objectives of the present thesis are the following:

1. To compare the design-based and model-based methods for the marginal modeling approach
    a. To determine the prevalence of asthma and associated risk factors in the adult Canadian female population, taking into account the complexity of the multi-stage sampling process.
2. To compare the design-based and model-based methods for event history data.
    a. To determine the incidence of asthma and associated risk factors in the adult Canadian female population.
3. To compare the variance corrected and frailty models for recurrent survival data using both the design-based and model-based approach.
4. To compare the robustness of data for completers versus incompleters using missing data analysis.

CHAPTER 2 - LITERATURE REVIEW

2.1 Introduction

Statistical methods used for analyzing data obtained from standard longitudinal studies can be easily extended to analyze longitudinal survey data. The major difference between standard longitudinal studies and longitudinal complex surveys is the sampling design. Simple random sampling (SRS) designs are often used to collect data for standard longitudinal studies. Commonly, for longitudinal complex surveys, stratified multi-stage sampling designs are used. Other types of sampling designs (e.g. stratified sampling, systematic sampling, cluster sampling etc.) are also available for complex surveys. In large-scale national surveys, multi-stage designs are used because of economical reasons. Such designs substantially reduce the traveling cost of interviewers. However, multi-stage sampling techniques have drawbacks too. Clusters tend to be internally homogenous and this increases the standard errors of estimates, which in turn, decreases the statistical efficiency. Another disadvantage arising due to clustering is that in such sampling, the variation arises due to between-cluster variation and within-cluster variation. Analysis of survey data should be able to account for the additional source of variation. The variation within clusters contributes to the total variation. The problem arising due to clustering can be easily rectified at the design stage, by using a large number of strata and then drawing more than one cluster per strata. For example, in the NPHS, approximately 3 clusters per strata are chosen.

The statistical methods discussed in the following sections are divided into longitudinal non-survey data and longitudinal survey data. The methods for longitudinal non-survey data analysis are reviewed first because these methods are extended to analyze longitudinal survey data. Statistical methods for survey data analysis must consider the design effects to achieve unbiased and correct estimates and their standard errors. Analytical or resampling techniques are then used to obtain variance estimates.

2.2 Statistical methods for binary outcomes from longitudinal non-survey data

Research in longitudinal data analysis was first started by Wishart [23], and gained momentum in developing models for linear outcomes around 1950's with the availability of computing facilities for statistical purposes [24]. The early efforts made by Box [25], Geisser and Greenhouse [26], Potthoff and Roy [27], Rao [28, 29] and Grizzle and Allen [30] have resulted in the rich variety of models for Gaussian data [24]. However, for non-linear outcomes such as binary outcomes, few methods were available until 1986. One of the main reasons for the inadequate development of analytical methods for non-linear outcomes with longitudinal data was the lack of multivariate distribution. For non-Gaussian longitudinal data, additional information is required to determine the likelihood, as the first two moments are not enough to determine the likelihood function. The mean and the variance could not be separated in non-Gaussian data, as the mean and variance is related and estimated using a single parameter [31] as in binomial distribution variance is a function of mean (μ*(1-μ)) and for Poisson distribution variance is equal to the mean (μ). The impossibility of modeling the mean and variance separately results in interpretational and computational problem in non-Gaussian data [24].

An alternative approach, which has gained a lot of attention, is the introduction of Generalized Linear Model (GLM) by Nelder and Wedderburn [32]. GLM extends the ordinary regression models to include the non- Gaussian responses such as discrete outcomes, and special cases of Poisson and survival. In a way, GLM unifies the different regression models [33]. GLM has three components: (i) a random component which identifies the response variable and its probability distribution; (ii) a systematic component which identifies the explanatory variables used in the linear predictor function; and (iii) a link function that relates the random and the systematic components [34]. GLM is a linear model that has a distribution in natural exponential family.

The traditional maximum likelihood approaches cannot be used for non-Gaussian data as the integral does not have a closed form, unlike the Gaussian data [35]. Numerical integration techniques are required to evaluate the likelihood. The likelihood estimates are often intractable and involves solving other nuisance parameters besides estimating regression coefficients, even with these additional assumptions [35]. To overcome these problems, Liang and Zeger [1] introduced the Generalized Estimating Equation (GEE). The GEE method is based on multivariate quasi likelihood theory and it can handle the complexities of longitudinal data.

2.2.1 Generalized Estimating Equations

The GEE approach proposed by Liang and Zeger [1] is a class of estimating equations which take into account the correlation arising due to a longitudinal study design, resulting in increased efficiency of standard error estimates. introduced by Wedderburn [36], the GEE approach is based on quasi likelihood theory and can be used for continuous as well as for discrete outcome [1, 37]. The GEE method is a multivariate generalization of quasi-likelihood, and this method is mainly proposed for marginal modeling with GLM [1]. This method avoids the use of multivariate distribution by assuming a functional form for marginal distribution at each time, making it useful for non-Gaussian outcomes [1]. The advantage of using the GEE method is that the solutions are consistent, i.e. the estimate of β are nearly efficient and asymptotically Gaussian, even when the time dependence is misspecified [37, 38].

Considering the GEE approach, let $\mathbf{Y_i}= (y_{i1},........y_{ini})^T$ denotes the outcome vector for subject (i=1,….N); $\boldsymbol{\mu}_\mathbf{i} = (\mu_{i1},……., \mu_{ini})^T$ denotes the mean vector, where $\mu_{it} = E(Y_{it})$; and $\mathbf{X_i}= (x_{i1},……..,x_{ini})^T$ be a $n_i\ x\ p$ matrix of explanatory variables for subject i.

The GEE approach also assumes a working correlation matrix **R(α)** for Y_{it} depending on parameter α. Let **R(α)** be the $n\ x\ n$ symmetric matrix and α be an $s\ x\ 1$ vector, then **R(α)** as defined by Liang and Zeger [1] is

$$\mathbf{V_i=A_i^{1/2}\ R(\boldsymbol{\alpha})A_i^{1/2}/\boldsymbol{\varphi}}$$

And v_i= cov (Y_i) if **R** is true correlation matrix for Y_i, and $\mathbf{A_i}$ = diag $\{a''(\theta_{it})\}$

When we have univariate GLM, then the quasi likelihood estimating equation have the form

$$\sum_{i}\left(\frac{\partial \boldsymbol{\mu}_{\mathbf{i}}}{\partial \boldsymbol{\beta}}\right)^{\mathbf{T}} = v(\boldsymbol{\mu}_{\mathbf{i}})^{-1}\left[\mathbf{y}_{\mathbf{i}} - \boldsymbol{\mu}_{\mathbf{i}}(\beta)\right] = 0 \qquad (2.2.1)$$

The analog of this in multivariate is the generalized estimating equation given by Liang and Zeger [1]

$$\sum_{i=1}^{N} \mathbf{D}_{\mathbf{i}}^{\mathbf{T}} \mathbf{V}_{\mathbf{i}}^{\mathbf{T}} \left[y_i - \boldsymbol{\mu}_{\mathbf{i}}(\beta)\right] = 0 \qquad (2.2.2)$$

where $\mathbf{D}_{\mathbf{i}} = \dfrac{\partial\left\{\mathbf{a}_{\mathbf{i}}^{\mathbf{T}}(\boldsymbol{\theta})\right\}}{\partial \boldsymbol{\beta}} = \mathbf{A}_{\mathbf{i}} \boldsymbol{\Delta}_{\mathbf{i}} \mathbf{X}_{\mathbf{i}}$ (2.2.3)

$(\partial \boldsymbol{\mu}_{\mathbf{i}}/\partial \boldsymbol{\beta})$ is a n_i x p matrix

$\mathbf{A}_{\mathbf{i}}$ denotes a diagonal matrix with main diagonal elements $a_i''(\theta_{it})$

$\boldsymbol{\Delta}_{\mathbf{i}}$ is a diagonal matrix with elements $\partial\theta_{it}/\partial\eta_{it}$ a n x n matrix.

It was shown by Liang and Zeger [1] that as the number of clusters n increases, asymptotic normality and consistency was obtained. $\sqrt{\hat{\beta} - \boldsymbol{\beta}} \rightarrow N(\mathbf{0}, \mathbf{V}_{\mathbf{G}})$

and $\mathbf{V}_{\mathbf{G}} = \lim\limits_{n\to\infty} \mathbf{V}_{\mathbf{G,n}}$ with

$$\mathbf{V}_{\mathbf{G}} = \lim_{n\to\infty} n\left[\sum_{i=1}^{n} \mathbf{D}_i^T \mathbf{V}_i^{-1} \mathbf{D}_i\right]^{-1} \left[\sum_{i=1}^{n} \mathbf{D}_i^T \mathbf{V}_i^{-1} COV(Y_i) \mathbf{V}_i^{-1} \mathbf{D}_i\right] \left[\sum_{i=1}^{n} \mathbf{D}_i^T \mathbf{V}_i^{-1} \mathbf{D}_i\right]^{-1} \qquad (2.2.4)$$

When COV($\mathbf{Y}_{\mathbf{i}}$)=$\mathbf{V}_{\mathbf{i}}$, and the working correlation structure is true one, then the asymptomatic covariance matrix $\mathbf{V}_{\mathbf{G}}$ simplified to $\left[\sum_{i=1}^{n} \mathbf{D}_i^T \mathbf{V}_i^{-1} \mathbf{D}_i\right]^{-1}$

The β estimated using the GEE approach is efficient and consistent even if the covariance structure of $\mathbf{Y}_{\mathbf{it}}$ is incorrectly specified [1]. However, the correlation structure in case of discrete data is not one of the best ways to express the within-subject correlation [34]. An alternative approach is the use of odds ratios, by modeling the log odds ratio for pairs in a cluster as exchangeable [34, 39, 40]. Another alternative is the iterative alternating logistic regression algorithm proposed by Carey [41].

Longitudinal data analysis has three extensions of the generalized linear models, (GLM) namely marginal models, random effects models and transitional models. In linear models with continuous outcomes, the interpretation of the regression parameter is independent of the correlation structure. However for non-linear models, different assumptions of correlation structure will result in regression coefficients with distinct interpretations [35]. The regression coefficient for linear models can have a marginal interpretation for all three approaches but this is not true for non-linear data [35]. Zeger et al. [42] showed that for the logistic model, the β estimate of marginal and random effects models are not equal, but

$$\beta \approx (c^2 v^2 + 1)^{-1/2} \beta^* \qquad (2.2.5)$$

where c is a constant and is equal to $16\sqrt{3}/(15\pi)$ with c2=0.346, and v^2 is the variance. β is estimated using a marginal model and β* is estimated using a random effects model. However, it is only in limited cases that the relationship between transitional and marginal models can be established for non-linear models [35]. As a consequence , one should be careful in the choice of the model for non-linear outcomes and this choice should depend on the research question being addressed [35].

In the next section, the marginal models for non-Gaussian outcomes are discussed.

2.2.1.1 Marginal models for non-survey data

In marginal models, the parameters characterize the marginal probability of success at a given point in time when the response is binary [43]. A fully specified marginal model taking into account the correlation and implementing likelihood inference for discrete data, was first proposed by Bahadur [44]. This model was also studied by Cox [45], Kupper and Haseman [46] and Altham [47]. The existence of severe constraints on correlation parameter space was the major drawback of the model proposed by Bahadur [44]. The log-linear models proposed by Bishop et al. [48] were the most widely used probability models for multivariate binary data. The canonical parameters were undesirable and their interpretation was dependent on the number of responses (N). The latter was a major drawback of the model proposed by Bishop et al. [48], because in longitudinal studies, the number of responses can vary across subjects.

Diggle et al. [35] tried to build a log-linear model by starting with marginal parameters μ_j= Pr (Y_j=1), j=1,……..N. They proposed a saturated log linear model that had 2^n-1 parameters, which could be obtained in three different ways:

(1) using μ_j, second and higher order canonical parameters, as proposed by Fitzmaurice et al. [38].

(2) Using log linear models which uses marginal means, as proposed by Bahadur [44]

(3) Parameterization of likelihood in terms of marginal odds ratio.

The problem with all three models was the unavailability of simple methods to calculate the third and higher order moments, and even with the model fully specified, the likelihood estimates were very complicated [35].

To overcome these problems, the GEE approach was proposed by Liang and Zeger [1]. The GEE approach was originally specified for modeling univariate marginal distributions, such as binomial and Poisson [34]. Prentice [49] extended the GEE approach by allowing the simultaneous estimation of parameter vector and variance-covariance matrix. The variance-covariance matrix obtained by these equations was more stable compared to the variance-covariance estimator proposed by Liang and Zeger [9].

Second order GEE were proposed by Zhao and Prentice [50] for continuous or categorical data and by Liang et al. [51] for categorical data. Liang et al. [51] compared the log linear models with the marginal models and suggested that the marginal models can be used when the log linear models become inefficient. Liang et al. [51] referred to the GEE approach proposed by Liang and Zeger [1] as GEE1 and their method as GEE2. The authors showed that the GEE1 method proposed by Liang and Zeger [1] was highly efficient in determining the β estimate, but highly inefficient for estimating α. The GEE2 method was highly efficient in estimating both parameters β, and α. The authors suggest the use of GEE1 when α is a nuisance parameter. Besides this aforementioned point, valid standard errors for $\hat{\beta}$ can be obtained using the empirical or "sandwich" estimator for the cov(β) estimate [1, 37].

An alternative approach to the GEE was given by Carey et al. [41], the so called "alternating logistic regression" (ALR) method. This method is different from all of the GEE methods discussed above, but because it is based on the odds ratio, has common features of GEE and GEE2 [43]. The advantage of the ALR method [52] is that it requires no working assumption of third and fourth order odds ratios, and combines marginal as well as a conditional specification [43]. Work by Zhao et al.[50], Fitzmaurice and Laird [38] and Fitzmaurice et al. [39] made the connection between the GEE approach and the likelihood-based methods [53]. The GEE approach and the "sandwich estimator" of cov(β) are the most widely used methods in marginal models with discrete outcomes, and most of the available software that implements the use of the GEE approach has made it a very popular technique for models with discrete outcomes [53].

2.2.2 Event history analysis for non-survey data

Survival analysis is a branch of statistics which primarily deals with death in biological organisms and failure in mechanical systems. Death or failure is called an "event" in the survival analysis literature, and therefore, models of death or failure are generically termed *time-to-event models*. Research in the field of survival analysis is very much influenced by the regression model developed by Cox [54], introduced in 1972 [45].

Cox extended the Kaplan and Meier [55] life table analyses to include the regression equation. Since then, this technique has become widely used for survival and other censored outcomes. Cox's proportional hazard model for the i th person, given the covariate value x, can be specified by the following equation:

$$\lambda_i\left(t \mid \mathbf{x}\right) = \lambda_0\left(t\right)\exp(\mathbf{x}_i(t)\beta) \tag{2.2.6}$$

where $\boldsymbol{\beta} = (\beta_1, ..., \beta_p)'$, is p x 1 column vector of coefficients and λ_o (t) represents baseline hazard and is a non negative function of time.

Assuming no ties, the inference on β can be estimated from the likelihood function:

$$L(\beta) = \prod_{i=1}^{n} \left\{ \frac{\exp(\boldsymbol{\beta}'\mathbf{x_i})}{\sum_{j \in \mathbf{R}(t_i)} \exp(\boldsymbol{\beta}'\mathbf{x}_j)} \right\}^{\delta_i} \tag{2.2.7}$$

where $\mathbf{R(t_i)}$ = $(j\text{: } t_j \geq t_i)$ and $(1\text{-}\delta_i)$ is an indicator of censoring, and later on Cox derived the equation 2.2.8 as partial likelihood function.

Survival analysis techniques are also applied to recurring or repeated events, commonly referred to as event history analysis. Examples of repeated events would be recurrent asthma attacks, the occurrence of diabetic retinopathy over time, and the decline of the CD4 count over a small period in AIDS patients. The recurrent events or the repeated event models are correlated, and hence, the assumption of independence is violated. Thus, the major disadvantage of using Cox's model for event history analysis or recurrent failure times data is that the basic assumption of independence is violated. The use of standard analytical approaches for correlated survival data results in reduced efficiency [56] and incorrect estimates of standard errors.

Various methods have been developed to account for dependencies due to repeated events at the variance estimation stage. Such methods are called variance corrected and frailty models, and are discussed in the next section.

2.2.3 Variance corrected models

Variance corrected models use robust variance estimation methods to account for heterogeneity among individuals and event dependence [57]. The most commonly used models for multiple events are Anderson Gill (AG), Wei, Lin and Weissfeld

(WLW) and Prentice, William and Peterson (PWP). The AG model is based on independent increment models, the WLW on marginal models and the PWP on conditional models.

Anderson and Gill extended Cox's Proportional Hazard Model to recurrent event data, commonly known as the AG model (also referred to as the "independent increment" model) [58]. Their generalization was based on the work of the multivariate counting process of Aalen [59]. The AG model intensity process for i^{th} subject is

$$\lambda_i\left(t \mid \mathbf{x}\right) = \lambda_0\left(t\right)\exp(\mathbf{x}_i(t)\beta) \tag{2.2.8}$$

and is identical to the Cox model (eq 2.2.7). The AG model is very similar to the Cox's model with a difference in the definition of λ_i (t). In the Cox's model λ_i (t) equals zero in case of an event whereas for AG model λ_i (t) equals 1 as event occurs [60]. Each subject in AG model is treated as a multi-event counting process with independent increments (see appendix A). This model requires a strong assumption of independent increments, especially if ordering of the event is necessary. Another assumption of the AG model is that multiple events for any particular observation are assumed to be independent [61]. The AG model can handle recurrence event data and the model usually assumes that the recurrences follow a non-homogeneous Poisson process and are not affected by the occurrence of earlier events [62]. Wei and Glidden [62] suggest that such strong assumptions can be relaxed by the including time dependent covariates in the model.

Wei, Lin and Weisfeld [63] (WLW) modeled the marginal distribution of failure time variable with a Cox's proportional hazards model. This method was based on a semi-parametric approach, with the regression model for the marginal relative risk being the parametric component and the marginal baseline hazard and dependence structure constituting the non-parametric part [64]. The usefulness of the semi-parametric approach over the full parametric approach was that it did not require as strong assumptions. As well, the modeling of multivariate failure time data has been made possible with the help of computer programs. The hazard function for the jth event for ith subject is

$$\lambda_{ij}\left(t \mid \mathbf{x}\right) = \lambda_{j0}\left(t\right)\exp(\mathbf{x}_i(t)\beta_j) \tag{2.2.9}$$

Here β_j represents separate hazard for each event and for strata by covariate interactions [60].

The Conditional Model, or the Prentice, William and Peterson (PWP) model [65] is based on the conditional method and can be analyzed using the partial likelihood principle. The model can be used to model multivariate failure time data. In the PWP model, a second event cannot occur unless the first event has occurred. The time dependent strata vary from event to event. The hazard function is defined as

$$\lambda_{ij}\left(t \mid \mathbf{x}\right) = \lambda_{j0}\left(t\right)\exp(\mathbf{x}_i(t)\beta) \tag{2.2.10}$$

This equation is similar to the WLW model, the only difference being that $\lambda_{ij}(t)$ has the value zero until the previous event has occurred.

Other marginal models for variance corrected models have been proposed. Wei, Ying and Lin [66] proposed an alternative inference procedure to estimate the variance. This alternative inference approach aids computation of the variances and it does not use the unstable non-parametric approaches. Lee, Wei and Ying [67] proposed a simple linear regression method to analyze highly stratified observations, based on a population averaged model, also known as a marginal model. This method does not require a complicated model and the estimates are stable and are not based on non-parametric approaches. These population-averaged models provide valid inferences about the parameter estimates without any distributional assumption. Lee, Wei and Amato [68] used the Cox regression model to model the hazard function of each failure time without imposing dependence among the related failure time observations. Liang , Self and Chang [64] (LSC) also used the marginal distribution approach to make inferences on the parameters in marginal hazard (when there is dependence between individuals). The proposed LSC method used semi- parametric approaches but was different from the WLW marginal model. In LSC model, the relative risk is the parametric component, and the marginal baseline hazard and dependence structure is the non-parametric component. LSC model assumed the dependence structure to be completely unspecified.

An alternative method to the Cox model is the accelerated failure time (AFT) model. The AFT model, which is based on regressing the logarithm of survival time over the covariate, can be easily extended to the multivariate case [66, 69]. One of the limitations of variance corrected models is that they are not suitable for modeling competing risks. Further research is needed in this area.

Gao and Zhou [70] compared the WLW and LSC models and found that under some regularity conditions (two pairs of observations from different clusters are independent), the LSC method provided robust estimates. However, they suggested the use of the WLW over the LSC method when all covariates are identical for failure data. Guo and Lin (1994) developed a grouped time version of marginal models, which is an advancement of the WLW model. Therneau and Hamilton [71] compared four models

(AG, WLW, PWP and the Prentice and Cai method) for survival analysis with multiple events per subject. They compared the AG [58] model, the WLW method [63], the PWP [65] and the Prentice and Cai method [72]. The PWP method used the conditional method and Prentice and Cai's method modeled correlations directly using Cox's framework.

Therneau and Hamilton [71] suggest the use of AG and WLW because of the availability of computer software to analyze repeated/correlated events data using these approaches. The PWP method is based on the conditional method and can be analyzed using the partial likelihood principle. Both the AG and the PWP models are sensitive to misspecification of dependence structures among recurrence times [63]. The AG, PWP and WLW methods can be analyzed using PROC PHREG in SAS [73]. Wei and Glidden (1997) suggest the use of the models WLW, Wei, Ying and Lin [66], Lee, Wei and Amato [68] and the model by Lee, Wei and Ying [67], as these models are robust and well developed.

Kelly and Lim [73] proposed four key elements to characterize the Cox based models: risk interval, baseline hazard, risk set and correlation adjustment. Based on these four key elements, they compared five models: the AG [58], the WLW [63], the PWP-CP [65] , the PWP-GT [65] and the LWA [67]. The PWP-GT (gap time) and the PWP-CP (total time) were developed by Prentice, William and Peterson [65]. Gap time is the time from the prior event. Once the event has occurred, the clock restarts. The total time is the time from the start of the treatment. The counting process is similar to total time, except that a subject may have a delayed/censored period before the subject becomes at or a risk for the event. The PWP-CP model is the stratified AG model, where the event specific baseline hazard is restricted. Gap time- unrestricted (GT-UR) assumes that the baseline hazard or the risk set is unrestricted and TT-R (Total Time - Restricted) assumes that the baseline hazard or the risk set is restricted or event-specific.

Kelly and Lim [73] concluded from their study that the PWP-GT model and the Total time-restricted (TT-R) model introduced by them are useful for analyzing recurrent data. They suggest the use of PWP-GT when within subject events are independent. The four models compared by Kelly and Lim [73] did not account for the within-subject correlation, even with robust variance. Kelly and Lim [73] recommend the use of PWP-GT and TT-R when within-subject event are independent for analyzing recurrent event data. AG and GT-UR both assume that they have common baseline hazards, but these models cannot be used, as they do not have versatility of event specific model. WLW models are more suitable for multi-type event data, where the baseline hazard is different for each type of events. For example, tumours at different sites of the body [73]. LWA is useful for clustered data when the baseline hazard is the same. For example in clustered data on a pair of eyes [73]. When the WLW model is applied to recurrent data, it leads to an over-estimation of the treatment effect. The LWA model allows the subjects to be at risk several times for same event.

2.2.4 Frailty models

The frailty or random effects model treats the repeated events as a special case of more general unit-level heterogeneity. The random effect is across individuals and constant over time. In Frailty models, a random effect is a continuous variable, which describes excess risk or frailty for distinct categories, such as individuals or families. This excess risk or frailty for distinct categories, like individuals and families, is described using a random effect, which is a continuous variable. Computation of frailty is observed as the unobserved covariate [60].

Univariate frailty models were first introduced by Vaupel [74]. Clayton [75] extended the Cox proportional hazard model [45] to multivariate life tables. The model proposed by Vaupel et al. had a fully parametric approach and later Clayton and Cuzick [76] extended the univariate model developed by Vaupel [74]. Their model was a generalization of the proportional hazard model and contained a random effect term to represent heterogeneity of "frailty." The model used a non-parametric approach and parameters were estimated by the maximum likelihood method. The proportional hazard model for subject i can be written as

$$\boldsymbol{\lambda_i}(t) = \boldsymbol{\lambda_o}(t) \exp(\mathbf{X_i}\beta + \mathbf{Z_i}\omega) \tag{2.2.11}$$

where $\mathbf{X_i}$ and $\mathbf{Z_i}$ are ith row of covariate matrices $\mathbf{X}$ and $\mathbf{Z}$, $\mathbf{X}$ and β corresponds to p fixed effects in the model and ω corresponds to a vector which contains information on q unknown random effects or frailties, $\mathbf{Z}$ is the design matrix [77].

Huster, Brookmeyer and Self [56] extended the fully parametric model of Clayton [75] and Oakes [78] to include covariate information, and the parameter estimates and robust variance estimators were obtained. Their independent working model (IWM) was computationally simple, but the only limitation was that it ignored the between pair association and resulted in a severe loss of information. On the other hand, the model proposed by Clayton and Oakes took into account between pair associations, but it was computationally intense and associations could only be positive.

Ross and Moore [79] developed methods for modeling discrete or grouped time survival time when groups or clusters are correlated. They specified the marginal hazard of failure for individual items within a cluster or group by using the linear log odds survival model, and the dependence structure was based on the gamma frailty model [75]. To estimate the parameters, they used a method which combined the GEE method and a pseudo likelihood method. The developed model could handle cluster sizes greater than two and assumed that dependence varied with cluster level covariates. Cox's frailty model [74, 75] allowed between cluster heterogeneity.

The mixed effects model developed by Ratcliffe et al. [80] extended the Cox frailty model for repeated measures to include both subject and cluster level random effects. This model was more efficient and less biased, and evaluated the effect of the treatment variable while accounting for the relationship between them. The mixed effects model can be extended to multiple common frailties, and the correlation between cluster level random effects and frailty can be easily overcome by the addition of frailty not linked with random effects. However, this method can be computationally intense.

Frailty models or random effects models can also be used when there is correlation present at different hierarchical levels. This multilevel random-effects model for survival data is new, and is gaining momentum due to its application in data where clustering is present between and within subjects at different levels of association. Some of the earlier work in this area is by Rodriguez [81] and Bandeen-Roche [82]. The model proposed by Bandeen-Roche and Liang [82] had the same properties of the multivariate frailty model. Their proposed model took into consideration clustering present at multiple levels and reduces to a univariate frailty model in the case of single clustering.

A nested frailty model for survival data was proposed by Sastry [83] when there was clustering at two hierarchical levels (community-level and family-level). The parameter estimates were obtained by using the EM-algorithm. Sastry suggests the use of such a model when there is clustering present at different levels as ignoring the clustering will result in upward bias of the estimates of variance at both levels. Gross and Huber [84] extended the partial logistic model to clustered survival data that may be censored. They assumed that individual survival times within clusters are correlated while the distinct clusters are considered independent.

2.2.5 Missing data due to dropouts

Missing data is common in longitudinal survey studies as they are the result of non-response or losses during the follow-up process. In longitudinal studies, missing data has three major implications [53]. First, the data set is unbalanced, as not all the participants have the same number of repeated measurements. Second, missing data results in a loss of information. Third, missing data may be missing at random thus resulting in misleading inferences [53].

Missing data can be categorized into three different types based on Rubin [85] and Little and Rubin [86] : (i) missing completely at random (MCAR), (ii) missing at random (MAR), and (iii) missing not at random (MNAR). Under the MCAR mechanism, the probability of an observation being missing is independent of the observation. For the MAR mechanism, the probability of an observation being missing is conditionally independent of the unobserved data. Finally for the MNAR mechanism, the probability of a measurement depends on unobserved data [43, 85, 86].

Some of the commonly used methods to analyze longitudinal data with missing data include complete case analysis (CC), last observation carried forward (LOCF), unconditional mean imputation [86] and conditional mean imputation [43, 86-88]. Complete case analysis is simple to describe and easy to use as most software assumes complete case analysis. However, there are some serious drawbacks associated with this method. Information is lost as only complete cases are included and thus, statistical efficiency is reduced leading to large standard errors [88, 89]. This analysis requires the stronger assumption that missing data is missing completely at random [43].

Another simple method is last observation carried forward (LOCF) [90, 91], where the last observation is substituted for any missing observation. This method can be applied to monotone or non-monotone missing patterns [43]. The disadvantage of using this method is that it increases the amount of information in the data by treating imputed and observed values in the same footing [43], thus affecting the variance structure, the correlation structure or random effects structure or the group difference. This has been shown for the linear mixed model setting by Verbeke and Molenberghs [92] .

The unconditional mean imputation method [86] was primarily developed for continuous data and its application to binary data will be problematic [43]. In this method, the averages of the observed values are used to replace the missing values on the same variable [43]. The drawback of this method is that the resulting model is often distorted as the imputed values of a subject are unrelated with other measurement on the same subject [92].

The conditional mean imputation method, also known as Buck's method, estimates the mean and covariance matrix assuming a normal distribution from the complete cases and then substitutes the conditional mean for the corresponding missing values. The conditional means are calculated from the regression of the missing component on observed component [43]. This conditional mean imputation method is better compared to the unconditional mean imputation and the LOCF method as the mean structure and the variance components are not distorted [43]. The methods discussed above are not very popular, due to their limitations and the unavailability of commercial software, which can perform the required complex analysis.

The weighted generalized estimating equations (WGEE) was devised by Robins, Rotnitzky and Zhao [93] for management of longitudinal data analysis with missing observations [93]. This method is valid under MAR assumption but requires specification of a dropout model in terms of observed outcome and/or covariates.

Two other available alternative methods are multiple imputation [94] and expectation-maximization (EM). Rubin [94] introduced the multiple imputation (MI) method and it requires the assumption that data are MAR. The method is highly efficient, even for small values of M imputations [43]. However, Molenberghs and Verbeke [43] suggest that the method of choice depends on the type of missing data. For monotone missing patterns with MNAR dropout, a Dale model was proposed by Molenberghs, Kenward and Lesaffre [95] for ordinal outcome and a logistic regression approach was suggested by Van Steen et al. [96]. For the non-monotone missing pattern (intermittent missing pattern), Baker et al. [97] proposed a family of models for two binary outcomes. This method was based on log-linear models for the four-way classification of both outcomes, together with their respective missingness.

Baker [98] proposed a model for three binary outcomes with non-monotone missing patterns, first one based on the marginal, second one on association models for the measurements, and the third one a logistic regression model for the missingness mechanism, depending on the last observed and last unobserved measurements.

The EM algorithm is an iterative algorithm used to compute the maximum likelihood in parametric models for incomplete data . The EM algorithm was proposed by Depmster, Laird and Rubin [99], the method did not produce estimates for the co-variance matrix of the maximum likelihood estimators, and convergence was slower in this model. The best feature of this method is that it can be used for MAR and MNAR data .

In the direct likelihood method, the EM and the MI are the three most powerful tools when we have MAR data to conduct likelihood inferences [43]. Another noticeable feature of WGEE, EM and MI methods are that they can be easily extended to MNAR settings and the detailed illustration of these works can be found elsewhere [43].

2.3 Cross-sectional and longitudinal Complex Survey designs

Multi-stage sampling design is used to collect data in large national survey studies. This survey design is used quite often for the reason discussed above and also because it simplifies data collection. The selection of individuals is conducted at more than one stage. The sampling units, or clusters, follow a hierarchy: in each stage, elements are sub-sampled from the larger clusters from the previous stage. One usually employs a combination of more than one method, such as simple random sampling, cluster sampling and/or stratified sampling. More homogeneous strata created by stratification helps reducing the variance of parameter estimates [5]. Hierarchical sampling allows both person-based and household-level estimation.

The primary objective of analyzing survey data is to make inferences about characteristics for the finite population of interest [5]. Appropriate analysis methods should account for the effects of clustering and stratification, and for unequal selection probabilities. To account for unequal inclusion probabilities, appropriate survey weights must be taken into account. Survey weights calculated as ($1/\Pi_i$), where Π_i is the sample inclusion probability. The principle behind the survey weights is that each individual in the sample, besides himself /herself, represents other people with the same or similar characteristics but who are not in the sample. The data arise from randomly chosen clusters within a stratum, thereby helping to reduce the cost of data collection and enhancing practical efficiency; however, as a result, the data forms into in the aforementioned cluster effect [5]. The practical efficiency of clustered designs is counter balanced by a reduced statistical efficiency.

The advantage of using complex survey sample in comparison to the simple random sample (SRS) is that this sampling scheme does not require a complete sampling frame of the population elements and is, therefore, more practical [100]. However, complex sampling scheme is less efficient than SRS and to obtain correct estimates of the data, the sampling design should be taken into account. The cluster effect occurs mainly because the individuals belonging to the same clusters tend to have some similar characteristics, or, in other words, are correlated. This correlation is often referred to as the *intra-cluster* effect [101]. The survey sample weight should be taken into account in order to obtain correct point estimates. Additional adjustments, such as non-response and post stratification, should be accounted for in the survey weights. To get correct variance estimates, the survey weights are not sufficient, as these weights do not account for clustering and stratification effects. Other adjustments are required to get correct variance estimates.

2.3.1 Analysis of complex survey data

The main purpose of the cross-sectional and longitudinal surveys is to produce unbiased estimates of population parameters, such as totals, means and regression coefficients. The statistical methods are well developed for cross-sectional survey designs; however, the methods are still in their developmental stage for longitudinal survey data. To account for the complexities of complex survey data, three approaches are commonly used: (i) model assisted approaches, (ii) model-based approaches and (iii) design-based approaches.

Model assisted estimation refers to a property of estimators that models the auxiliary information (those variables which helps in sampling design, for example in NPHS the auxiliary variables are age, sex and province) in the estimation procedure for the finite population parameters of interest such as regression coefficients. Incorporating the auxiliary variables in the sampling phase improves the accuracy of the estimates and decreases the design variances of the estimators [100]. The inferences are still design-based, even when incorporating the auxiliary or secondary variables in the model for estimation procedure. For this reason, this modeling approach is also called the design-based model assisted approach [9]. Sarandal et al. [102] have discussed the model-assisted techniques in detail.

The pure model-based methods ignore the complex survey design, or, in other words, design effects, such as clustering and stratification. The sample observations, $y_1,\ldots\ldots,y_n$, in a model-based approach are assumed to be random variables. Ordinary least squares (OLS) estimation is used when the data collection is done through a Simple Random Sample (SRS), but this approach cannot be used for complex survey sampling. Using OLS will result in biased estimates of model parameters and inconsistent variance estimates. If proper sampling design is not taken into consideration, then the model is misspecified and the conclusions are not valid [103]. There are several methods available which account for the clustering and stratification by calculating robust standard errors for cross-sectional design. The Generalized Estimating Equation (GEE) approach proposed by Liang and Zeger [1] takes into account the intra-class correlation. The work by Goldstein [104, 105], who proposed multi-level modeling approach, considers the clustering and stratification effects. Some other methods include hierarchical Bayes approach using Markov Chain Monte Carlo (MCMC) technique [106].

In the design-based approach, the complexities due to multi-stage sampling design such as clustering and stratification can be properly accounted for in the variance estimation.

In survey analysis, to obtain the parameter estimates it is very important to use the proper survey weights. Two common types of survey weight are the following: (i) expansion weights which is usually the reciprocal of the selection probability and (ii) relative weight which takes into account post- stratification and the non response. The use of expansion weights is usually problematic when calculating variance and needs to be adjusted [107]. To estimate the variances of parameter estimates, replicated sampling, balanced repeated replication (BRR), Jackknife Repeated Replication, Taylor Series Method, Rao-Wu Bootstrap method and Ratio estimation methods are available [107]. To calculate the variance estimates or standard errors, clustering and stratification should also be considered, as the sampling weights alone are not sufficient.

The design-based approach is the best method for analyzing survey data as it accounts for any complexity arising due to the sampling scheme, whereas the model-based approach ignores the sampling design. Model assisted approaches can also be used as an alternative to the design-based approaches. The use of this method improves the accuracy of estimates and decreases the design variances of the estimators [9]. Auxiliary information in stratified sampling helps to reduce the within-stratum variations [9]. However, for analyzing the longitudinal NPHS data, the focus is to compare the model-based and design-based approaches.

2.3.2 Longitudinal complex survey data

Longitudinal studies consist of repeated measures on two or more occasions on the same individuals over time. The stratification and clustering effects are often ignored in the standard analysis of longitudinal survey data. This results in biased estimates of model parameters and leads to false inference [6]. The main objective of longitudinal survey studies is to produce estimates of the net change that occurred in the population between two time points [108]. Previous work in this area dealt mostly with the analysis of longitudinal data for non-surveys. The work in the area of longitudinal survey can be summarized into two sections: (i) marginal modeling approach and (ii) event history analysis. The development in each area will be discussed in turn.

2.3.2.1 Marginal models for survey data

Rao [3] proposed Wald and quasi-score test for longitudinal survey design using the Taylor linearization and Jackknife method. This method accounts for the complexity of the survey design, as well as the longitudinal nature of the data. The marginal model proposed by Rao [3] is basically an extension of Liang and Zeger's work [1]. In this paper, Rao [3] uses the Taylor linearization method to compute the variance, as proposed by Binder [109]. The variance estimator should account for post-stratification and non-response adjustments. The formula to estimate variance is the following:

$$\mathbf{v}\left(\hat{\mathbf{S}}\right) = \sum_{\mathbf{h}} \frac{\mathbf{1}}{\mathbf{n_h(n_h-1)}} \sum_{\mathbf{i}} (\mathbf{e}^*_{\mathbf{h_i}} - \mathbf{e}^*_{\mathbf{h.}})(\mathbf{e}^*_{\mathbf{h_i}} - \mathbf{e}^*_{\mathbf{h.}})^T$$

Where h denotes the hth stratum, i denotes ith cluster within the hth stratum, $\mathbf{e}^*_{\mathbf{h.}} = \sum_{\mathbf{i}} \frac{\mathbf{e}^*_{\mathbf{h_i}}}{\mathbf{n_h}}$ assumes that the first stage clusters are either drawn with replacement in each stratum or first stage sampling fraction is negligible. This gets more complicated with non-response. Rao [3] also proposed the use of Jackknife method to estimate the variance.

The advantage of Jackknife method is that the post stratification and unit non-response is taken into account.

Skinner and Vieria [110] compared the linearization method and robust variance estimation method and they concluded that both of the methods produce similar results. They treated the linearization method as the "gold standard" for variance estimation because of its consistency. However, this method may be less efficient than the model-based variance estimation method when the model is correctly specified.

2.3.2.2 Even history analysis for survey data

Binder [111] extended the work of Lin and Wei [112] to fit the Cox's proportional hazard model from survey data. Binder [111] compared the design-based and model-based methods. The design-based methods accounts for the clustering, stratification and weighting, whereas the model-based method and the 'robust' method proposed by Lin and Wei [112] ignore the sampling weights. Binder concluded from his study that the design-based and 'robust' method gave similar coverage probabilities and Taylor linearization method to estimate variance performs better than model-based methods. The 'robust' method proposed by Lin and Wei [112] uses the same linearization as the design-based method except that it is based on unweighted estimates and assumes simple random sampling with replacement in variance calculation. Binder [111] concluded that design-based method is the best as it assumes that the survey data belongs to a finite population.

Lin [113] generalized Binder's [111] work to the context of super-population analytical inference. Lin [113] proposed an alternative approach which considered survey population as a random sample. The advantage of assuming survey population as a random sample was that the interpretation as the log hazard ratio and statistical conclusion applies to other populations as well. Lin [113] suggested that survey data analyzed within finite population or super population framework, is good for descriptive analysis and is not suited for regression analysis. When the survey population is fixed, there is no probability model governing the relationship between response variable and covariates. The interpretation and prediction of the regression is inept [113]. By treating survey population as random from super population and by adjusting for extra randomness in variance estimation, one can make an inference about parameters. These parameters have clear probabilistic interpretation and the statistical conclusion extend beyond the survey population under study [113]. The additional term in the variance estimator accounts for extra variation due to super population inference which assumes independence between all observations [113].

Lawless and Boudreau [114] discuss the methods available for duration data and review different approaches. In their paper, they used stratified Cox's proportional hazard model and then compared the weighted and unweighted analyses. For the weighted analysis, they used Binder's method [111] and Lin's method [113] and for the unweighted, they accounted for the clustering and stratification. The weighted analysis based on Binder's and Lin's methods produced identical results, indicating that the robust standard error method by Lin [113] works well. The unweighted and weighted estimates were close enough, indicating that there is slight difference between them.

Lawless [115] used the event history analysis approach for binary outcome. This approach can be used to understand the event history processes of an individual.

Lawless [115] used the US National Longitudinal Survey of Youth (NLSY) to study breastfeeding durations. He assumed the independence among individual responses. The covariates selected for analysis were related to the design factors. He conducted unweighted analysis, assuming that no cluster information was available. Two methods namely, Cox's semi-parametric proportional hazard model [45] and accelerated failure time model [114] were used for analysis. It was concluded from the study that both methods provided the same variance estimators and similar parameter estimates. Lawless [115], in his approach, did not consider the complexity of survey design, other than including covariates related design factors. He indicates that the variance estimation methods for event history survey data has not received much attention [115].

Boudreau and Lawless [116] proposed variance estimators that account for the intra-cluster correlation. They used the theory of estimating equations in conjunction with the martingale theory. Their proposed method is similar to the method developed by Lin and Wei [112], the only difference being that Lin et al. [112] had developed 'robust' variance estimator to protect against model misspecification.

The methods for longitudinal survey design are still under development. Most of the methods discussed above have their own limitation and the complexity of the survey data are further aggravated due to missing values, non-response, measurement error, and loss to follow-up. Some of the other areas that need development include methods for handling missing data, fitting multivariate and hierarchical models with incomplete data, and methods for handling response-selective sampling induced by retrospective collection of data. In the next section, the development of methods for longitudinal binary data are discussed when we assume simple random sampling.

2.4 Epidemiology of adult asthma

2.4.1 International asthma prevalence

The prevalence of asthma is increasing among adults worldwide and has been shown to vary by gender. However, there has been limited research regarding the prevalence and characteristics of asthma in adults. The reason for this could be that adulthood asthma is often confused with symptoms of airway obstruction mainly caused by smoking- related diseases [117]. Asthma is more prevalent in westernized countries and may be related to increasing urbanization. According to the Global Initiative for Asthma (GINA), the prevalence of clinical asthma in westernized countries was highest in Scotland (18.4%) and lowest in the United States of America (10.9%). In Canada, clinical asthma prevalence was found to be 14.1 %.

There seems to be a wide variation of asthma prevalence within and between countries due to: (1) the different methods used to identify asthma, (2) geographic variation in the distribution of asthma, (3) the different definitions of asthma between studies, (4) the lack of a standardized instrument to diagnose asthma, and (5) biases arising while translating the questionnaire-related symptoms into different languages. Studies that use identical methodologies are needed at the international level to assess the wide variation in asthma prevalence that has been reported.

In 1988, the European Community Respiratory Health Survey (ECRHS) was conducted, funded by the European Commission. The aim of this survey was to estimate variation in asthma prevalence throughout Europe. The study population was young adults age 20-44 years [118]. The results of the study showed that the international variation in asthma prevalence was due to geographical differences between countries [119]. The wide variation in asthma prevalence between countries is thought to be due to differences in environmental factors within countries [119, 120].

In a study by Woolcock and co-workers in Australia, asthma prevalence was measured by physician diagnosed asthma, self- reported wheeze, or by abnormal lung function and a combination of symptoms [121]. The ECRHS studies conducted in Australia showed that among adults aged 20-44 years, the prevalence of self-reported wheeze was fourth highest of all countries studied [122]. Ruffin et al. identified an increase in the prevalence of doctor diagnosed asthma in South Australia. Asthma prevalence increased from 8% (95% CI, 6.4%-9.6%) in 1990 to 12.8% (95% CI, 11.4%-14.2%) in 2001 [123].

U.S. researchers used the following asthma definition in the Behavioral Risk Factor Surveillance System (BRFSS) study: “Have you ever been told by a doctor, nurse, or other health professional that you have asthma” (lifetime asthma) and “Do you still have asthma?” (current asthma). According to the BRFSS survey, the prevalence of asthma has been rising in the United States since 1980. Doctor diagnosed asthma was reported to be 96.6/1,000 of the population and current asthma attacks were 40.7/1,000 of the population in 1997 . The prevalence rate of lifetime reported asthma in US adults was 11.0% (95% CI, 10.8%-11.2%) and current asthma was 7.7% (95% CI, 7.3%-8.1%) in 2001 [124].

The prevalence rate of physician diagnosed asthma among adults in the age group 20-44 years is about 15.5% [122] in a New Zealand study and 14.2% when using current symptoms and bronchial hyperresponsiveness (BHR) as the criteria for asthma [125, 126]. The prevalence of asthma was highest in the age group 20-24 years (about

17.8%) [126]. D'Souza et al. [127] showed that physician diagnosed asthma in New Zealand adults in the age group of 20-44 years was 15.9%, which is similar to that reported by the ECRHS [125].

The prevalence of current asthma in the United Kingdom among adults in the age group 18 to 55 years, between the time periods 1981 to 1990, increased by 21% [128]. In another study in Newcastle, UK, a postal questionnaire was sent to 6,000 adult subjects, aged 20-44 years. The result showed an increase in the prevalence of doctor diagnosed asthma from 12.7% in 1992-93 to 16.9% in 1998-99. The overall mean change was found to be 4.4% [129]. Asthma prevalence in women increased from 3.01% (95% CI,2.99-3.03) in 1990 to 5.14% (95% CI, 5.10-5.18) in 1998 and in men from 3.44% (95% CI, 3.41-3.46) in 1990 to 5.06%(95% CI, 5.02-5.10) in 1998 [130].

2.4.2 Adult asthma prevalence in Canada

Like in other countries, the study of asthma prevalence in Canada among adults is limited. Six reports were located that assessed adult asthma prevalence (See Table 2.1).

Table 2.1 Major Canadian studies of asthma prevalence in the general adult population

Study	Year	Age (Years)	Study Population	Asthma definition
Manfreda et. al. [131]	2004	20-44	Six Canadian cities	Q + LFT
Senthilselvan et al. [20]	2003	0-64	Saskatchewan	Physician diagnosed
Manfreda et. al. [132]	2001	20-44	Six Canadian cities	Q (Physician diagnosed)
Levesque et al. [133]	2001	All ages	Quebec	Q (Physician diagnosed)
Senthilselvan [22]	1998	0-64	Saskatchewan	Physician diagnosed
Manfreda et al. [134]	1993	All ages	Manitoba	Q (Physician diagnosed)

Q =Questionnaire reported asthma; LFT =Lung Function Test

Questionnaires that use a combination of physician diagnosis and asthma symptoms have been largely used to study asthma prevalence in Canada. According to the 2000-2001 National Population Health Survey in Canada, the prevalence of health professional diagnosed asthma in populations aged 12 and over increased slightly from 8.1% (2,014,933 people) in 1998-99 to 8.4% (2,170,748 people) in 2000-2001[6]. A cross-sectional study by Manfreda et al. [132] used a sampling strategy and standardized form of ECRHS among adults aged 20-44 years. They found that the prevalence of asthma and asthma-like symptoms varied between communities and by sex. For men, the prevalence of asthma was higher in Halifax (6.3%) and in Vancouver (6.1%). For females, asthma prevalence was highest in Halifax (9.5%) and Hamilton (8.8%) [132]. Compared to other international sites using the same survey [125], the median prevalence of bronchial hyper responsiveness (BHR) and asthma in Canada are

[6] (Source: Statistics Canada, CANSIM, table 104-0001, Catalogue no. 82-221-XIE)

still quite low at one third of median of other countries [131]. However, in a study by Senthilselvan et al. who examined data from Saskatchewan Health Databases for the years 1981 to 1998, asthma prevalence increased amongst adults aged 15-34 years from 1.2% in 1981 to 2.2% in 1990 [22]. There was an increase in prevalence from 2.2% in 1991 to 3.3% in 1998. A trend for stabilization of prevalence rates was noted in the latter part of 1990's [20].

An ECHRS study conducted among 20-44 year olds in Spain showed that the incidence of asthma was higher in females when compared to males (6.88 in females, 4.04 in males per 1000 person years) [135]. In a study conducted in Canada using the NPHS dataset, the two year cumulative incidence of asthma was higher in females (2.9%) as compared to males (1.6%) [16]. A study by Torren et al. on adults aged 20 to 50 years showed that the incidence rate of adult-onset asthma among females was 1.3 cases/1000 person-years compared with 1.0/1000 person-years for males [136]. A Norwegian study, conducted with 15 to 70 year old participants, showed a slightly different result. The 11 year cumulative incidence was higher in males (4.0%) than females (3.5%) [137]. A Finnish study on adult males and females aged 18 to 45 years, showed that there was no increase in asthma incidence from 1982 to 1990 [138].

To conclude, adult asthma prevalence is increasing worldwide and is more prevalent in westernized, English speaking countries. The studies confirm that there is a gender difference and asthma prevalence is higher in females than males. Studies on the incidence of asthma also show higher incidences among females with a few exceptions. The study of asthma prevalence and incidence is limited among adults and there is a need for more longitudinal studies examining variation in the incidence and prevalence of asthma over time in Canada.

2.4.3 Gender differences

Several epidemiological studies have shown that childhood asthma is more prevalent in boys than girls [134, 139, 140]. During adolescence, asthma prevalence is more or less the same in both sexes [142, 144] and during early adulthood, females begin to outnumber males in asthma prevalence. As well, adult females appear to have more severe asthma [19, 21, 134, 141, 145, 146].

Table 2.2 presents an examination of asthma prevalence for men and women in selected countries. With the exception of the UK, adult females in those countries reporting asthma prevalence by gender have higher asthma prevalence than males.

de Marco et al. [19] analyzed the ECRHS data set to study gender differences in children and adults. The age of the subjects varied from 0 to 44 years and 18,659 subjects participated in the survey. de Marco et al. concluded that during and after puberty, a reversal in asthma prevalence occurs, with females becoming more susceptible to asthma than males. This change could partly be because of airway size, along with hormonal changes in females [141].

Table 2.2 International prevalence of doctor diagnosed asthma among males and females

Country	**Age**	**Asthma Prevalence**			**Year**
		Males	**Females**	**Total**	
New Zealand [125]	20-44 years	-	-	15.5%	1996
South Australia [147]	15 years plus	9.8%	15.3%	12.8%	2001
UK [130]	15-64 years	5.1%	5.1%	-	1998
Canada [148]	12 years plus	7.1%	9.6%	8.4%	2003
USA [124]	18 years plus	5.1%	9.1%	-	2001

In a Danish study of adults by Omland et al. [149], researchers found that asthma was more prevalent among smokers and in women. Chen et al. [18] studied gender difference in asthma among adults in a rural Saskatchewan population. This was a cross-sectional study that defined asthma by physician diagnosis. The results of this study showed asthma prevalence to be higher in women (10.0%) than men (5.7%) and that the risk of asthma was positively associated with obesity in women but not in men.

Gustafsson et al. [145] studied 55 persons with asthma from childhood to adulthood. The mean age group at the beginning and end of the study was 9.4 years and 30 years, respectively. They found that with increasing age, lung function deteriorated among females but got better for males. Males with poor lung conditions at the beginning of the study showed an improvement of lung function, whereas this was not true for females. Nicolai et al. [150] found that the changing gender ratio for asthma in adulthood compared to childhood appeared to be related to later increase in incidence of asthma among adolescent girls . Sears et al. [151] studied risk factors for the persistence and relapse of asthma in adulthood. They found that being female or having an early age of onset were major risk factors for persistence or relapse of asthma in adulthood .

To summarize, both cross-sectional and longitudinal studies show that there are gender differences associated with asthma. Studies conducted across countries indicate higher asthma rates in young males and higher prevalence in females after puberty.

2.4.4 Rural/ urban differences for asthma

Very little research has examined rural/urban differences of asthma in Canada or internationally. Earlier studies only focused on rural population [152-154]. In a Danish study by Omland et al. [149], the effect of farming exposure on asthma-like symptoms and lung status was studied in young farming students and non-farming students staying in rural areas. There were no differences between farming and non-farming groups on bronchial hyper-responsiveness.

Geographical variations of asthma were studied by Lewis et al. [155] in a large cross-sectional study in New Zealand. They studied adults 20-44 years old, using the asthma symptom questionnaire. They concluded that asthma was more prevalent in females (17.0%) as compared to males (13.2%) and more prevalent among urban than rural dwellers. A study conducted in Australia by Woods et al. [156] compared asthma prevalence in rural and urban populations. This was a cross-sectional study in adults 20-44 years old using the ECRHS questionnaire. They found that there were significant rural/urban differences in asthma prevalence ($p<0.001$) and that asthma was more prevalent in the rural population as compared to the urban population. In a Canadian population- based study using the physician services database of the Saskatchewan Health Department, asthma prevalence (defined as at least one physician visit in a calendar year) was lower in rural than urban populations for all age groups [108]. A cross-sectional study conducted in South Germany by Filipiak et al. [157] also compared rural/urban differences in asthma prevalence in adults aged 25-75 years. They used a self-administered questionnaire to study asthma prevalence. Unlike other studies, they found no differences in asthma prevalence between rural and urban populations. Eduard et al. [158], compared south east Norway (farming population) with south west Norway (general population). Using a questionnaire survey to identify physician diagnosed asthma, they found that the farming population (4%) had a lower prevalence of asthma compared to a general urban population (7.6%). They concluded that this lower prevalence can be attributed to the “healthy worker effect”.

Based on this review, there appears to be a limited amount of research examining rural/urban differences in adult asthma. Of those that do exist, the results have been mixed. However, most studies with rural populations have not had an urban comparison group.

2.4.5 Other risk factors of asthma

Besides location of residence (rural/urban) and gender, there are a variety of other risk factors for adult asthma that have been identified in the research literature. These factors include obesity (measured by body mass index), smoking, exposure to second hand smoke, race/ethnicity and socioeconomic status.

Body mass index (BMI): The relationship between asthma and BMI is not clear. Several studies have shown a positive relationship between asthma and BMI among females but not among males [13, 16, 159]. Several other studies have also shown an association between asthma incidence and BMI equally among males and females [160-163].

Smoking: Smoking may be another risk factor for asthma, but a direct relationship between smoking and adult asthma has not been clearly determined. Some studies have shown that there is no direct link between active smoking and risk of asthma [135, 159, 164-167], whereas others have shown that smoking is a risk factor for asthma [136, 165, 167-169]. In a Canadian study examining gender differences, Chen et al. found a relationship between smoking and asthma for females but not for males [17].

Second hand smoke: The relationship of exposure to second hand smoke, particularly parental or maternal smoking and asthma, is well documented among children, but there is limited evidence for adult populations. No relationship between asthma and second hand smoke exposure was found among non-smoking adults [13]. Eisner [170] suggested a causal relationship between environmental tobacco smoke (ETS) exposure and asthma incidence among adults. Eisner [171] found that ETS exposure was associated with decreased pulmonary function in adult females, especially those with asthma. In another study by Eisner et al. [172], self-reported ETS exposure was associated with greater asthma severity, worse health status, and increased health care utilization in adults with asthma.

Race/Ethnicity: Research examining the relationship between race or ethnicity and asthma has shown contradictory results. Studies have shown that asthma prevalence was higher among the black population [173, 174] compared to the Caucasian population.

One of the studies found significant variation in asthma incidence especially among south Asian population and Afro-Caribbeans as compared to UK born Whites [175].

Socioeconomic status: Studies exploring the relationship between socioeconomic status and asthma have also shown opposing results. Several studies have found asthma prevalence and incidence to be higher among populations with lower than higher socioeconomic status [17, 18, 173]. De Marco et al. found no association between asthma and income [159] and Chen et al. found yet a different pattern of socioeconomic inequalities with respect to asthma [174]. Further research is clearly needed to explore the association of asthma with socioeconomic status.

To summarize, the development of statistical methods for longitudinal data with binary outcomes are available and widely used. However, there has been limited research conducted in the field of longitudinal survey data. Some of the areas in this field have received little attention and methodological developments are needed. These areas include handling missing data and repeated events and/or clustered data analysis for survival data. Research in this area is of interest and will be great value to researchers.

Regarding the epidemiology of asthma in adults, the prevalence of asthma varies by country, rural/urban location, and gender. Asthma is more prevalent among adult women than men. Currently, there have been few studies of asthma incidence and trends in asthma prevalence in the Canadian population concerning females only. Potential risk factors for asthma in the adult population include obesity, smoking, socioeconomic status and ethnicity. At present, the risk factors discussed above could be potential risk factors for asthma incidence or prevalence. Further research is clearly needed to clarify the nature of these relationships.

CHAPTER 3 - DATASET DESCRIPTION

3.1 Study design

The NPHS is an ongoing longitudinal study which collects information on the general health of the Canadian population. In the present analysis, all of the five cycles with complete data were used [Cycle 1 (1994-95), Cycle 2 (1996-97), Cycle 3 (1998-99), Cycle 4 (2000-01), and Cycle 5 (2002-2003)], resulting in a retrospective cohort design for the current study.

3.2 Sampling strategy

The sampling procedure of the household component of the NPHS was based on a multi-stage sampling design. As discussed in Chapter 1, this type of sampling design is a cost-effective and efficient way to collect data. In all of the provinces except Quebec, the same sampling design was adopted. In the first stage, homogeneous strata were formed by dividing each province into three types of areas, namely major urban centres, urban town and rural areas. Based on these separate geographic and /or socioeconomic status, strata were formed (Figure 3.1).

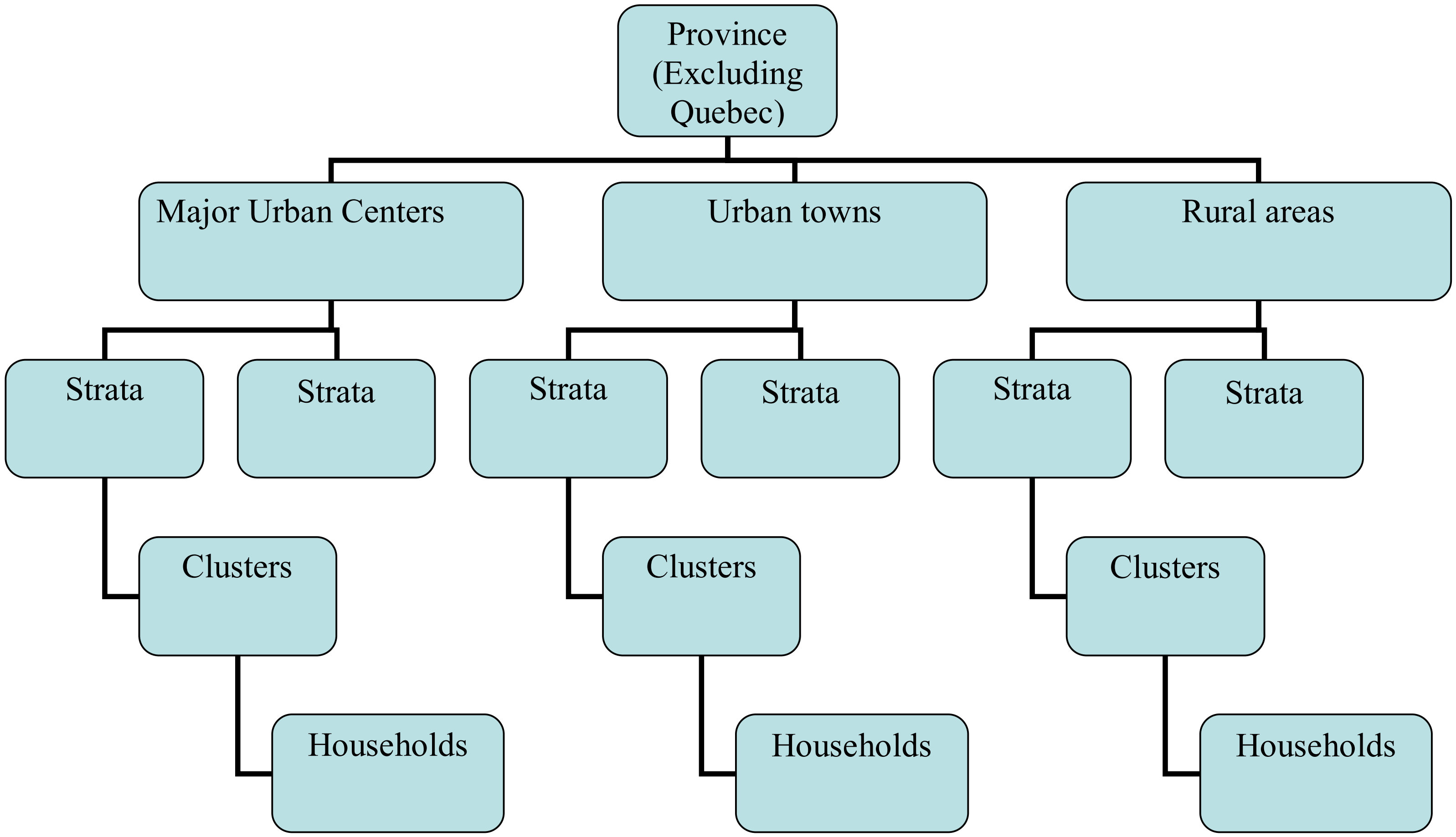


Figure 3.1 Complex Survey Design for Longitudinal Health Survey data

In most strata, independent samples of clusters (heterogeneous) were selected with *probability proportional to size* (PPS) from each stratum. PPS is a sampling technique commonly used in multi-stage cluster sampling, in which the *probability* that a particular sampling unit will be selected in the sample is *proportional* to some known variable (e.g., in a population survey, the population *size* of the sampling unit). PPS is useful when populations of sampling units vary in size and when units *do not* have the same probability of selection (unequal weights). In the second stage, a dwelling list was prepared for each cluster chosen and from this list, households were then selected. Further, the country was divided into 1000 strata and approximately 3000 clusters were formed which are the primary sampling units. Within each cluster, dwellings were selected at random which comprised the secondary sampling units, and finally, one individual was selected from each household producing the tertiary sampling units.

In Quebec, the NPHS samples were selected from dwellings which participated in the 1992-1993 Quebec health survey, *Enquete sociale et de sante* (ESS). The survey sampled 16,010 dwellings using a two-stage sampling design similar to that of the other nine provinces. The province was geographically subdivided by crossing 15 health areas with four urban density classes: Montreal Census Metropolitan Area, regional capitals, small urban agglomerations and the rural sector. Clusters were stratified based on socioeconomic characteristics and selected using PPS sample. Random samples of dwelling were drawn from each cluster. For further details, please refer to longitudinal documentation provided by Population Health Survey Program [176].

3.2.1 Longitudinal sample weights

The principle behind estimation in a NPHS probability sample is that a person in the sample represents, beside himself/herself, several other persons who are not in the sample. The weights are to be included in the study to derive meaningful estimates from the survey. The survey weights used in the longitudinal household component of the NPHS are adjusted such that these weights reflect the probability of selecting the individuals at Cycle1 (represents the population of 1994-95) and not in subsequent cycles. The weights also represent the probability of selection of the unit of analysis at the time of sample selection. In addition, the weights are also adjusted for the non-response and post-stratification features. Post-stratification weights are calculated by further post-stratifying Cycle1 stripped weights to the 1994-1995 population estimates based on 1996 Census counts by age group (0-11, 12-24, 25-44, 45-64, 65 and older) and sex within each province. The post-stratification adjustment is given by (Statistics Canada: Longitudinal NPHS documentation):

$$\frac{\text{Population estimate in a province/age/sex category}}{\text{Sum of ``stripped'' weights of respondent household members in a province/ age/ sex category.}}$$

3.3 Description of National Population Health Survey

The National Population Health Survey (NPHS) is an ongoing longitudinal study of the health of the Canadian population. To date, the household component of NPHS have completed five cycles or data collection periods: NPHS Cycle1 (1994-95), NPHS Cycle 2 (1996-97), NPHS Cycle 3 (1998-99), NPHS Cycle 4 (2000-01) and

NPHS Cycle 5 (2002-03). Only those individuals surveyed in the year 1994-95 were studied in subsequent cycles. Data from the NPHS has been collected every second year and will continue so until 2014. The target population of the household component includes all household residents in all provinces in 1994-95, but does not include those residing on Indian reserves, Crown lands, in health institutions, on Canadian Forced Bases and in some remote areas in Ontario and Quebec. The survey collected data on economic, social, demographic, occupational and environmental correlates of health. The questionnaire included questions related to health status (self perception of health, functional ability, chronic conditions and activity restriction), use of health services, socio-demographic information such as age, sex, education, household income and labour force status.

Initially, 19,600 households were contacted, with a minimum of 1200 households for each province. The final longitudinal sample, also called the "longitudinal panel", was composed of 17,276 individual's ages 0 to 99 years who were selected in Cycle 1 and completed at least the general component of the questionnaire in Cycle1. By Cycle5 all longitudinal respondents were 8 years old and over. The response rate of persons participating in the survey decreased from one cycle to the next and this is mainly due to non-respondents, refusals and individuals who could not be traced. Table 3.1 shows the sample size of longitudinal sample at the start of survey i.e. Cycle 1 (1994-95) and complete response at the end of Cycle 5 (2002-03) A detailed description of the survey can be found elsewhere [176].

Table 3.1 Longitudinal sample size of Cycle1 and Cycle 5 by Province

Province	**Longitudinal Sample Cycle 1 (1994-95)**	**Longitudinal Sample Cycle 5 (2002-03) Complete Response**
Newfoundland	1,082	822
Prince Edward Island	1,037	803
Nova Scotia	1,085	775
New Brunswick	1,125	824
Quebec	3,000	2,189
Ontario	4,307	2,990
Manitoba	1,205	921
Saskatchewan	1,168	922
Alberta	1,544	1,111
British Columbia	1,723	1,189
Total	**17,276**	**12,546**

3.3.1 Study population

The longitudinal panel data were based on 20,095 in-scope persons who had completed at least General Survey component. Of the in-scope persons selected, 17,276 responded to the general component and 16,794 people responded to the health component of the survey. After Cycle 3, the NPHS was purely longitudinal and the general or health component questionnaires were no longer distinguished. The longitudinal panel data consists of 17,276 participants for Cycle 1 and all subsequent Cycles.

The present study is based on female respondents aged 18-64 years in Cycle 1. All those females who were less than 18 years and more than 64 years at the start of Cycle 1 were excluded from the study. Women who were pregnant in Cycle 1 were also excluded from the study. The reason for including only participants aged18 to 64 years in this analysis was based on the evidence that body mass index, which was an important covariate in the study, was calculated only on adults 18 to 64 years of age. Furthermore, pregnant females were also excluded from the study as body mass index is not calculated for these individuals. The final sample size consisted of 5841 female subjects. The flowchart of the final sample size selection is provided in Figure 3.2.

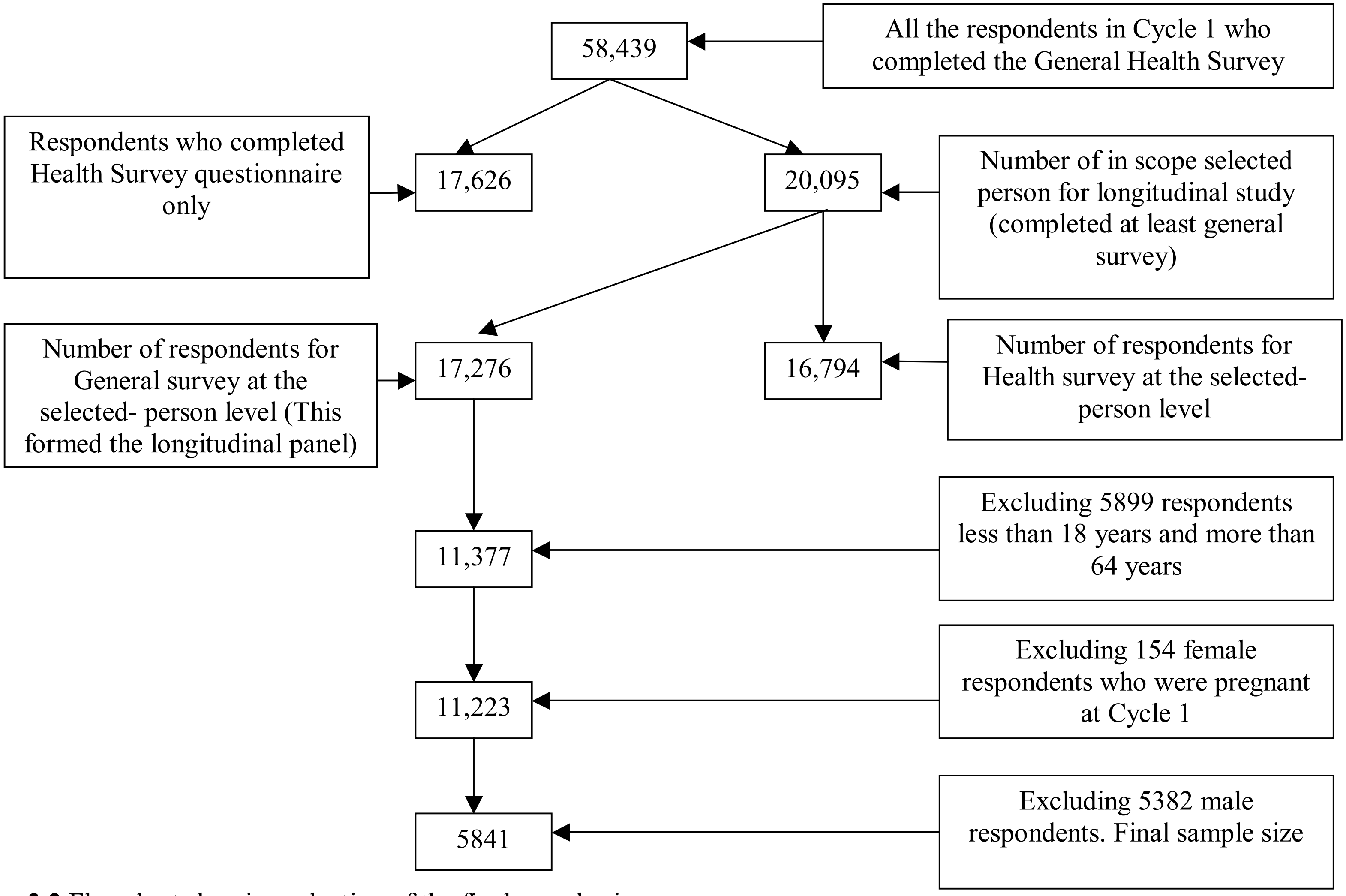

58,439
All the respondents in Cycle 1 who completed the General Health Survey
Respondents who completed Health Survey questionnaire only
17,626
20,095
Number of in scope selected person for longitudinal study (completed at least general survey)
Number of respondents for General survey at the selected- person level (This formed the longitudinal panel)
17,276
16,794
Number of respondents for Health survey at the selected-person level
11,377
Excluding 5899 respondents less than 18 years and more than 64 years
11,223
Excluding 154 female respondents who were pregnant at Cycle 1
5841
Excluding 5382 male respondents. Final sample size

Figure 3.2 Flowchart showing selection of the final sample size

3.3.2 Data collection and non-responses

The survey questions were designed for a computer assisted interview (CAI) [176]. This CAI application was extensively pilot tested to identify errors. Interviewers were part time employees hired and trained specifically to conduct the survey using CAI interviewing techniques. In general, the respondents were contacted by telephone. Proxy reporting was done for respondents under 12 years of age, and 4.8% of the data were collected by proxy interview for respondents over 12 years of age who were medically infirm or who were otherwise incapacitated. Several methods were used by interviewers to trace non-respondents including personal visits and repeated telephone calls. A detailed description of survey methods can be found in Statistics Canada documentation for longitudinal surveys [176].

The response rate for Cycle 1 was calculated using the formula:

$$\frac{\text{(\# of selected persons responding to the survey in 1994-95)}}{\text{all in-scope selected persons}} \quad \text{X } 100$$

The response rate for consecutive cycles was calculated as:

$$\frac{\text{(\# of panel members responding or who have died or been institutionalized)}}{\text{\# of longitudinal panel members (17,276)}} \quad \text{X } 100$$

In this survey, no panel members were classified out of scope, hence any participant who had died, moved or were interviewed in a health institution (Cycle 2 and above) were counted as a response for longitudinal purpose [176]. Table 3.2 summarizes the response rate, refusal rate, attrition rate and cumulative attrition rate of the longitudinal panel for each cycle. Refusals were the most significant source of non-response, and about 49% of the non-response in Cycle 2, 56% in Cycle 3 and 61% in

Cycle 4 and 5 were a result of refusals. The refusal rates provided in Table 3.2 were based on all the 17,276 records, i.e. all the new refusals as well as the refusals that were not sent out. The refusal rate increased over the ten year time period. Attrition rates, calculated between two consecutive Cycles, were mainly due to loss in sample size due to non-respondents or participants moving out of scope (e.g. participants moving out of Canada and untraceable individuals). The fifth column provides the cumulative attrition rate which was obtained by totaling rates of the consecutive cycles. The cumulative attrition rate at the end of Cycle 5 was 27.4%

Table 3.2 Response, refusal, attrition and cumulative attrition rate of 17,276 panel members for each Cycle

Cycle	Response Rate	Refusal Rate	Attrition rate	Cumulative Attrition rate
Cycle 1	86%*	-	-	-
Cycle 2	93.6%	3.1%	9.3%	9.3%
Cycle 3	88.9%	6.2%	6.7%	15.4%
Cycle 4	84.8%	8.9%	7.1%	21.4%
Cycle 5	80.6%	11.3%	7.6%	27.4%

* Cycle 1 response rate are based on 20,095 in-scope persons selected to form the panel

3.4 Study variables

3.4.1 Outcome variable of interest

Asthma was defined from a general questionnaire item that assessed a variety of chronic health conditions that lasted or were expected to last at least 6 months or more and that had been diagnosed by a health professional. The question was asked as “Do you have asthma?” The responses to this question were measured as a dichotomous (yes or no) outcome.

3.4.2 Risk factors of asthma in adult population

Thirteen possible covariates that were expected to be independent risk factors, confounders or effect modifiers for asthma were also examined: food allergies, other kinds of allergies, chronic bronchitis/emphysema, intestinal problems, rural/urban location, region of residence (province), body mass index, ethnicity, immigration status, current smoking status, exposure to second hand smoke, age group, income, and cycle (time).

Similar to the definition of asthma, food allergies, other allergies, emphysema/chronic bronchitis and intestinal problems were defined under chronic health conditions or long term conditions that had lasted or were expected to last six months or more and that had been diagnosed by a health professional. The questions asked in the questionnaire were regarding? "Do you have food allergies (yes/no), other allergies (yes/no) chronic bronchitis or emphysema (yes/no) stomach or intestinal problems (yes/no.)?" Negative responses to these questions were considered as the reference category.

Rural/urban –place of residence: Rural areas were defined as a "population living outside places of 1,000 people or more" [177-179]. Urban areas were continuously built up areas having a population concentration of 1000 or more and a population density of 400 or more per square kilometer [176]. Urban areas included urban core, urban fringe and urban area outside census metropolitan areas (CMA). The place of residence variable was a derived variable and according to the 1998 and 2000 follow-up, the rural location included the participant staying in a rural fringe or rural area outside CMAs. The variable was derived based on a link between the postal code of the respondent’s residence and the January 2003 postal code conversion file (PCCF). All the unmatched postal codes, those with no postal code provided, or where postal codes were not stated were considered missing and coded 9.

Region: The province or region of residence variable represents the participant’s province or region lived in at the time of data collection. This variable was collected separately at each Cycle. All ten provinces were accounted for by this variable. Some of these provinces (based on the sample size of the province) were recoded into regions. Newfoundland and Labrador, Prince Edward Island, Nova Scotia and New Brunswick formed Region 1. Quebec was Region 2; Ontario was Region 3 which was also the reference category. Manitoba, Saskatchewan and Alberta formed Region 4 and British Columbia formed Region 5.

Body Mass Index (BMI): Body mass index (BMI) was calculated as:

$$\left[\frac{\text{Weight in kilograms}}{(\text{Height in centimeters})^2} \right] \text{X } 10{,}000$$

The height and weight of the participants was self-reported. It was not calculated for anyone less than three feet or more than seven feet tall. This classification was meant to align with the World Health Organization’s recommendations[7] which are adopted internationally and was not intended for use with those under 18 years of age, or for pregnant and lactating females.

For the purpose of the present analysis, the baseline BMI was used. BMI was recoded into four categories: underweight (BMI < 18.5), normal weight (reference category-BMI >=18.5 and < 25.0), overweight (BMI >= 25.0 and < 30.0) and obese (BMI >= 30.0 and above). The obese category was obtained after combining obese class

[7] Canadian Guidelines for Body Weight Classification in Adults; www.healthcanada.ca/nutrition

I (BMI >= 30.0 and < 35), II (BMI >= 35.0 and < 40.0) and III (BMI >= 40.0 and above).

Ethnicity: The question on ethnicity was asked to all respondents. The question asked was "How would you best describe your race or colour?-White". Those answering no were classified as others. The ethnicity variable was recoded as Caucasian versus non-Caucasian (reference category). A refusal to answer, a "not stated", or a "do not know" response were coded as missing and not included in the analysis.

Immigration Status: The question of immigration status asked respondents to identify their immigration status only at the time during the first interview, i.e. 1994-95 year (Cycle 1). The response to this particular question was dichotomous (yes/no) and all "not stated" or "do not know" responses were excluded from the analysis. Immigration status was a yes/no category. A positive response to this question included the participants who held immigrant status at the start of Cycle 1 (1994-95). A 'no' response (reference category) included all those panel members who were Canadian citizens by birth. This question was not repeated at any other cycle of participation and the baseline value was used for analysis.

Smoking status: The question to assess smoking status was "At the present time do you smoke cigarettes daily, occasionally or not at all?" Based on this question, the variable had six categories: daily smoker, occasional smoker but former daily smoker, always an occasional smoker, former daily smoker, former occasional smoker, never smoked and not applicable.

Smoking status was recoded further into three categories for analytical purposes. The three categories were current smoker, ex-smoker and non-smoker. The current smoker category was obtained by combining three categories: daily smoker, occasional smoker but former daily smoker and always an occasional smoker. Ex-smokers included former daily smokers and former occasional smokers. Non-smokers (reference category) included those who never smoked. Not applicable and not stated categories were coded as missing.

Exposure to second hand smoke: The question was "Does anyone in the household smoke regularly inside the house?" The response to this question was also dichotomous (yes/no), and the not applicable, refusal and not stated categories were coded as missing. The reference category was a negative response

Age: This was a continuous variable and was asked in every cycle during the time of interview. The study population included 18-64 year old female panel members at baseline (Cycle 1). Age was categorized as the primary interest was in studying and comparing the different subgroups of age. Based on quartiles, the age variable was re-categorized into: 18-29 years, 30-49 years, 50-64 years and 65-72 years (reference category). This approach of categorizing continuous variable is used in practice for preliminary analyses which can result in easily understood summary measures[180].

Socioeconomic status: Income adequacy was used as a measure of socioeconomic status. Four income adequacy groups were formed based on total household income and the number of people living in the household. (Table 3.3 provides detailed description of the categories.)

Table 3.3 Income adequacy level based on the household income and size

Coded value	Description	Income	Household Size
1	Lowest Income	Less than $ 15,000	1 or 2 persons
		Less than $ 20,000	3 or 4 persons
		Less than $ 30,000	5 or more persons
2	Lower Middle Income	$ 15,000 to $ 29,000	1 or 2 persons
		$ 20,000 to $ 39,000	3 or 4 persons
		$ 30,000 to $ 59,000	5 or more persons
3	Upper Middle Income	$ 30,000 to $59,000	1 or 2 persons
		$ 40,000 to $ 79,000	3 or 4 persons
		$ 60,000 to $ 79,000	5 or more persons
4	Highest Income	$ 60,000 or more	1 or 2 persons
		$ 80,000 or more	3 or 4 persons

The derived income adequacy variable was further recoded for analysis purposes into three levels: lowest income (reference category), middle income (lower and upper middle income combined), and highest income.

Time: This variable was created to identify the cycle of participation for each respondent. Based on the five cycles, this variable had five categories: 1994-95 (Cycle 1), 1996-97 (Cycle 2), 1998-99 (Cycle 3), 2000-01 (Cycle 4) and 2002-03 (Cycle 5). Cycle 1 was considered to be the reference category for this variable.

3.5 Data Management

The "longitudinal square" subset of the National Population Health Survey was used in this study. This subset included all panel members, irrespective of their response pattern. Full/complete responses included panel members who provided full responses, were deceased or institutionalized. Institutionalized panel members were those who were interviewed through the NPHS Health Institution Surveys.

The general dissemination of longitudinal NPHS data in public use microdata file (PUMF) format is not allowed, but it can be accessed through Health Statistics Division-Population Health Surveys Remote Data Access services[8]. To obtain access to the remote data, a researcher has to obtain formal approval from the Health Statistics Division. The procedure involves submitting the title of the survey, goals/objective and brief description of the research project. After successful acceptance of the research project by the Health Statistics Division, researchers are provided with dummy data files supplied on a CD-ROM, which mimics the actual master files. Researchers develop and test their own computer program using the dummy data and submit their programs to a dedicated email address. These programs are then run on the master microdata files on an internal secure server. The outputs or the results are vetted for confidentiality reasons and then returned to the researcher via e-mail. Direct on-site access to the NPHS master microdata files is also possible at Statistics Canada's Research Data Centers (RDC). The nearest RDC for researchers at the University of Saskatchewan, Saskatoon, Saskatchewan is at the University of Alberta, Edmonton. Since the University of Saskatchewan did not have the facility of RDC at the time of analysis, the services of the remote data access unit were used.

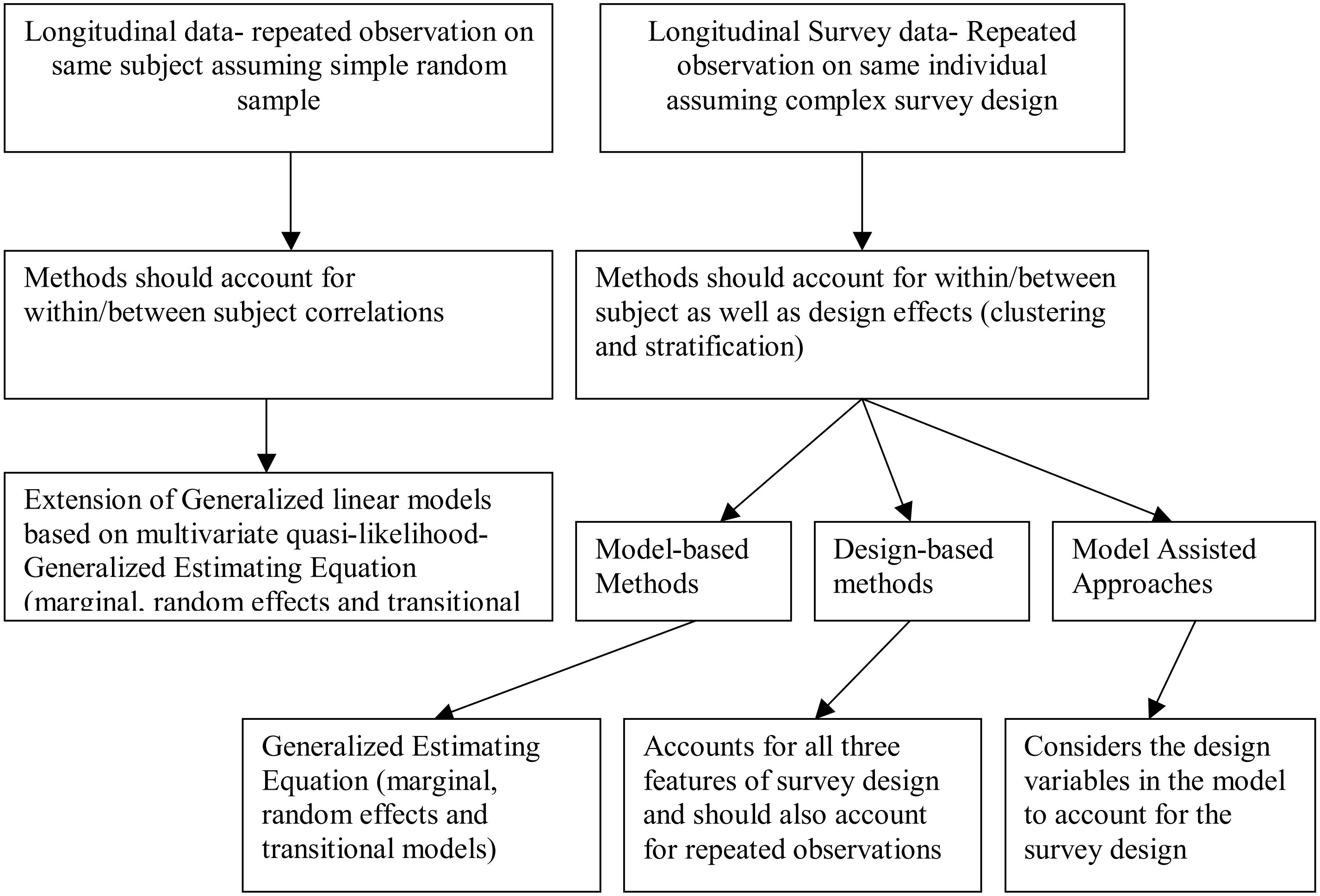
[8] http://www.statcan.ca/english/rdc/index.htm

CHAPTER 4 - METHODS: MODELS FOR DISCRETE LONGITUDINAL SURVEY DATA

4.1 Introduction

In longitudinal survey data, the methods should account for the longitudinal nature, as well as account for the three features of complex survey design: clustering, stratification and unequal probability of selection. For a list of the available statistical methods for longitudinal data and longitudinal survey data, see Figure 4.1.

In this chapter, the statistical methods that account for the longitudinal nature of the data as well as the complexity of survey design will be discussed in detail. Methods for each objective will be discussed separately and in detail. The marginal modeling approach was used for objective 1 in order to determine the risk factors for prevalence of asthma. For objective 2, Cox's proportional hazard model and the discrete proportional hazard model were used to determine the risk factors for the incidence of asthma. The variance corrected and frailty model approaches were used for objective 3. Finally, for objective 4, the missing data approach was used to analyze the data.



Longitudinal data- repeated observation on same subject assuming simple random sample
Methods should account for within/between subject correlations
Extension of Generalized linear models based on multivariate quasi-likelihood- Generalized Estimating Equation (marginal. random effects and transitional
Longitudinal Survey data- Repeated observation on same individual assuming complex survey design
Methods should account for within/between subject as well as design effects (clustering and stratification)
Model-based Methods
Design-based methods
Model Assisted Approaches
Generalized Estimating Equation (marginal, random effects and transitional models)
Accounts for all three features of survey design and should also account for repeated observations
Considers the design variables in the model to account for the survey design

Figure 4.1 Statistical methods available for longitudinal data assuming simple random sampling and complex survey sampling

4.2 Objective 1: Marginal modeling approach

The primary focus of the first objective was to compute the crude and adjusted prevalence rates for asthma, using the longitudinal NPHS data set. In section 4.2.1, the methods used to calculate the crude prevalence rate using model-based and design-based approach will be discussed. To estimate the adjusted prevalence rate, marginal modeling approach was used. The model-based and design-based variance estimates of regression coefficients were compared. The model-based analysis based on the GEE approach is discussed in section 4.2.2. The design-based approach for variance estimation proposed by Rao [3] is discussed in section 4.2.3. The notations of the matrices and vectors, to understand the mathematical theory in the following sections, are given in appendix A.

4.2.1 Crude prevalence estimation

Prevalence proportion is defined as "the proportion of people in a population that has disease" [181]. Prevalence proportion in equation form can be written as:

$$\frac{\text{(P individuals in the population those who have disease at a given time)}}{\text{(Population of size N)}}$$

The prevalence proportion calculated for complex survey design should take into account the weight variable. The weight variable accounts for the unequal probability of selection. However, survey weight which is calculated specially for the longitudinal survey data by methodologists at Statistics Canada is not enough to calculate the standard error or 95% confidence interval. If the clustering and stratification along with the weight variable is not taken into account to estimate the variance, it can result in biased or false standard errors.

To calculate the standard error and the 95% confidence interval, two most commonly used methods are the bootstrap method and the Taylor linearization method. These two methods take into account the complexity of survey design to provide correct estimates of standard errors and hence 95% confidence interval. In the following section, the Rao-Wu Bootstrap and Taylor linearization methods are explained in detail.

4.2.1.1 Rao and Wu Bootstrap Method for variance estimation of crude prevalence

Resampling methods for independent and identically distributed (i.i.d.) data of fixed sample size n have been studied by Efron [182]. Rao and Wu [2] extended the i.i.d. bootstrap to multi-stage sampling designs to calculate nonlinear statistics. Later, the Rao and Wu [2] resampling method was modified by Rao, Wu and Yue [183] to include the non-smooth statistics, and this method was implemented in the NPHS to calculate the nonlinear statistics and their standard errors [183, 184]. Consider the L design strata, h^{th} stratum with N_h clusters and $n_h \geq 2$ sampled clusters with $h = 1,\dots\dots,L$ *and* $i = 1,\dots\dots,n_h$. An estimator of the total Y, is obtained using y_{hik} and design weights, w_{hik}, associated with k^{th} sample element in i^{th} cluster of stratum h by [183, 184],

$$\hat{\mathbf{Y}} = \sum_{\mathbf{(hik)}\in\mathbf{S}} \mathbf{w}_{hik}\, \mathbf{y}_{hik}$$

The variance is calculated as follows [184]:

(1) The bootstrap weights are independently calculated by first selecting a simple random sample with replacement of n_h-1 clusters from n_h sampled clusters for each stratum.

$$\mathbf{w}^{*}_{\mathbf{hik}} = \frac{\mathbf{n_h}}{\mathbf{n_h} - \mathbf{1}} \mathbf{m}^{*}_{hi} \mathbf{w}_{hik} \tag{4.2.1}$$

$\mathbf{m}^{*}_{hi}$ is defined as number of times $(hi)^{\text{th}}$ cluster is selected and $\sum_{\mathbf{i}} \mathbf{m}^{*}_{\mathbf{hi}} = \mathbf{n_h} - \mathbf{1}$

(2) The bootstrap weights obtained are post stratified in the same way as the survey weights to get the final weights. The estimates $\hat{\theta}^{*}$ are obtained by replacing the survey weights with the final bootstrap weights.

(3) Steps 1 and 2 are replicated B (e.g., 500) times to calculate the estimates,

$\hat{\theta}^{*}_{(1)}, \ldots\ldots \hat{\theta}^{*}_{(500)}$

(4) Finally the bootstrap variance estimator for $\hat{\theta}$ is calculated as:

$$v_{\mathbf{B}}\left(\hat{\boldsymbol{\theta}}\right) = \frac{1}{B} \sum_{\mathbf{b}} \left(\hat{\boldsymbol{\theta}}^{*}_{\mathbf{(b)}} - \hat{\boldsymbol{\theta}}^{*}_{\mathbf{(.)}} \right)^{2}, \text{ where } \hat{\boldsymbol{\theta}}^{*}_{\mathbf{(.)}} = \frac{1}{B} \sum_{\mathbf{b}} \hat{\boldsymbol{\theta}}^{*}_{\mathbf{(b)}}. \tag{4.2.2}$$

4.2.1.2 Taylor Linearization Method

This methodology is used to obtain an approximation of some nonlinear function through a linear or higher-order polynomial function. In the literature, the linear version of this method is also referred to as linearization, delta method and propagation of variance method [107]. For complex surveys, the Taylor approximation is applied to the Primary Sampling Units (PSU) totals within that particular stratum. The variance estimate is formed as a weighted combination of

$$\mathbf{V}(\theta) \dot{=} \mathbf{V}\left[\sum w_i \sum \left({\partial f}/{\partial y_j} \right) y_{ij} \right], \tag{4.2.3}$$

across the PSUs within the same stratum. Here $\theta = f(x_1, x_2, \ldots\ldots, x_c)$, where x_i are *c* random variables in a sample of n observations, w_i is the weight for observation *i*, *i=1,……,n* (sample observations) and *j=1,……,c* (random variables). The above formula was suggested by Woodruff [185]. While this formula seems complex, it does have some advantages, no covariance calculation is needed and it is efficient in terms of computation time compared to replication based methods such as balanced repeated replication and jackknife replication [107]. Jackknife replication method can only be used to obtain the variance estimate for mean, the regression coefficients and, for example, cannot be used for median and other percentiles [107].

4.2.2 Adjusted prevalence rates using marginal modeling approach

Marginal models based on the GEE approach to analyze longitudinal complex survey data are known as model-based. These model-based models accounts only for within-subject correlations arising due to repeated measurements per subject. To account for the design effects, such as stratification and clustering, a replicate approach for the variance estimation is needed. Design-based models which accounts for design effects are explained in section 4.2.2.1

4.2.2.1 GEE for binary data[9]

Consider $Y_{ij,}$ a dichotomous outcome variable which assumes the logit model for the first order marginal probabilities

$$logit\ [Pr(Y_{it}=1)] = logit\ \mu_{it} = \log(\frac{\mu_{it}}{1-\mu_{it}}) = \boldsymbol{\beta}_s^T \mathbf{x}_{is} + \boldsymbol{\beta}_t^T \mathbf{x}_{it}, \tag{4.2.4}$$

$t = 1,\ldots\ldots, T$(occasions) and i= $1,\ldots\ldots,m$ (individuals), β_s^T is a vector of stationary covariates, and $\boldsymbol{\beta}_t^T$ is a vector of time varying covariates

$\mu_{it} = \dfrac{\exp\{\boldsymbol{\beta}'_s \mathbf{x}_{is} + \boldsymbol{\beta}'_t \mathbf{x}_{it})}{1+\exp\{\boldsymbol{\beta}'_s \mathbf{x}_{is} + \boldsymbol{\beta}'_t \mathbf{x}_{it}\}}$, where $\mathbf{x_{is}}$ = design-matrix of time stationary covariates and

$\mathbf{x_{it}}$ = design-matrix of time varying covariates

A set of score equations for a marginal normal model is given by

$$\mathbf{U}(\boldsymbol{\beta}) = \sum_{\mathbf{i=1}}^{\mathbf{N}} \mathbf{D_i^T} (\mathbf{A}_i^{1\backslash 2} \Re_{\mathbf{i}}(\alpha) \mathbf{A}_i^{1\backslash 2})^{-\mathbf{1}} (y_i - \mu_i) = \mathbf{0}, \tag{4.2.5}$$

where $\mathbf{D}_{\mathrm{i}} = {\partial \boldsymbol{\mu}_{\mathrm{i}}} \big/ {\partial \boldsymbol{\beta}^T}$ and μ_i is the mean function, and $\mathbf{V_i}$ is a working covariance matrix of outcome variable $\mathbf{Y_i}$=$(Y_{i1,\ldots\ldots,} Y_{ij})^T$ a $t\ x\ 1$ vector of $i=1,\ldots\ldots,m$ individuals observed at T occasions, $\mathbf{X_i} = (X_{i1},\ldots\ldots,X_{ij})^T$ is $t\ X\ P$ matrix of covariates for individual i. In equation 4.2.5 the working covariance structure, $\mathbf{V_i}$ is written in a decomposed form: $\mathbf{V_i} = \mathbf{A_i^{1\backslash 2}} \Re_{\mathbf{i}}(\alpha) \mathbf{A_i^{1\backslash 2}}$, where $\mathbf{A_i}$=*diag [var(Y$_{i1}$),……..,var(Y$_{ij}$)]*, and $\Re_{\mathbf{i}}(\boldsymbol{\alpha})$=*corr (Y$_i$)* is a $T\ X\ T$ "working" correlation matrix and α is a vector of parameters which are usually associated with a specified model for *corr(Y$_i$)* [186]. The above equations

[9] This section is developed from Internal report, January 2006, Statistics Canada and personal communication with Susana Rubin Bluer of Statistics Canada

reduce to independent equations if $\Re_i(\alpha)$ is the identity matrix. $\boldsymbol{R}(\boldsymbol{\alpha})$ is usually estimated by a method of moments; all the elements, including the diagonal elements are estimated by $\hat{\mathbf{R}}(\boldsymbol{\alpha}) = (\hat{\rho}_{tu})_{tu}$ are

$$\hat{\rho}_{tu} = \frac{1}{M}\sum_i \frac{(Y_{it} - \mu_{it})(Y_{iu} - \mu_{iu})}{\sqrt{\mu_{it} - \mu_{it}^2}\sqrt{\mu_{iu} - \mu_{iu}^2}}, \quad t, u = 1,2,3,4,5. \tag{4.2.6}$$

The GEE estimator $\hat{\beta}_{GEE}$ is the solution of the set of score equations 4.2.9. The solution of the census GEE is obtained by iteration:

$$\boldsymbol{\beta}^{(k)} = \boldsymbol{\beta}^{(k-1)} - \left(\frac{\partial \mathbf{U}_{GEE}}{\partial \boldsymbol{\beta}}\right)^{-1} (\boldsymbol{\beta}^{(k-1)}) \cdot \mathbf{U}_{GEE}(\boldsymbol{\beta}^{(k-1)}) = \boldsymbol{\beta}^{(k-1)} + \left(\sum_{i=1}^{M} \mathbf{D}_i' \mathbf{V}_i^{-1} \mathbf{D}_i\right)^{-1} \sum_{i=1}^{M} \mathbf{D}_i' \mathbf{V}_i^{-1} (Y_i - \mu_i) \tag{4.2.7}$$

Note that in the equation 4.2.5, $\left(\frac{\partial \mathbf{U}_{\mathbf{GEE}}}{\partial \boldsymbol{\beta}}\right)$ is replaced by its expected value

$\sum_{\mathbf{i=1}}^{\mathbf{M}} \mathbf{D_i' V_i^{-1}}\ \mathbf{D_i}$, where $\mathbf{V_i^{-1}} = \mathbf{A_i^{-1/2} R^{-1} A_i^{-1/2}}$.

and all matrices above are calculated at $\boldsymbol{\beta}'^{(k-1)} = \left(\boldsymbol{\beta}_S'^{(k-1)}, \boldsymbol{\beta}_1'^{(k-1)}, \ldots, \boldsymbol{\beta}_T'^{(k-1)}\right)$:

$$\mathbf{D_i'} = \begin{pmatrix} \mathbf{x}_{is}\boldsymbol{\mu}_{i1}(\mathbf{1}-\boldsymbol{\mu}_{i1}) & \mathbf{x}_{is}\boldsymbol{\mu}_{i2}(\mathbf{1}-\boldsymbol{\mu}_{i2}) & \mathbf{x}_{is}\boldsymbol{\mu}_{i3}(\mathbf{1}-\boldsymbol{\mu}_{i3}) & \mathbf{x}_{is}\boldsymbol{\mu}_{i4}(\mathbf{1}-\boldsymbol{\mu}_{i4}) \\ \mathbf{x}_{i1}\boldsymbol{\mu}_{i1}(\mathbf{1}-\boldsymbol{\mu}_{i1}) & \mathbf{0} & \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \mathbf{x}_{i2}\boldsymbol{\mu}_{i2}(\mathbf{1}-\boldsymbol{\mu}_{i2}) & \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \mathbf{x}_{i3}\boldsymbol{\mu}_{i3}(\mathbf{1}-\boldsymbol{\mu}_{i3}) & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \mathbf{0} & \mathbf{x}_{i4}\boldsymbol{\mu}_{i4}(\mathbf{1}-\boldsymbol{\mu}_{i4}) \end{pmatrix}$$ where all the means are

calculated by

$$\mu_{it}(\boldsymbol{\beta}^{(k-1)}) = \frac{\exp\left\{\boldsymbol{\beta}_s'^{(k-1)}\mathbf{x}_{is} + \boldsymbol{\beta}_t'^{(k-1)}\mathbf{x}_{it}\right\}}{1 + \exp\left\{\boldsymbol{\beta}_s'^{(k-1)}\mathbf{x}_{is} + \boldsymbol{\beta}_t'^{(k-1)}\mathbf{x}_{it}\right\}} \tag{4.2.8}$$

Similarly, the matrix

$$\mathbf{A}_{\mathbf{i}}^{\mathbf{-1/2}} = Diag\left(\frac{1}{\sqrt{\mu_{i1} - \mu_{i1}^2}}, \ldots, \frac{1}{\sqrt{\mu_{i5} - \mu_{i5}^2}} \right) \text{with } \boldsymbol{\mu}_{\mathbf{it}} = \mu_{it}(\boldsymbol{\beta}^{(k-1)}),\ \ t = 1,2,3,4,5. \qquad (T = 5),$$

and the estimated correlation matrix $\hat{\mathbf{R}} = (\hat{\rho}_{tu})_{tu}$ with

$$\hat{\boldsymbol{\rho}}_{\mathbf{tu}}(\boldsymbol{\beta}^{(\mathbf{k-1})}) = \frac{1}{M} \sum_i \frac{(Y_{it} - \mu_{it}(\boldsymbol{\beta}^{(k-1)}))(Y_{iu} - \mu_{iu}(\boldsymbol{\beta}^{(k-1)}))}{\sqrt{\mu_{it}(\boldsymbol{\beta}^{(k-1)}) - \mu_{it}^2(\boldsymbol{\beta}^{(k-1)})}\sqrt{\mu_{iu}(\boldsymbol{\beta}^{(k-1)}) - \mu_{iu}^2(\boldsymbol{\beta}^{(k-1)})}},\ t \neq u. \qquad (4.2.9)$$

The variance of $\hat{\beta}_{GEE}$ is consistently estimated by

$$\left(\sum_{\mathbf{i=1}}^{\mathbf{M}} \mathbf{D}_{\mathbf{i}}' \mathbf{V}_{\mathbf{i}}^{-1} \mathbf{D}_{\mathbf{i}} \right)^{-1} \left(\sum_{\mathbf{i=1}}^{\mathbf{M}} \mathbf{D}_{\mathbf{i}}' (Y_i - \mu_i)(Y_i - \mu_i)' \mathbf{D}_{\mathbf{i}} \right) \left(\sum_{\mathbf{i=1}}^{\mathbf{M}} \mathbf{D}_{\mathbf{i}}' \mathbf{V}_{\mathbf{i}}^{-1} \mathbf{D}_{\mathbf{i}} \right)^{-1}. \qquad (4.2.10)$$

The GEE accounts for within-subject correlation, which results in consistent estimates. Efficiency increases when the assumed correlation structure is closer to the true correlation structure. The main inference is on the model-based coefficients, while the intra-cluster dependence is merely a nuisance characteristic, merely accounted for, but not subject to modeling in the classical sense. GEE method can be used for Gaussian and non-Gaussian outcomes alike [37]. The GEE method provides consistent estimates of regression coefficients even under minimal assumption about the time dependence [37].

4.2.2.2 Survey GEE accounting for the design effects[10]

Consider a longitudinal study with *T* occasions of measurements and the finite longitudinal population of size *M* are clustered into *N* primary sampling units, also known as primary sampling units (psu). The subscript *i* in equation 4.2.4 is changed to

[10] Refer to Appendix C.1 for SAS macro

hik in survey data, where *h* is the strata, *i* is the cluster in h^{th} strata, and *k* is the subject in i^{th} cluster and h^{th} strata. For each stratum *h*, N_n and M_{hi} are, respectively, the number of clusters in stratum h and the number of secondary units in the cluster *hi*, *i = 1,……..,* N_n and *h = 1,……..,L*

Assume the same logit model for the first order marginal probabilities as in eq 4.2.4

The Survey independent estimating equations (IEE) estimators are [3]

$$\hat{\mathbf{U}}_{\mathbf{IEE}}(\boldsymbol{\beta}) = \sum_{hik\in S_l} \omega_{hik}\mathbf{D}'_{hik}\mathbf{V}^{-1}_{hik}(y_{hik}-\mu_{hik}) = 0 \qquad (4.2.11)$$

S_l represents the longitudinal sample and ω_{hik} represents the longitudinal weight.

To calculate the survey IEE estimator $\hat{\beta}_{IEE}$, we do the iteration

$$\hat{\boldsymbol{\beta}}_{\mathbf{IEE}}(K) = \hat{\boldsymbol{\beta}}_{IEE}(K-1) - \left(\frac{\partial \hat{\mathbf{U}}_{IEE}}{\partial \boldsymbol{\beta}}\right)^{-1}\left(\hat{\boldsymbol{\beta}}_{IEE}(K-1)\right).\hat{\mathbf{U}}_{IEE}\left(\hat{\boldsymbol{\beta}}_{IEE}(K-1)\right) \qquad (4.2.12)$$

Where $\hat{U}_{IEE}$ is the survey estimate of the independent estimating equation defined above and $\left(\frac{\partial \hat{\mathbf{U}}_{IEE}}{\partial \boldsymbol{\beta}}\right)$ is replaced by its expectation: $\left(\frac{\partial \hat{\mathbf{U}}_{\mathbf{IEE}}}{\partial \boldsymbol{\beta}}\right) \approx \sum_{hik\in S_l} \omega_{hik}\mathbf{D}'_{hik}\mathbf{A}^{-1}_{hik}\mathbf{D}_{hik}$

Where $\mathbf{A}^{-1}_{hik} = Diag\left(\frac{1}{\mu_{hik1}-\mu^2_{hik1}},\ldots\ldots..,\frac{1}{\mu_{hik4}-\mu^2_{hik4}}\right)$

The Survey Generalized Estimating Equation (GEE) estimator proposed by Rao (1998) is of the form:

$$\hat{\mathbf{U}}_{GEE}(\beta) = \sum_{hik\in S_l} \omega_{hik}\mathbf{D}^{`}_{hik}(\beta)\boldsymbol{\Delta}^{-1/2}_{hik}(\beta)\hat{\mathbf{R}}^{-1}\boldsymbol{\Delta}^{-1/2}_{hik}(\beta)(y_{hik}-\mu_{hik}(\beta)) = 0 \qquad (4.2.13)$$

Where the matrix of "correlation" $\hat{R}$ now has the form $\hat{R} = (r_{tu})_{tu}$: with

$$\mathbf{r}_{tu} = \sum_{hik \in S_l} \omega_{hik} \frac{\left(y_{hikt} - \mu_{hikt}\left(\overset{\wedge}{\boldsymbol{\beta}}_{IEE}\right)\right)\left(y_{hiku} - \mu_{hiku}\left(\overset{\wedge}{\boldsymbol{\beta}}_{IEE}\right)\right)}{\sqrt{\mu_{it}\left(\overset{\wedge}{\boldsymbol{\beta}}_{IEE}\right) - \mu_{it}^2\left(\overset{\wedge}{\boldsymbol{\beta}}_{IEE}\right)}\sqrt{\mu_{iu}\left(\overset{\wedge}{\boldsymbol{\beta}}_{IEE}\right) - \mu_{iu}^2\left(\overset{\wedge}{\boldsymbol{\beta}}_{IEE}\right)}}$$

where $\sum_{hik \in S_l} \omega_{hik}$, t and u = 1, ……..,5

The estimator $\overset{\wedge}{\boldsymbol{\beta}}_{GEE}$ is defined as the solution of the survey GEE (4.2.13).

$\overset{\wedge}{\boldsymbol{\beta}}_{GEE}$ is calculated through iteration, where the $\overset{\wedge}{\boldsymbol{\beta}}_{GEE}$ (K-1) change at each iterations, but $\overset{\wedge}{\mathbf{R}} = (r_{tu})_{tu}$ is fixed throughout the iterations to calculate $\overset{\wedge}{\beta}_{GEE}$

The variance matrix of $\overset{\wedge}{\beta}_{GEE}$ can be consistently estimated by

$$\mathbf{v}\left(\overset{\wedge}{\beta}_{GEE}\right) = \overset{\wedge}{\mathbf{J}}_G^{-1}\left(\overset{\wedge}{\boldsymbol{\beta}}_{GEE}\right).v\left(\overset{\wedge}{\mathbf{U}}_{GEE}\right).\overset{\wedge}{\mathbf{J}}_G^{-1}\left(\overset{\wedge}{\boldsymbol{\beta}}_{GEE}\right) \tag{4.2.14}$$

evaluated at $\beta = \overset{\wedge}{\beta}_{GEE}$ with

$$\overset{\wedge}{\mathbf{J}}_{\mathbf{G}}(\beta) = -\sum_{hik \in S_l} \omega_{hik} \mathbf{D}'_{hik}(\beta)\mathbf{A}_{hik}^{-1}(\beta)\mathbf{D}_{hik}(\beta) \text{ and } v\left(\hat{U}_{GEE}\right), \tag{4.2.15}$$

evaluated at $\beta = \overset{\wedge}{\beta}_{GEE}$, is the survey design variances of a survey total and can be estimated by bootstrap, calculating for each one of the 500 sets of bootstrap weights estimated.

$$\overset{\wedge}{\mathbf{U}}_{GEE}(b)\left(\overset{\wedge}{\beta}_{GEE}\right) = \sum_{hik \in S_l} \omega_{hik}(b)\mathbf{D}'_{hik}\boldsymbol{\Delta}_{hik}^{-1/2}\overset{\wedge}{\mathbf{R}}^{-1}\boldsymbol{\Delta}_{hik}^{-1/2}(y_{hik} - \mu_{hik}) \tag{4.2.16}$$

b= 1,.., 500

And then calculate:

$$\mathbf{v}\left(\sqrt{n}\,\hat{\mathbf{U}}_{GEE}\right) = n\frac{1}{500}\sum_{b=1}^{500}\left(\hat{\mathbf{U}}_{GEE}^{(b)} - \overline{\hat{\mathbf{U}}}_{GEE}^{(b)}\right)\left(\hat{\mathbf{U}}_{GEE}^{(b)} - \overline{\hat{\mathbf{U}}}_{GEE}^{(b)}\right)'$$

For inference, we estimate the variance of $\sqrt{n}(\hat{\boldsymbol{\beta}}_{GEE} - \beta_{GEE})$, which is $nv\left(\hat{\beta}_{GEE}\right)$.

4.2.3 Statistical application: Objective 1

4.2.3.1 Crude prevalence of asthma

The crude prevalence proportion of asthma was calculated using model-based and design-based approaches. SAS procedure GENMOD was used for the model-based method. SAS (available on version 9 onwards) procedure SURVEY LOGISTIC and BOOTVAR macro was used for the design-based method. SURVEY LOGISTIC procedure fits linear logistic regression models for discrete survey data by the method of maximum likelihood. This procedure incorporates complex survey design. The variances of the regression estimates and odds ratios are computed using Taylor expansion approximation [109]. BOOTVAR macro was developed by the methodologists at Statistics Canada, was used as another design-based method. This macro is based on Rao-Wu's [2, 187] bootstrap method to calculate the parameter estimates and standard errors.

4.2.3.2 Adjusted prevalence of asthma using marginal modeling approach

The adjusted prevalence of asthma was computed by utilizing a logistic regression model adjusted for important covariates. The adjusted model was fitted using SAS procedure GENMOD for the model-based approach. Two macros in SAS language were written in order to compute the variance estimates. The first SAS macro based on the marginal modeling approach proposed by Rao [3] was written to account for the complex survey design[11]. The second SAS macro was an extension of the BOOTVAR macro developed by methodologist at Statistics Canada. The extension of the BOOTVAR macro used the GEE approach to account for the longitudinal nature of the data, as well as the complex survey design. BOOTVAR macro was modified by Prof. Lam [188] at Queen's University, Canada, to account for the complexities of the survey design and the longitudinal nature of survey data.

Standard model building strategies were used to choose the final model, and also to check for potential outliers. Wald statistics was used to assess the model assumptions and model fit. The design variables were also included in the final model even if these variables were not significant at univariate level.

The SAS procedure GENMOD and the two SAS macros used to fit the marginal model assumed four different correlation structures: independent, exchangeable, Auto regressive (first order) and unstructured. The independent correlation structure assumes that the repeated observations are not correlated. The exchangeable correlation matrix assumes all the off diagonal elements of the covariance matrix are the same, i.e., the correlation between any two repeated observations are the same. The unstructured

[11] Refer to Appendix c.2 for SAS macro

correlation matrix assumes that the off diagonal elements of the covariance matrix are to be estimated. Finally, the auto regressive correlation matrix based on equally spaced observations assumes that the correlation decreases over time. A detailed description of the correlation structures can be found else where [189].

The methods used to obtain crude and adjusted prevalence rate of asthma is summarized in Figure 4.2

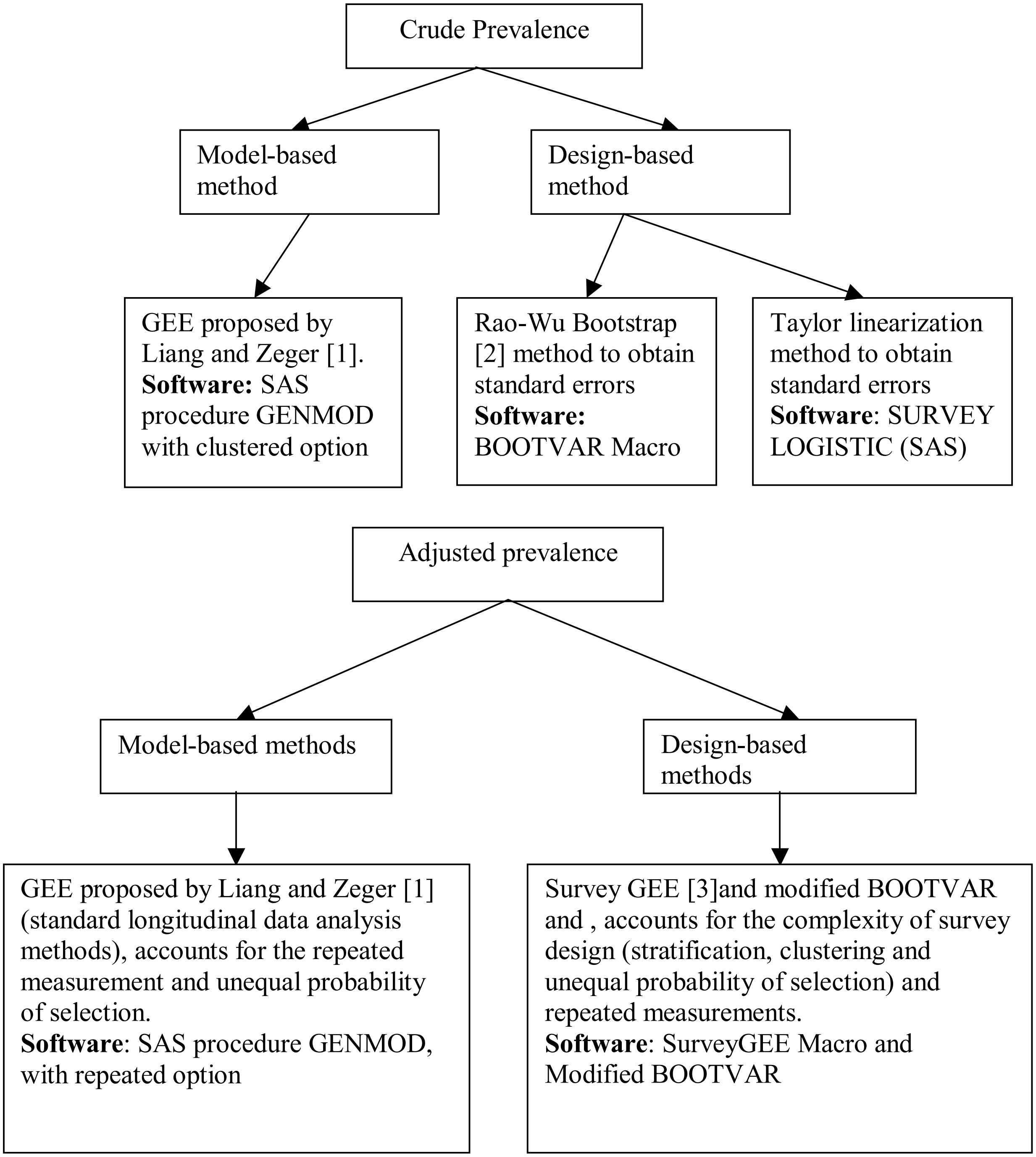

Crude Prevalence
Model-based method
Design-based method
GEE proposed by Liang and Zeger [1]. **Software:** SAS procedure GENMOD with clustered option
Rao-Wu Bootstrap [2] method to obtain standard errors **Software:** BOOTVAR Macro
Taylor linearization method to obtain standard errors **Software**: SURVEY LOGISTIC (SAS)
Adjusted prevalence
Model-based methods
Design-based methods
GEE proposed by Liang and Zeger [1] (standard longitudinal data analysis methods), accounts for the repeated measurement and unequal probability of selection. **Software**: SAS procedure GENMOD, with repeated option
Survey GEE [3]and modified BOOTVAR and , accounts for the complexity of survey design (stratification, clustering and unequal probability of selection) and repeated measurements. **Software**: SurveyGEE Macro and Modified BOOTVAR

Figure 4.2 Methods used to obtain prevalence of asthma

4.3 Objective 2: proportional hazard model

To determine the adjusted incidence rates of asthma in the female Canadian population, the proportional hazard model was used. The crude incidence rate was calculated using incidence density and the cumulative incidence formula (see section 4.3.1). To examine the effect of risk factors (or covariates) on incidences of asthma, see the discrete proportional hazard model discussed in section 4.3.2 and Cox's proportional hazard model discussed in section 4.3.3.

4.3.1 Crude incidence analysis

Incidence is defined as "the number of new events of a specific disease during a specified period of time in a specified population" [190]. In the present analysis, two different methods were used to calculate the incidence rate. The incidence rate is defined as "the rate at which new events, or new cases, occur in a specified time in a defined population that is at risk of experiencing the condition or event" [190].

$$\text{Incidence rate} = \frac{\text{(Number of new events in a specified period)}}{\text{(Number of people exposed to risk in this period)}} \tag{4.3.1}$$

The methods explained below are for cumulative incidence and incidence density. The basic difference between incidence and cumulative density is that the first one tells how likely an event is to happen at any moment in time, whereas the second one provides the rate for a defined population and for a specified period of time. If the time period is short, then both the density rates are same. Usually for determining the incidence of a population incidence, density rate is preferred over the cumulative density rates for the reason stated above.

Cumulative Incidence is defined as “the number of people who become infected during a specific period of time as a proportion of a specific population at risk of the disease” [190].

$$\text{Cumulative Incidence} = \frac{\text{(Number of new cases during a given period of time)}}{\text{(Population at risk)}} \qquad (4.3.2)$$

Incidence density is a more precise estimate of the rate of occurrence of a particular disease, as it accounts for the varying time periods of follow up [190].

$$\text{Incidence density} = \frac{\text{(Number of new cases during a given period)}}{\text{(Total person-time of observation)}} \qquad (4.3.3)$$

The numerator of the cumulative incidence and the incidence density are the same: the difference is only in the denominator. The denominator for the cumulative incidence is the population at risk where as for incidence density is the sum of each individual’s time at risk or the sum of the time that each person remained under observation and free from disease [190].

4.3.2 Cox’s proportional hazard model

Cox [45] introduced a large family of models which focused directly on the hazard function. Proportional hazard model is the simplest member of the family, where the hazard at time for an individual with covariates X_i is assumed to be

$$\lambda_i(t \mid \mathbf{X}_i) = \lambda_0(t)\exp\{\mathbf{X}_i^T \beta\} \qquad (4.3.4)$$

where $\lambda_0(t)$ is the baseline hazard function that describes the risk for individual with

$X_i = 0$; $\exp\{\mathbf{X}_i^T \beta\}$ is the relative risk, a proportionate increase or reduction in the risk associated with the set of characteristics ***Xi***

$\lambda_i(t \mid \mathbf{X}_i) = \lambda_0(t)$ if $X_i = 0$ (risk at time t in group zero)

$= \lambda_0(t)\exp\{\beta\}$ if $X_i = 1$

$r = \exp\{\beta\}$ represents the ratio of the risk on group one relative to group zero at any time t

Taking log on both sides of equation 4.3.1 we get,

$$\log \lambda_i(t \mid \mathbf{X}_i) = \log\left[\lambda_0(t)\exp\{\mathbf{X}_i^T \beta\}\right]$$

$$= \log(\lambda_0(t)) + \mathbf{X}_i^T \beta$$

$$= \alpha_0(t) + X_i^T \beta \qquad (4.3.5)$$

where $\alpha_0(t) = \log(\lambda_0(t))$ is the log of the baseline hazard.

If we integrate equation 4.3.5 from *0 to t*, we get cumulative hazards

$$\int_o^t \log \lambda_i(t \mid \mathbf{X}_i) = \int_0^t \alpha_0(t) + \int_0^t \mathbf{X}_i^T \beta$$

$\Lambda_i(t \mid \mathbf{X}_i) = \Lambda_0(t)\exp\{\mathbf{X}_i^T \beta\}$ are the cumulative hazards.

The time varying covariates and time dependent effects may be combined to give the most general version of the hazard rate model as,

$$\lambda_i(t \mid \mathbf{X}_i(t)) = \lambda_0(t)\exp\{\mathbf{X}_i^T(t)\boldsymbol{\beta}(t)\}$$

Where $\mathbf{X}_i(t)$ is a vector of time varying covariates representing the characteristics of individual *i* at time *t* and **β(t)** is a vector of time dependent coefficients.

4.3.3 Discrete proportional hazard model

In survival analysis, the outcome measure is time to an event. In the NPHS dataset, the exact time to event occurrence is not reported, and only the time interval is known, hence such kind of data are called 'interval censored data' and such phenomenon is called 'interval censoring'.

Let p_i = probability that an individual is diagnosed with asthma in their interval of observation. Then $p_i = \Pr\{R_i \in (t_i^0, t_i^f) | R_i \geq t_i^0\}$

Where R_i is the time to failure for ith individual, a non-negative random variable

t_i^0 is the inception time, or the start time (in our case it is the start of the Cycle 2)

t_i^f is the final time (in our case end of Cycle 5)

The hazard rate *(λ_i)* is defined as the rate of failing at time *t* given survival until that time. If we assume that the incidence process fits a proportional hazards model, then the hazard rate for subject *i* depend on subject factors X_i in a log-linear fashion, independent of time $t_{i.}$

$$\log\lambda_i(t) = \log\lambda_0(t) + \mathbf{X}_i^T\beta \qquad (4.3.6)$$

where $\lambda_0(t)$ is baseline hazard rate (for those individuals with $X_i = 0$)

The discrete hazard or probability λ_{ij} (that an individual *i* will die in the interval *j* given that the individual was alive at the start of the interval) can be written as:

$$\lambda_{ij} = 1 - \Pr\{R_i \in (t_i^0, t_i^f) | R_i \geq t_i^0\}$$

$$= 1 - \exp\left\{ -\int_{t_i^0}^{t_i^f} \lambda(t | \mathbf{X}_i)dt \right\}$$

$$= 1 - \exp\left\{-\int_{t_i^0}^{t_i^f}\left(\lambda_0(t)e^{\mathbf{X}_i^T\beta}dt\right)\right\}$$

$$\lambda_{ij} = 1 - \exp\left\{-\int_{t_i^0}^{t_i^f}\lambda_0(t)dt\right\}^{e^{\mathbf{X_i^T}\beta}}$$

$$1 - \lambda_{ij} = \exp\left\{-\int_{t_i^0}^{t_i^f}\lambda_0(t)dt\right\}^{e^{\mathbf{X}_i^T\beta}}$$

Taking log on both sides

$$\log(1-\lambda_{ij}) = \log\left\{\exp\left\{-\int_{t_i^0}^{t_i^f}\lambda_0(t)dt\right\}^{e^{\mathbf{X}_i^T\beta}}\right\}$$

$$= e^{\mathbf{X}_i^T\beta}\int_{t_i^0}^{t_i^f}\lambda_0(t)dt$$

Again taking log on both sides we get,

$$\log(-\log(1-\lambda_{ij})) = \log\left(e^{\mathbf{X}_i^T\beta}\int_{t_i^0}^{t_i^f}\lambda_0(t)dt\right)$$

$$= \log(e^{\mathbf{X}_i^T\beta}) + \log\left(\int_{t_i^0}^{t_i^f}\lambda_0(t)dt\right) \qquad (4.3.7)$$

The expression $\int_{t_i^0}^{t_i^f} \lambda_0(t)dt$ is the baseline risk on time interval $\left(t_i^0, t_i^f\right)$, as long as λ_0 (t) does not vary greatly over time span of interest approximately $\int_{t_i^0}^{t_i^f} \lambda_0(t)dt \approx \left(t_i^f - t_i^0\right)\bar{\lambda}_0$ where $\bar{\lambda}_0$ is the mean baseline hazard.

Equation 4.3.7 can be rewritten as: $\log(-\log(1-\lambda_i)) = \mathbf{X}_i^T \beta + \log(t_i^f - t_i^0)\,\bar{\lambda}_0$

$$= \mathbf{X}_i^T \beta + \log(\bar{\lambda}_0) + \log\left(t_i^f - t_i^0\right)$$

$$= \mathbf{X}_i^T \beta + \beta_0 + \log\left(t_i^f - t_i^0\right)$$

where $\log(\bar{\lambda}_0) = \beta_0$

When expanding this formula for the multiple data i.e. for repeated events there is separate record for each subject for different time points.

$$\log\left(-\log\left(1-\lambda_{ij}\right)\right) = \mathbf{X}_{ij}^T \beta + \beta_{0j} + \log\left(t_{ij}^f - t_{ij}^0\right)$$

where λ_{ij} is the hazard for individual i at jth time point or cycle, $\left(t_{ij}^f - t_{ij}^0\right)$ is the risk time, and β_{0j} allows possible variation in the baseline hazards across cycles or time points.

4.3.3.1 Discrete survival and the complimentary log-log link

The extension of the proportional hazard model to discrete time proposed by Cox [45] by working with the conditional odds of dying (an event) at each time t_j, he proposed the model $\frac{\lambda(t_j \mid X_i)}{1-\lambda(t_j \mid X_i)} = \frac{\lambda_0(t_j)}{1-\lambda_0(t_j)} \exp\{\mathbf{X}_i^T \beta\}$ (4.3.8)

Where $\lambda(t_j \mid \mathbf{X}_i)$ is hazard at time t_j for an individual with covariate values X_i

$\lambda_0(t_j)$ is the baseline hazard at time t_j and $\exp\{\mathbf{X}_i^T \beta\}$ is the relative risk associated with covariate values X_i.

On taking log on both sides of equation 4.3.8, we get

$$\log\left(\frac{\lambda(t_j \mid X_i)}{1-\lambda(t_j \mid X_i)}\right) = \log\left(\frac{\lambda_0(t_j)}{1-\lambda_0(t_j)} \exp\{\mathbf{X}_i^T \beta\}\right)$$

$$= \log\left\{\frac{\lambda_0(t_j)}{1-\lambda_0(t_j)}\right\} + \log\left[\exp\{\mathbf{X}_i^T \beta\}\right]$$

$$logit\left(\lambda\left(t_j \mid X_i\right)\right) = logit\left(\lambda_0(t_j)\right) + X_i^T \beta = \alpha_j^0 + X_i^T \beta$$

where $\alpha_j = logit \lambda_0(t_j)$ is the *logit* of the baseline hazard. $X_i^T \beta$ is the effect of the covariates on the *logit* of hazard. The model treats time as a discrete factor by introducing one parameter α_j for each possible time of death (event) t_j.

The survival function in a proportional hazard framework can be written as

$$S(t_j \mid X_i) = S_0(t_j)^{\exp\left[\mathbf{X}_i^T \beta\right]}$$

where $S(t_j \mid \mathbf{X}_i)$ is the probability that an individual with covariate values X_i will survive up to time point t_j and $S_0(t_j)$ is the baseline survival function.

The compliment of hazard function $1-\lambda\left(t_j \mid X_i\right)=\left[1-\lambda_0(t_j)^{\exp[X_i^T\beta]}\right]$, from this equation hazard function can be obtained for individual *i* at time point t_j is

$$\lambda\left(t_j \mid \mathbf{X}_i\right)=1-[1-\lambda_0(t_j)]^{\exp\{\mathbf{X}_i^T\beta\}}$$

This model can be fitted to discrete survival data by generating pseudo observations and fitting a generalized linear model with binomial error structure and complementary log-log link.

4.3.4 Statistical application: objective 2

4.3.4.1 Data arrangement for incidence analysis

The crude incidence rate was calculated using the incidence density rate and cumulative incidence rate. Before starting with the incidence rate calculations, the dataset needed to be rearranged to perform survival analysis. Three new variables were created: event, agein and ageout. Event variable was a dichotomous variable with values of 1 and 0. Event was equal to 1 if the individual responded yes to the asthma question or, in other words, was diagnosed with asthma. Event was equal to 0 if the individual was not diagnosed with asthma i.e. the individual was considered censored. As soon as the individual experienced the event, a value equal to one was assigned, and any further information from the rest of the cycles were not considered for further analysis. The other two variables created were agein and ageout. Agein is the age of the individual at the start of the cycle. Ageout is the age of the individual at which the person was diagnosed with asthma. The time scale used is the subject's age as this was the only scale that had a common meaning across all the subjects.

For example, an individual who experienced an event, i.e., was diagnosed with asthma in Cycle 3, then will have values for event, agein and ageout of (0, 34, 36), (0, 36, 38), (1,38,40) and (.,40,42). The event variable will have the following value (event 1: 0, event 2: 1, event 3:., event 4:.), and for an individual who was not diagnosed with asthma in any of the cycles will have value (event 1: 0, event 2: 0, event 3: 0, event 4: 0). Figure 4.3 provides a diagrammatic representation of selecting new asthma cases.

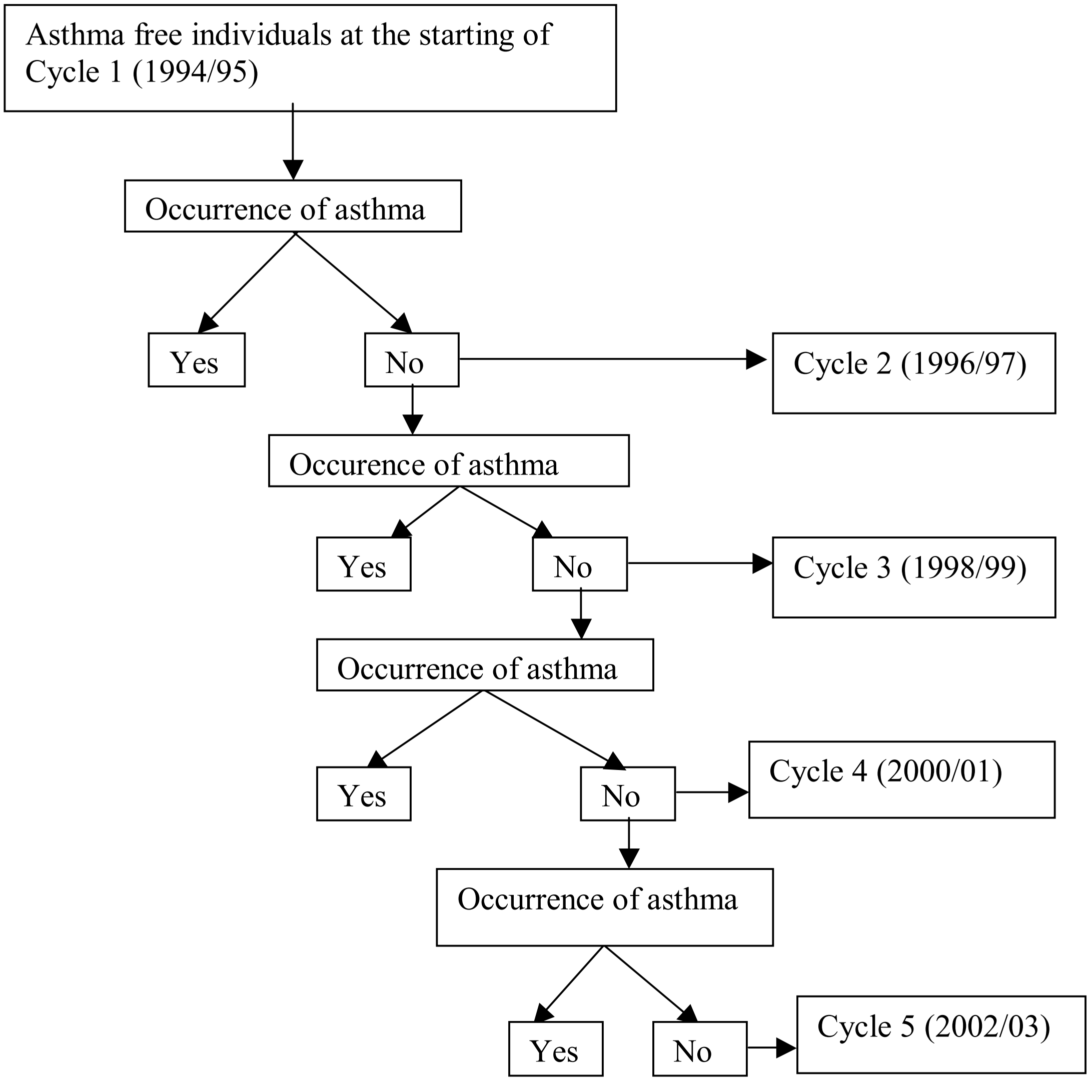


Figure 4.3 Diagrammatic representation of selecting new cases of asthma at each cycle

4.3.4.2 Crude incidence analysis

The incidence density rate was calculated using the equation 4.3.3. The data were collected every two years, and the exact time to asthma occurrence was not available. Hence, the person years of follow up was calculated as $(t_i^f - t_i^o) - \frac{1}{2}$ (length of the last between wave intervals) [191]. t_i^f is the time at which the individual may or may not have had asthma and t_i^o the inception or start time at which the individual did not had asthma.

Total person years were calculated as: (new cases at cycle 2*2 + new cases at cycle 3*4 + new cases at cycle 4*6 + new cases at cycle 5*8 + all censored cases*8).

The person time and the incidence rate of new cases was calculated using STATA command STPTIME. The incidence rate was calculated for:

1. new cases of asthma - overall
2. stratified by cycle
3. stratified by each of the categorical covariates included in the final model

   Weighted and unweighted analyses were performed to obtain the incidence rates.

Cumulative incidence rate was hand calculated as follows:

Total number of new cases at the end of Cycle 5 = New cases at (Cycle 1 + Cycle 2 + Cycle 3 + Cycle 4 + Cycle 5)

Total number of new cases at the end of cycle 5 was = 128 + 90 + 62 + 48 = 328

Total population at risk = 3977

Cumulative incidence rate over a period of 8 years i.e. from end of Cycle 1 to end of Cycle 5 = $\frac{328}{3977}\times 100 = 8.24\%$

Cumulative incidence rate over 2 year period i.e. Cycle 1 to Cycle 2 =

$2\times\frac{8.24}{8} = 2.06\%$

Cumulative incidence rate over 4 year period i.e. Cycle 1 to Cycle 3 =

$$4\times\frac{8.24}{8}=4.12\%$$

Cumulative incidence rate over 6 year period i.e. Cycle 1 to Cycle 4 =

$$6\times\frac{8.24}{8}=6.19\%$$

The crude rate ratio was calculated using the STATA command STMH command. The ratio of the rates between two groups was also calculated. These rate ratios were calculated for all the important risk factors or covariates with respect to the reference category, and were calculated using the STATA command STMH. The rate ratio was estimated as RR= $\frac{a_1}{T_1}\Big/\frac{a_2}{T_2}$ and the 95% confidence interval was calculated as RR $\times e^{\pm 1.96\sqrt{1/a_1+1/a_2}}$, where a_1 and a_2 is total number of event and T_1 and T_2 is the total person year for group 1 and 2 respectively. STMH command in STATA calculates the stratified rate ratio and significance tests using a Mantel-Haenszel type method .

4.3.4.3 Adjusted incidence of asthma

To examine the effect of risk factors or covariates on incidence of asthma, a discrete version of the proportional hazard regression model was used. The purpose of proportional hazard regression model was to find a parsimonious form which can describe the incidence rate of asthma between t_i^o (start of cycle 2) and t_i^f (final time, end of cycle 5). Outcome measure was time to an event (asthma). Since the exact time of asthma occurrence was not reported, the time interval was used for these analyses. Such kind of data as mentioned before are called ‘interval censored’ [192].

The first step involved calculating the unadjusted rate ratios, which were calculated with just one covariate in the model. Standard model building strategies were used to choose variables for the final model. Design variables were included in the model even if these variables were not significant at the univariate level. Schoenfeld residuals were used to test the proportional hazard model assumptions and model fit. The discrete proportional hazard model and Cox proportional hazard models were used to obtain the most parsimonious model.

The discrete proportional hazard model is a discrete survival analysis that enables regression techniques to be applied for relating incidences of a disease, such as new asthma cases, to subject level covariates, such as body mass index and smoking [191]. This method is a discrete version of the proportional hazard regression model which is commonly used in survival analysis [192, 193]. The complementary log-log transformation was used to obtain the hazard rates[191, 193], as it has been shown that this log-log transformation also follows a linear model in X_i.

For the discrete proportional hazard model, the GLM command was used in STATA. The GLM command fits the generalized linear model, using the Newton-Raphson optimization method. When the weight option is specified in the GLM statement, then robust is implied meaning that the Huber/White/Sandwich estimator of variance is used in place of traditional calculations. The robust standard errors are calculated using RGLM [194] command in STATA using robust generalized linear.

RGLM fits the generalized linear models and calculates a Huber (Sandwich) estimate of variance co-variance matrix of estimates.

For fitting the Cox's proportional hazard model, the STCOX command was used in STATA. Cox's proportional hazard model using the STCOX command is fitted via the maximum likelihood approach. Prior to using the STCOX command, the data needs to be declared survival-time data. In the STSET command when the weight option is specified, by default, it calculates the jackknife variance estimates. To calculate the robust standard errors for Cox's proportional hazard model, the robust option was specified in the STCOX statement, and the survival data was reset without specifying any sampling weights. When the robust option is specified, the variance-covariance matrix is calculated using Lin and Wei's [112] robust estimation method instead of the traditional method. The robust calculation is usually conducted to obtain the efficient score residual for each subject in the data for calculating the variance. The proportionality hazard assumption was tested using the STPHTEST, which is/was based on Schoenfeld residuals.

Methods used to calculate the incidence of asthma (crude and adjusted) are summarized in Figure 4.4

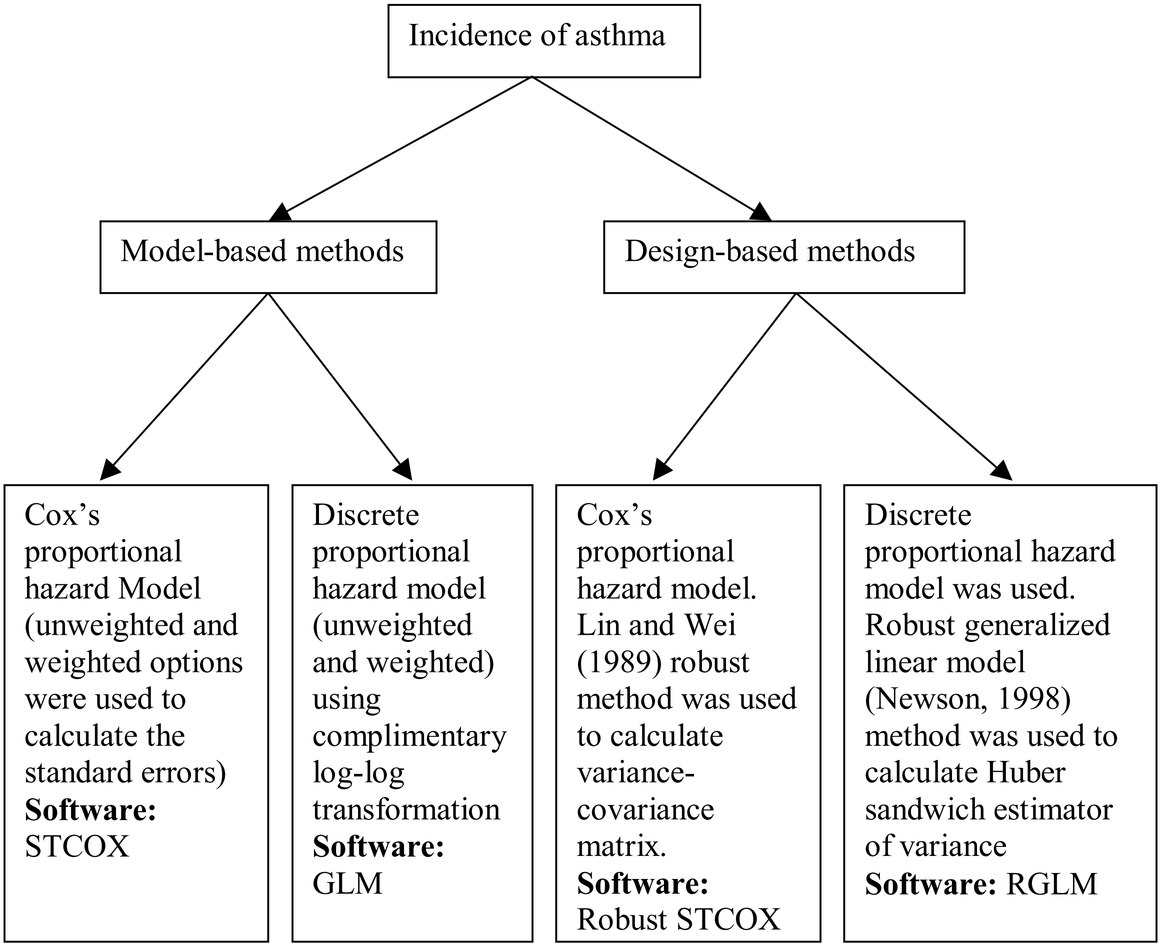

Incidence of asthma
Model-based methods
Design-based methods
Cox's proportional hazard Model (unweighted and weighted options were used to calculate the standard errors) **Software:** STCOX
Discrete proportional hazard model (unweighted and weighted) using complimentary log-log transformation **Software:** GLM
Cox's proportional hazard model. Lin and Wei (1989) robust method was used to calculate variance-covariance matrix. **Software:** Robust STCOX
Discrete proportional hazard model was used. Robust generalized linear model (Newson, 1998) method was used to calculate Huber sandwich estimator of variance **Software:** RGLM

Figure 4.4 Methods used to calculate incidence of asthma

4.4 Objective 3: Variance corrected and frailty models

The third objective was to compare the variance corrected model and the frailty model for recurrent event data. In recent years, the focus was to apply survival analysis techniques to analyze data with multiple events per subject for non-survey data. Most of the methods developed are an extension of the Cox's proportional hazard model. The Cox proportional hazard model assumes that observations are independent and the model is not applicable to data consisting of multiple events per subjects, which leads to correlated observations per subject. Several methods have been proposed in the literature to analyze data which consists of correlated events per subject. Variance corrected models are discussed in section 4.4.1 which are an extension of the Cox's proportional hazard model for multiple events data. Frailty models discussed in section 4.4.2 are utilized when there is unobserved heterogeneity present.

4.4.1 Variance corrected models

In this section, the marginal modeling approach will be discussed. The variance corrected approach has more in common with the generalized estimating equations approach proposed by Liang and Zeger [1] and Zeger and Liang [37]. Three common approaches used for the variance corrected models are: the Andersen and Gill (AG) [58] model, Wei, Lin and Wiessfeld (WLW) [63] and Prentice, Williams and Petersen (PWP) [65]. Section 4.4.1.1 explains the AG approach, the WLW model is explained in section 4.4.1.2, and finally, the PWP method is explained in section 4.4.1.3.

4.4.1.1 Andersen and Gill approach

This method is the simplest of all the three methods which are discussed; however, it makes very strong assumptions of independent increment (see appendix A for definition), especially if ordering of event is necessary. It is very close to the Poisson regression and can be accurately approximated with the Poisson regression software [60]. In this process, rows of data with time intervals (entry time, first event], (first event, second event], …….., (*mth* event, last follow-up] are used to represent each subject [60]. The first observation may or may not begin at zero, depending on the time scale. The intensity process for the i^{th} subject when the time scale is "time since entry" is given as: $\lambda_i(t)dt = E\{dN(t) \mid F_{t-}\} = \lambda_0(t)e^{(X(t)\beta')}dt$ (4.4.1)

where *N(t)* be the number of events per subject over the interval [0 (entry time), *t*(last follow-up time)], *X(.)* be the covariate process of the subject, $F_{t\text{-}}$ represents all the information of the processes *N* and *X* up to time *t*, $\lambda_0(t)$ is an arbitrary baseline intensity function and *β* is the vector of regression coefficients.

The above equation has two components: the covariates have multiplicative effects on the instantaneous rate of the counting processes and the influences of the prior events on future recurrences, is done through the time-dependent covariates. AG model is similar to Cox's model, the difference being in the definition of $\lambda_i\,(t)$. With recurrent data, $\lambda_i\,(t)$ is equal to one in case an event occurs for the AG model. Whereas for Cox's model, the individual ceases to be at risk when the event occurs and the value of λ_i goes to zero [60]. As suggested by Therneau and Grambsch [60], this method is best suited for the cases when the assumption of mutual independence of observations with a subject is made. Which is similar to the assumption of counting processes when "the numbers of events in non-overlapping time intervals are independent, given the covariates" [60].

4.4.1.2 Wei, Lin and Wiessfeld (WLW) model

Another method for analyzing multiple events data proposed by Wei, Lin and Weissfeld [63] is the WLW model, also known as the marginal Cox model. The intensity or hazard function for the j^{th} event and i^{th} subject is given by the following equation: $\lambda_{ij}(t) = \lambda_{0j}(t)\exp\left(\mathbf{X}_i(t)\boldsymbol{\beta}_j\right)$ (4.4.2)

where $\lambda_{0j}(t)$ is the event-specific baseline hazard function for the j^{th} event, βj is the event specific column vector of regression coefficients for the j^{th} event. WLW method estimates $\beta_1, \beta_2,$ …...... β_j by maximum partial likelihood estimates $\hat{\beta}_1, \hat{\beta}_2, \ldots\ldots\ldots, \hat{\beta}_j$, respectively, and uses a robust sandwich covariance matrix estimate for $\left(\hat{\beta}_1', \hat{\beta}_2', \ldots\ldots\ldots, \hat{\beta}_j'\right)$ to account for the dependence of the multiple failure times. The value of $\lambda_{ij}(t)$ is one until the occurrence of the j^{th} event, it takes the value zero in case of censoring or non-occurrence of an event.

4.4.1.3 Prentice, William and Peterson (PWP) model

The PWP model proposed by Prentice, William and Peterson [65] is also called the conditional model. The assumption of this model is based on the condition that the second event cannot occur until the first event has occurred [60]. In general, it can be summarized that a subject or individual is not at risk at k^{th} time point if that subject has not experienced $(k\text{-}1)^{th}$ the event.

The PWP model considers two time scales. One is the total time, which considers time from the beginning of the study, and the other one is called gap time following immediately after failure time. This model is a stratified Cox-type model, and the shape of the hazard functions depends on the characteristics of *N (t)*, the number of events an individual experiences by time *t* and ***X(t)*** the covariate vector of an individual at time *t*. The total time model is given by the formula:

$$\lambda(t \mid F_{t-}) = \lambda_{0\mathrm{j}}(t)\exp(\beta_j^{'} X(t)), \qquad t_{j-1} < t \le t_j \tag{4.4.3}$$

and the gap time model is given by the formula:

$$\lambda(t \mid F_{t-}) = \lambda_{0\mathrm{j}}\left(t - t_{j-1}\right)\exp\left(\beta_j^{'} X(t)\right),\ t_{j-1} < t \le t_j \tag{4.4.4}$$

Where λ_{0j} is an arbitrary baseline intensity functions and β_j is a vector of stratum specific regression coefficients. When a subject who experiences only one event moves from the first stratum to the second stratum after the event occurs and remains in the second stratum until the end of follow-up

4.4.2 Frailty Model Approach

In survival models, the addition of the random effects term in the models has become a source of major research. In this setting, the random effect term or the frailty is continuous, which describes the excess risk for distinct categories. For example, individuals or families [60]. The basic idea behind the frailty model is that individuals have different frailties and the most frail individual will die (here death refers to occurrence of an event) earlier than others [60].

4.4.2.1 Gamma frailty

The proportional hazard model when a random effect term is considered can be written as $\lambda_i(t) = \lambda_0(t)\exp(\mathbf{X}_i\beta + \mathbf{Z}_i\omega)$ (4.4.5)

where $\mathbf{X_i}$ and $\mathbf{Z_i}$ are covariate matrix of dimension *nxp*, **X** and β correspond to *p* fixed effects in the model and ω is a vector containing q unknown random effects or frailties,

Z is a design matrix, and Z_{ij} is equal to 1 if the subject belongs to the group *j* otherwise it has value 0.

The proportional hazard shared frailty model for subject *i* who belongs to the group *j* can be written as $\lambda_{i(j)}(t) = \lambda_0(t)\varpi_j \exp(\mathbf{X}_i\beta)$, where ϖ_j is the frailty for group *j* and with *i* ranging over all subjects can be written as $\varpi_j = \exp(\omega_j)$ and rest of the terms have same as defined above. Let us assume that the frailty has a Gamma distribution with a mean of 1 and a variance of 1/v. The log of density function of ϖ can be written as:

$$\log[f(\varpi;\nu)] = (\nu-1)\log(\varpi) - \nu\varpi + \nu\log(\nu) - \log\Gamma(\nu)$$

(4.4.6)

4.4.3 Statistical application: objective 3

4.4.3.1 Arrangement of the data for recurrent survival data

In the present analysis, the focus was on females who had reported asthma in Cycle 2 (1996-97) and for other consecutive cycles. The focus of the present objective was to investigate the risk factors of asthma recurrence in females who had asthma at the start of Cycle 2 and who also experienced asthma episodes in later cycles. In the analysis, intermittent missing data was also included. Table 4.1 summarizes the recurrent asthma events from Cycles 2 through 4. First recurrence was only who reported asthma in Cycle 2 and not in other cycles, second recurrence was those females who reported asthma in Cycle 2 and in either Cycle 3, or 4 or 5. Third recurrence included asthma in Cycle 2, and either in Cycle 3, and 4, or Cycle 3 and 5 or Cycle 4 and 5. Fourth recurrence included females reporting yes in all the four cycles.

Table 4.1 Recurrent asthma events included in the analysis to fit parsimonious model of asthma free females at the end of Cycle 1

Cycle 2	Cycle 3	Cycle 4	Cycle 5
First recurrent event			
Yes	No	No	No
Second recurrence			
Yes	Yes	No	No
Yes	No	Yes	No
Yes	No	No	Yes
Third recurrence			
Yes	Yes	Yes	No
Yes	Yes	No	Yes
Yes	No	Yes	Yes
Fourth recurrence			
Yes	Yes	Yes	Yes

To arrange the data in the format discussed above, four new variables were created. The three variables created were status, visit, tstart and tstop. The initial time or start time was considered to be Cycle 1 as no prior information was available for the initiation time to occurrence of asthma for those who reported asthma in Cycle1. Hence the time of origin was Cycle 1 and the individuals were studied over time. The status variable was dichotomous, with values of 1 and 0. Status was equal to 1 (recurrence) if the female individual answered yes to the asthma question, which was also the definition of an event and value 0 (censored) otherwise. Censored cases were those individuals who were not diagnosed with asthma at any particular Cycle or did not report asthma during the study period. Visit variable was a categorical variable with four categories, visit = 1 represented Cycle 2, visit = 2 represented Cycle 3, visit = 3 represents Cycle 4, and visit = 4 represents Cycle 5. Tstart variable is the time of the (E-1)th recurrence for visit = E (potential asthma recurrence), or a value equal to 0 for visit = 1, or the follow-up time if the (E-1)th recurrence did not occur. Tstop variable is the E th recurrence if visit = E, or the follow-up time if the E th recurrence does not occur. The duration or the follow-up time was calculated as: (age at the end of the risk interval) – (age at the start of the risk interval).

For example, a female who experienced asthma episodes in Cycle 2 and 4 will have following values for variable Visit, Status, Tstart and Tstop: (1,1,0,2), (2,0, 2,4), (3,1,4,6) and (4,0,6,8). Another variable gaptime was created which was calculated as (tstop-tstart).

4.4.3.2 Computer software of Variance corrected and frailty model

The SAS procedure PHREG was used to fit the following variance corrected models: the Anderson Gill (AG) method, the Wei, Lin and Weissfeld (WLW) model and the Prentice, William and Peterson (PWP) model.

Standard model building strategies were used to build the final model, and some of the design variables were also included even if these variables were not significant at univariate level. Schoenfeld residuals were used to test the proportionality hazard model assumptions and model fit.

The Cox's regression with shared frailty model was fitted using STATA software with a STCOX command. In STATA software, special procedures are available to fit the Gamma shared frailty model. Usually, the Newton-Raphson iteration method is used to solve the penalized model [60]. A shared frailty model is the survival-data analog to regression model when we have random effects or unobserved heterogeneity. The data was re-arranged to fit the frailty model. The Cox shared frailty model was fitted by specifying gamma distribution. When we specify gamma distribution in the shared statement, the frailties are treated as having a gamma distribution. Here, we assume, using the shared statement, that observations with a group are correlated as they share the same frailty.

The procedures to fit the frailty model are not available in SAS; hence, a SAS macro “Gamfrail” was used to fit the Gamma frailty model[12]. The frailty model was then fitted using this SAS macro and according to the specification of the macro, the dataset should be arranged in time (follow up time), status (whether recurrent event or censored data), identity variable and the variables or covariates in the model. The dataset was arranged in the above discussed manner and the gamma frailty macro was used.

The methods used for recurrent event data is provided in Figure 4.5. All the three variance corrected models were fitted using SAS procedure PHREG.

[12] http://www.biostat.mcw.edu/software/SoftMenu.html

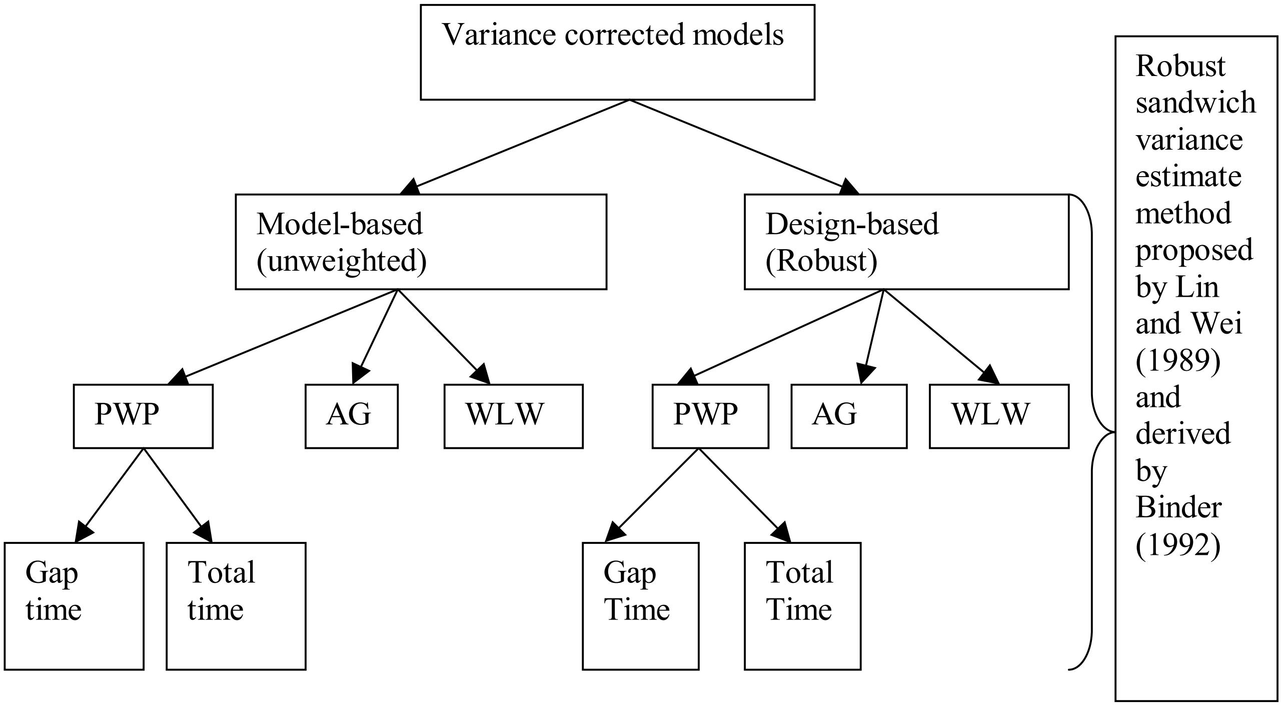

Variance corrected models
Model-based (unweighted)
Design-based (Robust)
PWP
AG
WLW
PWP
AG
WLW
Gap time
Total time
Gap Time
Total Time
Robust sandwich variance estimate method proposed by Lin and Wei (1989) and derived by Binder (1992)

Figure 4.5 Variance corrected methods used for recurrent event data

4.5 Objective 4: Missing data analysis

Missing data is very common in longitudinal studies, mainly due to non-responses or if the individuals have moved or are lost to follow-up. The missingness can occur if the individual have intermittent missing pattern, i.e., dropping out of the study and again return back at some point during the study period. In the past few decades, a considerable amount of work has been conducted in this area. The major reason for the development of the statistical model in this area was due to the fact that in early days, researchers used to analyze only completed data and this resulted in loss of information. Ignoring the missingness resulted in biased or wrong estimates. Research into missing data has gained momentum in the past few years due to the availability of most of the methods in commercial software.

Some of the previous work in this field focused on algorithmic or computational solutions [195, 196]. Later on, some Expectation Maximization (EM) algorithms were proposed by Dempster et al. [197]; however, while these methods provided solutions for missing data analysis, they were very cumbersome. Some of the recently used methods are complete case analysis, last observation carried forward (LOCF), direct likelihood, weighted generalized estimating equation (WGEE) and sensitivity analysis.

In the following section, the weighted generalized estimating equation approach and the random effects modeling approach will be discussed. In section 4.5.1, the notation and the arrangement of the dataset is explained, followed by discussions on the WGEE approach in section 4.5.2, and the random effect approach in section 4.5.3.

4.5.1 Notation and arrangement of the data

Let R_{ij} be an indicator variable such that

$R_{ij} = 1$ if subject i is observed at time point j

$= 0$ if subject i was not observed at time point j.

The dependent variable with n time points is a $nx1$ vector defined as

$$\mathbf{y}_i^{'} = (y_{i1,}y_{i2},........,y_{in})$$

The nx1 missing data indicator vector for a subject is defined as

$$\mathbf{R}_i^{'} = (R_{i1}, R_{i2},........, R_{in})$$

R_{ij} has same notation as above and it depends on whether y_{ij} is observed or not. The complete dependent variable can be partitioned based on R_i into y_i^O i.e. observed component and y_i^M into unobserved component for subject *i*. y_i^O is actually the observed dependent variable and y_i^M is the dependent variable vector which was planned to be observed, but could not be done.

When we have data missing completely at random (MCAR), the missingness R_i is independent of the observed y_i^O and the unobserved y_i^M vectors. For data missing at random (MAR), the missingness depends on covariates X_i and the observed dependent variable vector y_i^O. When missing not at random (MNAR) is considered the missingness is related to the unobserved dependent variable y_i^M after accounting for the observed variables X_i and y_i^O.

Little [198] introduced the "pattern-mixture model" for analyzing incomplete or missing data. In this model, the dataset can be subdivided into different groups based on the missing data pattern. For the NPHS dataset, we have five time points, and there are 2^5 i.e. 32 possible missing data patterns. For example, if we have three time points, then 2^3 combinations i.e. 8 possible pattern will be as follows (O = Observed and M = Missing)

Pattern Group	Time1	Time2	Time3
1	O	O	O
2	M	O	O
3	M	M	O
4	O	O	M
5	O	M	M
6	M	O	M
7	O	M	O
8	M	M	M

Figure 4.6 Missing data patterns: using an example with three time point study

When the main interest is studying completers versus incompleters, a dummy variable is created with value equals zero if present in all the cycles or time points and a value equal to one if missing observation at any time point. However, the last pattern will not be included as there is no available information. The combination of complete versus incomplete pattern is useful when we have a large percentage of individuals completing the study.

Pattern	Coding Scheme Used (Completers versus Incompleters)
OOO	0
MOO	1
MMO	1
OOM	1
OMM	1
MOM	1
OMO	1

Figure 4.7 Coding scheme of missing data pattern, shown with the help of an example with three time points (O-observed; M-missing)

4.5.2 Weighted Generalized Estimating Equation (WGEE)

The generalized estimating equation (GEE) proposed by Liang and Zeger [1] assumed that the data are missing completely at random (MCAR) and inferences are valid under this strong assumption. Robins et al. [199] extended the GEE model and proposed a class of weighted generalized estimating equations which allows the data to be missing at random. This approach leads to consistent and asymptotically normal estimators of β_0, and this method is computationally simple and does not require specification on the joint distribution of the data [199]. The marginal distribution of Y_{it} given X_i is given as: $E(\mathbf{Y}_{it} \mid \mathbf{X}_i) = g_t(\mathbf{X}_i, \beta_0)$, where the vectors have same notation as discussed above and $g_t(. , .)$ is fixed function and β_0 is a $px1$ vector of unknown parameter for $i = 1,..,n$.

The basic concept of WGEE is to weight each individual's measurements in the GEEs by the inverse probability that an individual drops out of the study at particular time point [43]. The weight is calculated as:

$$w_{ij} \equiv P(D_i = j) = \prod_{k=2}^{j-1} \left[1 - P\left(\mathbf{R}_{ik} = 0 \mid \mathbf{R}_{i2} = ... = \mathbf{R}_{i,k-1} = 1\right)\right] \times P\left(\mathbf{R}_{ij} = 0 \mid \mathbf{R}_{i2} = ... = \mathbf{R}_{i,j-1} = 1\right)^{I\{j \le n_i\}} \tag{4.5.1}$$

if the individual dropouts by time j or at the end of measurement of time point otherwise,

$$w_{ij} \equiv P(D_i = j) = \prod_{k=2}^{j} \left[1 - P(\mathbf{R}_{ik} = 0 \mid \mathbf{R}_{i2} = ... = \mathbf{R}_{i,k-1} = 1)\right] \tag{4.5.2}$$

The mean μ_i can be partitioned into observed (μ_i^O) and missing components (μ_i^M). The score equations for the weighted GEE approach to estimate β will be as follows:

$S(\beta)=\sum_{i=1}^{N} W_i \frac{\partial\mu_i}{\partial\beta'}\left(\mathbf{A}_i^{1/2}\mathbf{R}_i\mathbf{A}_i^{1/2}\right)^{-1}(y_i-\mu_i)=0$ where W_i is a diagonal matrix with the elements of w_i vector of weights for the i^{th} subject along the diagonal. This method can be adapted to the MNAR setting as well [43].

4.5.3 Random effects models

When there are discrete repeated measurements, the most commonly used method for random effects modeling is the generalized linear mixed model. Let Y_{ij} be the outcome variable has the notation definition as above. Y_{ij} have density function of the form:

$$f_i\left(y_{ij} \mid b_i,\beta,\phi\right)=\exp\left\{\phi^{-1}\left[y_{ij}\theta_{ij}-\psi\left(\theta_{ij}\right)\right]+c\left(y_{ij},\phi\right)\right\} \tag{4.5.3}$$

where μ_{ij} is the mean modeled through a linear predictor containing fixed and random parameters, b_i is a *qx1* random vector, normally distributed *N(0, D)* with $\eta\left(\mu_{ij}\right)=\mathbf{x}_{ij}'\beta+\mathbf{z}_{ij}'b_i$ for a known link function η (.), $\mathbf{x}_{ij}$ is a p-dimensional design matrix for fixed effects covariates and $\mathbf{z}_{ij}$ is a *q* dimensional design matrix for random effects covariates and φ is the scale parameter.

There are several methods available for estimating the coefficients. One of the methods is using an approximation of the integrand, and other is approximation of the data. For objective 4, the focus is only on the approximation of the data. To estimate the coefficients using this approach, the data is decomposed into mean and an error term. The decomposition is done with a Taylor series of expansions of the mean, which is a non-linear function of the linear predictor [43]. When we have binary outcome, i.e., with a logistic natural link function, the mean μ_{ij} can be written as:

$$\mu_{ij} = P(Y_{ij} = 1) = \pi_{ij} = \frac{\exp\left(\mathbf{x}'_{ij}\beta + \mathbf{z}'_{ij}b_i\right)}{1 + \exp\left(\mathbf{x}'_{ij}\beta + \mathbf{z}'_{ij}b_i\right)} \tag{4.5.4}$$

And the decomposition of the data is into mean and error term, hence ε_{ij} equals $1 - \pi_{ij}$ with probability π_{ij} and equals $-\pi_{ij}$ with probability $1 - \pi_{ij}$ [43].

The estimates can be calculated using a/the penalized quasi likelihood. Using this method, the estimates are obtained from optimizing a quasi likelihood function, which involves first and second order conditional moments, made larger with a penalty on random effects [43]. As shown by Molenberghs et al. [43], to approximate the mean, μ_{ij} a Taylor expansion of

$$Y_{ij} = \mu_{ij} + \varepsilon_{ij} = h\left(\mathbf{x}'_{ij}\beta + \mathbf{z}'_{ij}b_i\right) + \varepsilon_{ij} \tag{4.5.5}$$

around fixed effect ($\hat{\beta}$) and random effect ($\hat{b}_i$) results in:

$$Y_{ij} \approx h(\mathbf{x}'_{ij}\hat{\beta} + \mathbf{z}'_{ij}\hat{b}_i) + h'\left(\mathbf{x}'_{ij}\hat{\beta} + \mathbf{z}'_{ij}\hat{b}_i\right)\mathbf{x}'_{ij}\left(\beta - \hat{\beta}\right) + h'\left(\mathbf{x}'_{ij}\hat{\beta} + \mathbf{z}'_{ij}\hat{b}_i\right)\mathbf{z}'_{ij}(b_i - \hat{b}_i) + \varepsilon_{ij} \tag{4.5.6}$$

and the above equation can be re written as:

$$Y_{ij} = \hat{\mu}_{ij} + v\left(\hat{\mu}_{ij}\right)x'_{ij}\left(\beta - \hat{\beta}\right) + v\left(\hat{\mu}_{ij}\right)\mathbf{z}'_{ij}\left(b_i - \hat{b}_i\right) + \varepsilon_{ij}$$

(4.5.6)

where $\hat{\boldsymbol{\mu}}_{ij} = h\left(\mathbf{x}'_{ij}\hat{\beta} + \mathbf{z}'_{ij}\hat{b}_i\right)$.

The above equation 4.5.7 can be rewritten in vector notation as:

$$Y_i \approx \hat{\mu}_i + \hat{V}_i \mathbf{X}_i \left(\beta - \hat{\beta} \right) + \hat{V}_i \mathbf{Z}_i \left(b_i - \hat{b}_i \right) + \varepsilon_i \tag{4.5.7}$$

where $\mathbf{X_i}$ and $\mathbf{Z_i}$ are the design matrices for fixed effects and random effects and the estimate of $\hat{V}_i$ equals to the diagonal matrix with diagonal entries equal to $v\left(\hat{\mu}_{ij} \right)$.

4.5.4 Statistical application: objective 4

4.5.4.1 Data arrangement for handling missing data

To analyze data using a/the pattern mixture model, a dummy variable drop was created. This drop variable had a value of 0 if the person was present in all the five cycles, and a value of 1 if otherwise. The other category included all kind of missing patterns, i.e., intermittent missing as well as non intermittent missing data. The different possible missing patterns were explained with the help of an example (Figure 4.7).The SAS procedure MI was used to obtain the possible missing data patterns, presented in Table 4.2

Table 4.2 Possible missing data patterns and the frequency of the outcome variable "Self reported health professional diagnosed asthma"

Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	N (%)
X	X	X	X	X	6433 (69.7)
X	X	X	X	.	709 (7.7)
X	X	X	.	X	184 (2.0)
X	X	X	.	.	491 (5.3)
X	X	.	X	X	136 (1.5)
X	X	.	X	.	54 (0.6)
X	X	.	.	X	45 (0.5)
X	X	.	.	.	453 (4.9)
X	.	X	X	X	69 (0.8)
X	.	.	X	X	36 (0.4)
X	.	.	.	.	525 (5.7)
X	.	X	X	.	F
X	.	X	.	X	F
X	.	X	.	.	F
X	.	.	X	.	F
X	.	.	.	X	F

F: Results flagged as per the restriction imposed by Statistics Canada, refer to Appendix B for further details

A total of 70% of the females had complete information in all the five cycles, and about 30% of the females had missing data in at least one cycle. The different missing patterns given in Table 4.2 were combined together to form the drop variable with a value equal to 1, and 0 included the first pattern with all data present in all the five cycles. Since there are a large percentage of subjects who have completed the study, the completers versus the incompleters were the most reasonable combination for pattern mixture modeling approach.

The drop variable created was included in the final model of Objective 1 as we are interested in studying if there is any difference between completers and incompleters. As suggested by Hedeker et al.[200] , a model was fitted with the final model obtained from objective 1, and was modified by including a drop variable and its interaction with the main effect variables and the interaction term variables which results in the pattern mixture model. The next step was using these variables together in the model to fit the weighted generalized estimating equation (WGEE) and random effect modeling approach.

4.5.4.2 Application of WGEE analysis

To analyze the data using the WGEE approach, a weight variable was computed. This weight variable was different from the ones provided by Statistics Canada with the data set. To compute the WGEE estimates and standard errors, the SAS macro "dropout"[13] was used [43], and in the first step, the dropout model was fitted using logistic regression. Using this macro, two variables are created, namely the 'dropout' and 'prev' variables. The outcome variable 'dropout' is a binary variable and it indicates whether or not dropout occurred at a given time from the start of the measurement until the end of the study period [43]. "The covariate sin the model are the outcomes at previous occasion ('prev' variable), supplemented with genuine covariate information" [43].Once these two variables have been created, they are used in the SAS macro "dropwgt" [43]. This macro computes the necessary weights for the WGEE analysis which accounts for the dropouts. Since we are using survey data and the weight variable are specially created for longitudinal data to account for the complexity of the survey design, a new weight variable was created using the weight variable for dropouts and longitudinal weights. The new weight variable was equal to

[13] Refer to Appendix C.3 for SAS macro

(weight variable for dropouts) * (weight variable for survey data). This weight variable was used in the WGEE analysis.

The final model fitted for the marginal models were pattern mixture model (PMM) which included the drop variable. Another was using WGEE analysis, where the missingness is taken into account by implementing the special weights. The SAS procedure GENMOD was used for both of these approaches of marginal models.

4.5.4.3 Application of Random Effect Modeling

The SAS procedure GLIMMIX was used for the Quasi Likelihood. The Penalized Quasi Likelihood (PQL) method was implemented in the SAS procedure. This procedure is still in the experimental stage in the SAS version 9.1.3. Procedure GLIMMIX fits statistical models to data with correlations when responses are not necessarily normally distributed. The restricted maximum likelihood (REML), as well as the maximum likelihood (ML) method, can be used for the Penalized quasi likelihood. The restricted or the residual methods accounts for the fixed effects in the construction of the objective function. This reduces the bias in covariance parameter estimates. In REML, the covariance parameter estimates are the maximum likelihood estimates, and the fixed effects estimates are estimated generalized least square estimates. In ML, covariance parameters and fixed effects estimates are maximum likelihood estimates. For a detailed description of PROC GLIMMIX, refer to the SAS procedure GLIMMIX manual, page 97[14]. The REML estimates of variances and covariance are unbiased.

Separate models were fitted with/without drop variable and other covariates were fitted for random effect modeling approach. The final model from objective 1 was used. Model 1: PQL – ML (with drop variable), model 2: PQL-REML (with drop variable), model 3: PQL – ML (without drop variable), model 4: PQL-REML (without drop variable).

The methods used for missing data analysis (completers versus incompleters) is summarized in the Figure 4.8 below

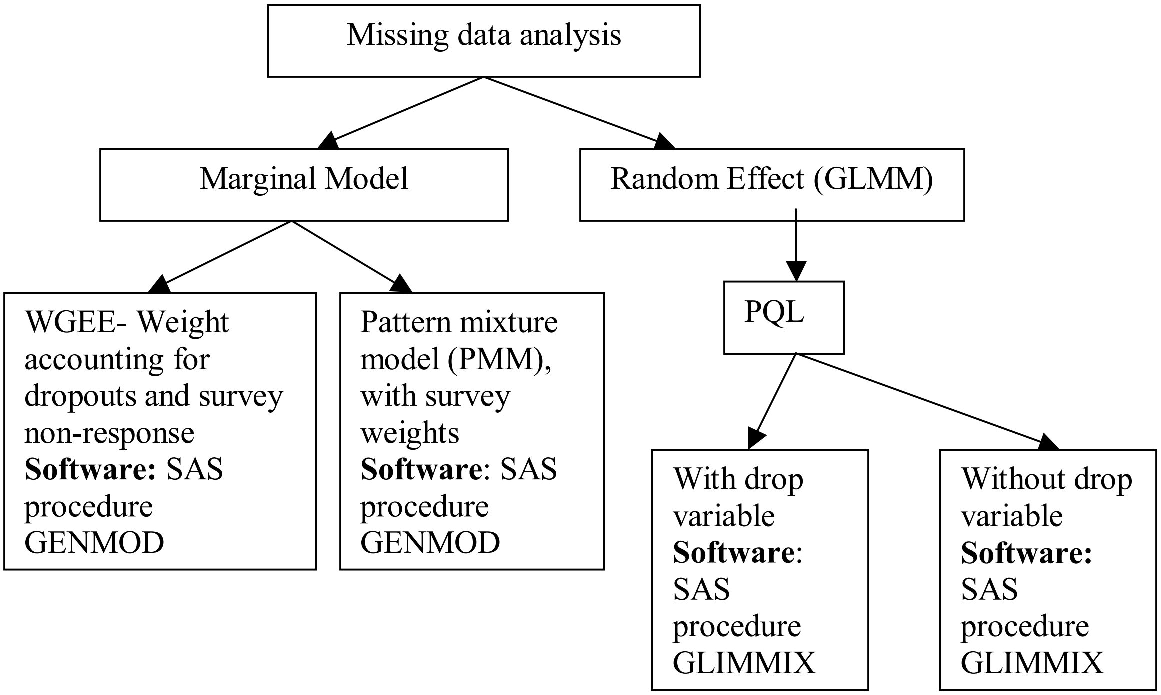

Missing data analysis
Marginal Model
Random Effect (GLMM)
WGEE- Weight accounting for dropouts and survey non-response **Software:** SAS procedure GENMOD
Pattern mixture model (PMM), with survey weights **Software**: SAS procedure GENMOD
PQL
With drop variable **Software**: SAS procedure GLIMMIX
Without drop variable **Software:** SAS procedure GLIMMIX

Figure 4.8 Missing data analysis using marginal and random effect modeling

[14] www.sas.com/statistics/doc.html- SAS procedure GLIMMIX documentation

CHAPTER 5 - RESULTS: MODELS FOR DISCRETE LONGITUDINAL SURVEY DATA

5.1 Introduction

The focus of this thesis was to compare model- based and design- based statistical approaches, using pre-existing and recently developed statistical models to analyze longitudinal complex survey data with a binary outcome. Section 5.2 provides a descriptive analysis of the subjects, followed by a description of the various covariates to be included in the statistical analyses in Section 5.3. Section 5.4 provides the results on the crude prevalence rates of asthma and the adjusted prevalence rates using the model- based and design- based methods. The incidence of asthma and its relationship with various risk factors are discussed in Section 5.5. Variance corrected models and frailty models are discussed in Section 5.6, followed by missing data analysis of completers versus incompleters in Section 5.7.

5.2 Subjects

The sample population of the NPHS contains 17,276 participants. For the present analysis, a subset of NPHS data was used comprised of adult Canadian females, aged 18 to 64 years at the start of Cycle 1 (1994/95). A total of 5841 females aged 18 to 64 years were included in the analysis.

5.3 Descriptive analysis

Table 5.1 provides the number of participants (%) stratified by asthma status and cycle. There was an increase in the number of asthma cases from Cycle 1 (1994-95) to Cycle 3 (1998-99), and there was a slight decrease in asthma cases after Cycle 3 (1998-99) to Cycle 5 (2002-03). The percentage of participants in the other category (no asthma) showed a decrease from 23% in Cycle 1 to 17% in Cycle 5. The last column in Table 5.1 presents the missing numbers for each Cycle. The missing category is mainly comprised of losses- to- follow- up and the "not stated" category.

The results based on further stratification of the covariates by cycle and asthma status could not be presented, as the numbers in some cells were smaller than 30, and thus cannot be reproduced due to restrictions imposed by Statistics Canada.

Table 5.1 Number of participants (%) stratified by asthma status for each Cycle of participation

Covariates	**Asthma (%)**	**No Asthma [15](%)**	**Missing#[16]**
Cycle 1 (1994-95)	391 (18.1)	5442 (23.2)	8
Cycle 2 (1996-97)	437 (20.3)	4971 (21.2)	433
Cycle 3 (1998-99)	456 (21.1)	4613 (19.7)	772
Cycle 4 (2000-01)	444 (20.6)	4360 (18.6)	1037
Cycle 5 (2002-03)	430 (19.9)	4094 (17.4)	1317

The baseline (Cycle 1-1994-95) characteristics of participants, by asthma status, are presented in Table 5.2.

Of the females who answered “yes” to having asthma in Cycle 1, 22.4% were obese, compared with 13.5% among those who did not report asthma in Cycle 1. Stratifying asthma status by age group showed that about 44.5% of females reporting asthma were in the age range 30 to 49 years, 34.3% were in the age range 18 to 29 years, followed by 21.2% in the age group 50 to 64 years. The percentage of asthmatic females was lowest in the 50 to 64 years age group.

Of females diagnosed with asthma, 23% reported food allergies, 56% reported other kinds of allergies, 19% reported emphysema, and 9.2% reported intestinal problems.

Among the women diagnosed with asthma, 82% of females who lived in urban areas and 18% resided in rural areas. The results for the ethnicity variable could not be presented due to low cell counts.

[15] Participants who did not report asthma.

[16] # - Total missing values presented for each Cycle

Stratifying females diagnosed with asthma by smoking status, 42.1% of them were current smokers, 25.8% of them were ex-smokers and 32.0% of them were non-smokers. On stratifying females diagnosed with asthma by exposure to second hand smoke, 44.2% of them were exposed to second hand smoke and 56% said no to exposure to second hand smoke.

Asthma status when studied by socio-economic status indicated 10.4% of the females belonging to higher socio-economic status, 56.4% belonging to middle socio-economic and 33.2% belonging to lower income group also answered yes to asthma question.

Percentage of females reporting asthma was higher among Canadian citizens (90.5%) as compared to non-Canadian citizens was 9.5%. Finally, on dividing asthma status by region, the number of females reporting asthma were higher in the Ontario region (26.3%), followed by the Atlantic region (24%), and the Prairie region (19.2%). The region of British Columbia (12.5%) and Quebec (17.9%) had the lowest percentage of participants who also answered yes to the asthma question.

Table 5.2 Baseline characteristics of the covariates included in the analysis, n (%)

Covariates	**Asthma (Yes)**	**Asthma (No)**	**Missing**#[17]
Body Mass Index (BMI)			221
Underweight	F[18]	F	
Normal Weight	179 (47.1)	2958 (56.5)	
Over Weight	102 (26.8)	1383 (26.4)	
Obese	85 (22.4)	706 (13.5)	
Age group			0
18-29 years	134 (34.3)	1334 (24.5)	
30-49 years	174 (44.5)	2778 (51.1)	
50-64 years	83 (21.2)	1330 (24.4)	
65-72 years	@[19]	@	
Food Allergy			8
Yes	90 (23.0)	340 (6.3)	
No	301 (77.0)	5102 (93.8)	
Other Allergy			8
Yes	219 (56.0)	1010 (18.6)	
No	172 (44.0)	4432 (81.4)	
Location			8
Rural	71 (18.2)	1234 (22.7)	
Urban	320 (81.8)	4208 (77.3)	
Ethnicity			
White	F	F	
Non-white	F	F	
Smoking Status			124
Current Smokers	163 (42.1)	1797 (33.7)	
Ex-Smokers	100 (25.8)	1471 (27.6)	
Non-Smokers	124 (32.0)	2062 (38.7)	
Second hand exposure to smoke			124
Yes	171 (44.2)	2114 (39.7)	
No	216 (55.8)	3216 (60.3)	
Socio-economic status			244
High Income	40 (10.4)	651 (12.5)	
Middle Income	216 (56.4)	3407 (65.3)	
Low Income	127 (33.2)	1156 (22.2)	
Emphysema/ Chronic Bronchitis			8
Yes	73 (18.7)	135 (2.5)	

[17] # - Total missing values presented for each category

[18] F- Results flagged as the cell numbers were very small and was suppressed as per restriction imposed by Statistics Canada

[19] @- Baseline characteristics and for age group variable participants aged 18 to 64 years only

Table 5.2 Cont'd

Covariates	**Asthma (Yes)**	**Asthma (No)**	**Missing**[#20]
No	318 (81.3)	5307 (97.5)	
Intestinal Problems			
Yes	36 (9.2)	189 (3.5)	8
No	355 (90.8)	5253 (96.5)	
Immigration Status			10
Citizen	354 (90.5)	4676 (86.0)	
Others	37 (9.5)	764 (14.0)	
Region			8
Atlantic	94 (24.0)	1363 (25.1)	
Quebec	70 (17.9)	983 (18.1)	
Prairies	75 (19.2)	1209 (22.2)	
British Columbia	49 (12.5)	528 (9.1)	
Ontario	103 (26.3)	1359 (24.5)	

As previously mentioned, the study subjects included 5841 adult Canadian females. This NPHS collects data from participants belonging to the entire ten Canadian provinces; hence, frequencies were obtained for these 5841 females divided by their province of residence. Table 5.3 provides the number of female participants included in the analysis for each cycle, stratified by province. Quebec and Ontario had the highest participation rate, followed by British Columbia and Saskatchewan. Prince Edward Island had the lowest participation rate compared to other provinces. Over the ten year study period, the participation rates for each province remained similar.

[20] # - Total missing values presented for each category

Table 5.3 Number of participants (%) stratified by cycles and province

Province	**Cycle 1 (1994-95)**	**Cycle 2 (1996-97)**	**Cycle 3 (1998-99)**	**Cycle 4 (2000-01)**	**Cycle 5 (2002-03)**
Newfoundland and Labrador	382 (6.5)	367 (6.3)	345 (5.9)	337 (5.8)	338 (5.8)
Prince Edward Island	332 (5.7)	320 (5.5)	317 (5.4)	310 (5.3)	308 (5.3)
Nova Scotia	356 (6.1)	355 (6.1)	351 (6.0)	341 (5.8)	342 (5.9)
New Brunswick	389 (6.7)	385 (6.6)	381 (6.5)	381 (6.5)	378 (6.5)
Quebec	1057 (18.1)	1059 (18.1)	1057 (18.1)	1061 (18.2)	1058 (18.2)
Manitoba	387 (6.6)	381 (6.5)	374 (6.4)	375 (6.4)	377 (6.5)
Alberta	364 (6.2)	351 (6.0)	352 (6.0)	344 (5.9)	334 (5.7)
Saskatchewan	533 (9.1)	549 (9.4)	571 (9.8)	589 (10.1)	598 (10.3)
British Columbia	578 (9.9)	598 (10.2)	596 (10.2)	597 (10.2)	586 (10.1)
Ontario	1463 (25.1)	1475 (25.3)	1494 (25.6)	1503 (25.8)	1495 (25.7)

As this study focuses on studying asthma in the adult female population, the total numbers of asthma cases in this age group were obtained for each cycle of participation (Figure 5.1). The results indicate that there was an increase in asthma cases from 404 in Cycle 1 (1994/95) to 472 in Cycle 5 (2002/03).

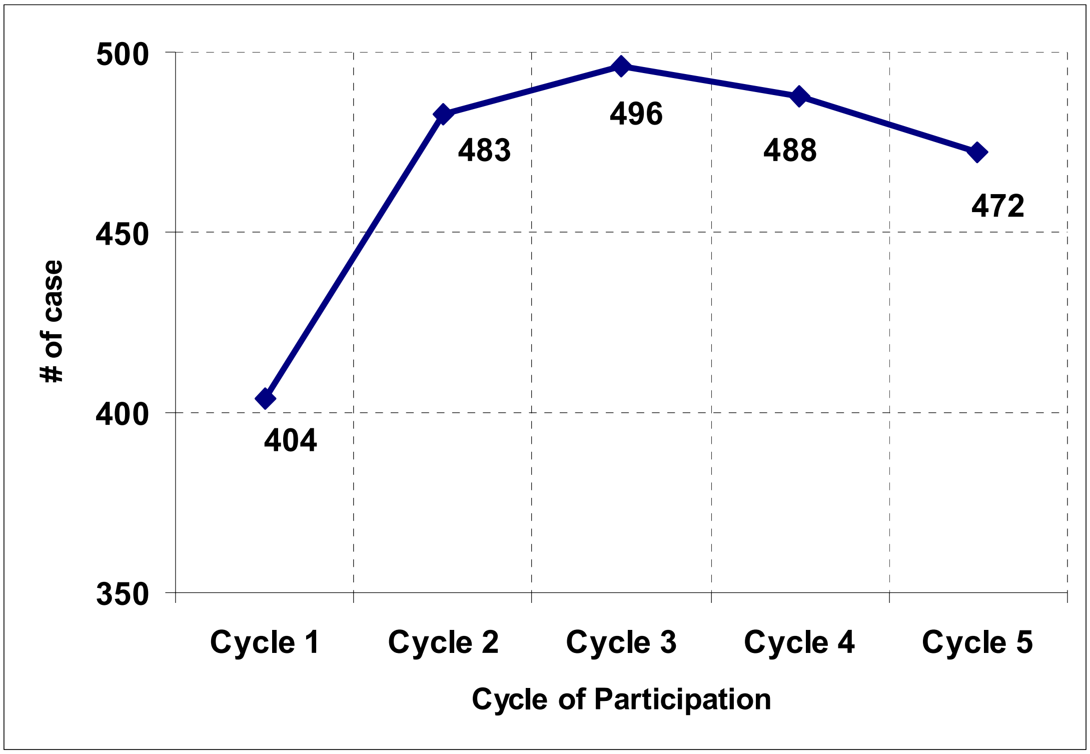


Figure 5.1 Asthma cases in the study sample of female participants in the age group 18-64 years stratified by Cycle of participation

The prevalence proportions for asthma and the corresponding 95% confidence interval were calculated using the BOOTVAR macro for all the five cycles (Table 5.4). The results indicated that the prevalence of asthma increased in females from 6.2% (5.5-7.0) in Cycle 1 to 6.9% (6.1-7.7) in Cycle 5. However, the increase was not statistically significant.

Table 5.4 Asthma prevalence and 95% confidence interval of adult females in 18-64 years age group

Cycles	Prevalence Proportion	95% Confidence Interval
Cycle 1 (1994-95)	6.2	5.5-7.0
Cycle 2 (1996-97)	7.2	6.4-8.0
Cycle 3 (1998-99)	7.4	6.5-8.2
Cycle 4 (2000-01)	7.1	6.3-7.9
Cycle 5 (2002-03)	6.9	6.1-7.7

The prevalence of asthma was further stratified by location of residence (rural/urban). Table 5.5 provides the asthma prevalence proportions and the 95% confidence intervals stratified by location for all the five cycles. The prevalence of asthma for rural and urban females was quite similar, with slightly a higher prevalence among urban females. At the end of Cycle 5 (2002-03), the prevalence of asthma was 7.1% (6.1-8.0) among urban females and 6.3% (4.6-8.1) among rural females. However, this difference was not statistically significant.

Table 5.5 Asthma prevalence and 95% CI of females for the age group 18-64 years stratified by location (Rural/Urban)

Cycles	Rural		Urban	
	Prevalence	95% C.I.	Prevalence	95% C.I.
Cycle 1 (1994-95)	6.1	4.2-8.0	6.2	5.4-7.1
Cycle 2 (1996-97)	6.7	4.7-8.6	7.3	6.4-8.2
Cycle 3 (1998-99)	7.1	6.2-9.1	7.4	6.5-8.4
Cycle 4 (2000-01)	7.0	5.1-8.9	7.2	6.3-8.1
Cycle 5 (2002-03)	6.3	4.6-8.1	7.1	6.1-8.0

5.4 Objective 1: Prevalence estimation

5.4.1 Crude prevalence rate calculation

The crude prevalence of asthma and the 95% confidence interval was calculated using the BOOTVAR macro provided with the dataset. Crude prevalence proportions were calculated for all the covariates which were included in the final model. These prevalence proportions and 95% confidence intervals are provided in Table 5.6.

The prevalence of asthma was highest in females in the age group 18 to 29 years, compared with other age groups; however, the prevalence for this age group decreased over time. For the age groups 30 to 49 years and 65 to 72 years, the prevalence increased from Cycle 1 through Cycle 5, and for the 50 to 64 years age group, it remained unchanged. Participants who reported chronic bronchitis/ emphysema, intestinal problems and food allergies showed an increase in asthma prevalence over the ten year study period. Female participants reporting allergies other than a food allergy showed a decrease in asthma prevalence over time. The prevalence of asthma for the participants residing in both rural and urban areas showed an increase in asthma prevalence over the ten year time period. The prevalence between rural and urban locations were not significantly different, but the prevalence was slightly higher for urban females,

Obese females had the highest prevalence of asthma, followed by overweight females and both of these groups showed a steady increase in prevalence rate over time. The prevalence of asthma for among those in the under weight category for Cycle 1 and 5 could not be presented due to restriction by Statistics Canada[21].

[21] Please refer to Appendix B (8.2.1)

The Ontario region had the highest asthma prevalence compared to other regions, however the rate decreased from Cycle 1 to Cycle 5. The Atlantic regions, which included the province of PEI, Newfoundland and Labrador New Brunswick and Nova Scotia, and the region of British Columbia, had the lowest prevalence of asthma in Cycle 1 but it increased over time. By the end of Cycle 5, these regions had the second and third highest asthma prevalence rate. Quebec and the Prairie regions had the lowest asthma prevalence.

With regard to ethnicity, the prevalence of asthma was higher among Caucasian females than non-Caucasian females. However, there was an increase in the prevalence over time for both Caucasian and non-Caucasian females.

Smokers had the highest prevalence of asthma in Cycle 1, but by the end of Cycle 5, ex-smokers had higher prevalence. Among ex-smokers, asthma prevalence increased from 5.8% (Cycle 1) to 10.5% (Cycle 5) ($p<0.05$). Likewise, the increase in asthma prevalence from 4.7% (Cycle 1) to 7.6% (Cycle 5) among non-smokers was also statistically significant ($p<0.05$). Females who answered yes to second hand exposure to smoke showed an increase in asthma prevalence from 7.4% in Cycle 1 to 10.0% in Cycle 5. Among those not exposed to second hand smoke, the prevalence increased from 5.5% in Cycle 1 to 8.8% in Cycle 5 ($p<0.05$).

Asthma prevalence was lowest in females belonging to higher socioeconomic groups (5.4% in Cycle 1; 8.2% in Cycle 5) and highest for those in lower socioeconomic groups (8.5% in Cycle 1; 13.7% in Cycle 5). For females belonging to the middle socioeconomic groups, the increase in prevalence from 6.0% in Cycle 1 to 8.5% in Cycle 5 was statistically significant at $p<0.05$ level. Canadian citizens had higher asthma prevalence than non-Canadian citizens. Over time, there was a further decrease in the prevalence of asthma for non- Canadian females (3.7% in Cycle 1 to 3.4% in Cycle 5), and for Canadian females, the prevalence increased from 6.8% in Cycle 1 to 7.8% in Cycle 5. However, these changes were not statistically significant.

Table 5.6 Asthma prevalence (95% confidence interval) for all the important covariates included in the final model

Covariates	**Cycle 1 (1994/95)**	**Cycle 2 (1996-97)**	**Cycle 3 (1998-99)**	**Cycle 4 (2000-01)**	**Cycle 5 (2002-03)**
Age Group					
18-29 years	9.1 (7.3-10.9)	10.1 (8.3-11.9)	10.0 (8.2-11.8)	9.6 (7.7-11.4)	7.9 (6.3-9.5)
30-49 years	5.4 (4.1-6.7)	6.0 (4.5-7.4)	5.7 (4.3-7.2)	7.0 (5.5-8.5)	7.0 (5.5-8.5)
50-64 years	5.6 (3.9-7.2)	6.8 (5.1-8.6)	6.1 (4.3-7.9)	5.4 (3.9-6.8)	5.6 (4.2-7.1)
65-72 years	5.0 (3.7-6.3)	6.1 (4.6-7.6)	7.5 (5.9-9.1)	6.6 (5.1-8.2)	7.0 (5.4-8.6)
Food Allergy	19.5 (14.8-24.2)	24.5 (19.9-29.1)	24.5 (19.6-29.5)	24.5 (19.8-29.3)	20.6 (16.5-24.7)
Other Allergy	17.6 (15.0-20.1)	17.6 (15.4-19.9)	18.3 (15.7-20.9)	17.5 (15.0-20.0)	17.4 (15.0-19.7)
Emphysema	35.4 (27.4-43.2)	33.7 (24.9-42.5)	47.2 (36.9-57.4)	44.8 (35.1-54.6)	41.4 (30.9-51.8)
Intestinal problems	13.3 (7.9-18.7)	13.8 (8.4-19.1)	20.6 (13.7-27.5)	21.5 (14.5-28.5)	20.9 (12.9-28.9)
Location					
Rural	6.1 (4.2-8.0)	6.6 (4.7-8.6)	7.1 (5.2-9.1)	7.0 (5.1-8.9)	6.3 (4.6-8.1)
Urban	6.2 (5.4-7.1)	7.3 (6.4-8.2)	7.4 (6.5-8.3)	7.2 (6.3-8.1)	7.1 (6.1-8.0)
Body Mass Index					
Underweight	F	4.9 (1.9-7.9)	4.7 (2.0-7.4)	4.6 (1.8-7.3)	F

Table 5.6 (Cont'd)

Covariates	**Cycle 1 (1994/95)**	**Cycle 2 (1996-97)**	**Cycle 3 (1998-99)**	**Cycle 4 (2000-01)**	**Cycle 5 (2002-03)**
Normal Weight	5.4	6.2	6.4	6.4	6.2
	(4.5-6.3)	(5.2-7.1)	(5.3-7.5)	(5.3-7.4)	(5.1-7.2)
Over Weight	6.4	7.4	7.2	7.1	7.0
	(4.9-8.0)	(5.8-9.0)	(5.6-8.9)	(5.5-8.7)	(5.4-8.7)
Obese	10.1	12.2	12.6	11.5	10.9
	(7.5-12.8)	(9.3-15.1)	(9.7-15.5)	(8.9-14.1)	(8.3-13.6)
Region					
Atlantic	5.3	5.5	6.5	7.0	7.2
	(3.9-6.7)	(4.1-6.9)	(4.9-8.2)	(5.3-8.6)	(5.4-9.0)
Quebec	6.2	7.3	6.2	6.9	6.3
	(4.5-7.9)	(5.7-8.9)	(4.5-7.8)	(5.2-8.7)	(4.6-8.0)
Prairies	6.0	7.4	7.9	7.0	6.7
	(4.7-7.2)	(6.0-8.8)	(6.4-9.3)	(5.6-8.3)	(5.4-8.0)
British Columbia	5.1	6.5	6.9	6.5	7.3
	(3.6-6.6)	(4.8-8.2)	(5.3-8.5)	(5.0-8.0)	(5.7-9.0)
Ontario	9.0	8.1	9.0	8.9	7.9
	(6.1-11.8)	(5.5-10.7)	(6.4-11.7)	(6.3-11.5)	(5.5-10.3)
Ethnicity					
Caucasian	6.5	8.2	9.2	9.3	8.3
	(5.7-7.3)	(7.2-9.2)	(8.1-10.2)	(8.3-10.4)	(7.3-9.4)
Non-Caucasian	3.5	3.6	3.1	3.8	3.8
	(1.5-5.6)	(1.8-5.4)	(1.1-5.0)	(1.4-6.2)	(1.3-6.2)
Smoking Status					
Current Smoker	8.6	10.0	10.2	9.5	8.8
	(7.0-10.1)	(8.3-11.7)	(8.3-12.1)	(7.5-11.5)	(6.8-10.8)

Table 5.6 (Cont'd)

Covariates	**Cycle 1 (1994/95)**	**Cycle 2 (1996-97)**	**Cycle 3 (1998-99)**	**Cycle 4 (2000-01)**	**Cycle 5 (2002-03)**
Ex-Smoker	5.8*	8.6	8.9	9.7	10.5*
	(4.4-7.2)	(6.8-10.4)	(7.1-10.7)	(8.1-11.4)	(8.9-12.2)
Non-Smoker	4.7*	5.9	7.1	7.5	7.6*
	(3.7-5.7)	(4.7-7.1)	(5.7-8.5)	(5.9-9.0)	(5.9-9.3)
Socio-economic status					
High Income	5.4	7.2	9.4	8.8	8.2
	(3.4-7.5)	(4.8-9.6)	(7.1-11.6)	(6.8-10.8)	(6.4-9.9)
Middle Income	6.0*	6.9	7.9	8.2	8.5*
	(5.0-6.9)	(5.8-8.0)	(6.7-9.1)	(6.9-9.5)	(7.0-9.9)
Low Income	8.5	11.6	9.5	11.9	13.7
	(6.6-10.5)	(9.0-14.3)	(6.8-12.2)	(8.2-15.7)	(9.5-18.0)
Immigration Status					
Citizen	6.8	8.1	8.3	8.2	7.8
	(6.0-7.7)	(7.2-9.0)	(7.3-9.3)	(7.2-9.1)	(6.8-8.7)
Others	3.7	3.6	3.5	2.9	3.4
	(2.3-5.2)	(2.1-5.1)	(2.2-4.9)	(1.6-4.1)	(2.0-4.9)
Exposure to second hand smoke					
Yes	7.4	9.7	9.5	9.7	10.0
	(6.1-8.7)	(8.1-11.3)	(7.7-11.3)	(7.8-11.6)	(7.7-12.3)
No	5.5*	6.7	8.1	8.5*	8.8*
	(4.6-6.4)	(5.6-7.8)	(6.9-9.2)	(7.3-9.6)	(7.6-9.9)

F- Results flagged as the cell numbers were very small and was suppressed as per restriction imposed by Statistics Canada
$* p < 0.05$

5.4.2 Marginal modeling approach for cross-sectional survey data

To determine the robustness of findings for prevalence of asthma, the adjusted odds ratio and 95% confidence interval for Cycle 1 (1994-95) was compared using the Taylor linearization (SAS procedure SURVEY LOGISTIC) method, the macro LOGREG as the BOOTVAR technique, and the SAS procedure GENMOD. The first two methods were design-based approaches, i.e., these methods accounted for the clustering and stratification along with the unequal probability of selection. The last method was a model-based approach. The purpose of the analysis was to compare the design-based and model-based approaches at the cross-sectional level. The intent was to examine if these three methods provided similar results and could account for the complex survey design. Table 5.7 provides the adjusted odds ratio and 95% confidence interval using the three methods discussed above.

The odds ratio obtained using the design-based and model-based methods produced similar results. The results suggest that the SAS procedure GENMOD does account for the complexity of the design, as does the design-based approach. In absence of any gold standard method analysis with survey design, it was assumed that the BOOTVAR method produced unbiased results. The 95% confidence intervals, using the BOOTVAR macro, were slightly wider than the other two methods used.

Table 5.7 Comparison of design-based versus model-based, adjusted odds ratio (95% confidence interval) for Cycle 1 (1994-95)

Covariates	**Proc SURVEY LOGISTIC**	**BOOTVAR Macro**	**Proc GENMOD (Exchangeable)**
Province (Ontario)			
Newfoundland	0.52	0.52	0.52
and Labrador	(0.33-0.84)	(0.31-0.87)	(0.33-0.82)
Prince Edward	0.74	0.74	0.74
Island	(0.47-1.15)	(0.47-1.16)	(0.47-1.15)
Nova Scotia	0.91	0.91	0.91
	(0.58-1.42)	(0.55-1.49)	(0.57-1.44)
New Brunswick	0.65	0.64	0.64
	(0.41-1.02)	(0.40-1.04)	(0.42-0.99)
Quebec	0.98	0.98	0.98
	(0.72-1.32)	(0.71-1.34)	(0.73-1.31)
Manitoba	0.79	0.79	0.79
	(0.52-1.21)	(0.51-1.24)	(0.50-1.25)
Saskatchewan	0.63	0.62	0.62
	(0.40-0.97)	(0.41-0.96)	(0.39-0.99)
Alberta	0.78	0.78	0.78
	(0.50-1.20)	(0.50-1.22)	(0.52-1.17)
British	1.07	1.07	1.07
Columbia	(0.76-1.53)	(0.74-1.55)	(0.75-1.52)
Allergy (No)			
Yes	4.84	4.84	4.84
	(3.45-6.79)	(3.38-6.94)	(3.47-6.74)
Emphysema (No)			
Yes	8.10	8.10	8.10
	(5.72-11.47)	(5.64-11.63)	(5.70-11.50)
Intestine (No)			
Yes	1.54	1.54	1.54
	(1.01-2.36)	(0.99-2.40)	(0.99-2.38)
Age Group (18-24)			
25-34 years	0.77	0.77	0.77
	(0.56-1.07)	(0.55-1.08)	(0.76-0.77)
35-64 years	0.43	0.43	0.43
	(0.32-0.59)	(0.32-0.59)	(0.32-0.59)
BMI (Normal Weight)			
Under weight	0.64	0.64	0.64
	(0.30-1.37)	(0.29-1.41)	(0.30-1.36)
Over weight	1.27	1.27	1.27
	(0.97-1.64)	(0.97-1.65)	(0.97-1.66)

Table 5.7 (Cont'd)

Covariates	Proc SURVEY LOGISTIC	BOOTVAR Macro	Proc GENMOD (Exchangeable)
Obese Class I	1.30 (0.90-1.88)	1.30 (0.89-1.89)	1.30 (0.90-1.87)
Obese Class II	2.83 (1.56-5.12)	2.83 (1.53-5.24)	2.83 (1.56-5.11)
Obese Class III	1.80 (0.92-3.54)	1.80 (0.83-3.91)	1.80 (0.92-3.53)
Smoking (Non-Smokers)			
Smokers	1.23 (0.95-1.58)	1.22 (0.95-1.58)	1.22 (0.94-1.59)
Ex-Smokers	1.14 (0.85-1.54)	1.14 (0.84-1.55)	1.14 (0.85-1.53)
Location (Urban)			
Rural	0.93 (0.68-1.27)	0.93 (0.67-1.29)	0.93 (0.69-1.25)

Reference categories are provided in parentheses

5.4.3 Marginal modeling approach for the longitudinal survey data

The marginal model approach used for cross-sectional analysis was extended for this longitudinal data analysis. The adjusted odds ratio and 95% confidence interval were calculated using three approaches: Survey GEE [3], BOOTVAR GEE and GENMOD [1] procedure. The variables for the final model were chosen using the standard model building strategies. Bivariate analysis was conducted with asthma (yes/no) as an outcome or dependent variable with all the important covariates thought to be as the risk factors for asthma prevalence. The covariates for the multi-variable marginal model were selected based on the $p<0.25$ significance level or if the covariates had clinical or biological significance.

The final model included age groups (age variable categorized), self reported food allergies, any other kind of allergies, rural/urban location, body mass index, region of Canada, ethnicity, smoking status, exposure to second hand smoke, socio-economic status and immigration status.

The model with exchangeable correlation matrix was chosen as the final model. The independent correlation matrix was not chosen as it assumes that observations are independent and which is not true when we have longitudinal data. Unstructured and auto regressive correlation matrices of first order were not chosen, when using these working correlation structure the convergence criteria was not satisfied and the Hessian matrix was not positive definite. However, the problem with convergence and the Hessian matrix not positive definite was true only for the model-based approaches, i.e., when using the SAS procedure GENMOD. The convergence criteria was satisfied for the exchangeable working correlation matrix and Hessian matrix was positive definite.

The results based on the exchangeable working correlation structure for all three methods are presented in Table 5.8. The parameter estimates obtained from the model-based and the design-based approaches were similar. However, the standard errors and 95% confidence intervals were different using these two methods. The standard errors using the Rao [3] method were larger compared to Liang and Zeger [1] ,as well as using the design-based Bootstrap approach. For some of the variables, the standard errors were very similar (like for under weight and over weight categories of BMI, rural location, high income category of the socio-economic status, rural and ex-smokers interaction, ethnicity and socio-economic status interaction, second hand smoke exposure and time interaction, 18 to 29 years age group as well as the 30 to 49 years age group with high income category interaction). Based on the standard errors, the significance level was very different for exchangeable working correlation structures using the model-based and design-based methods.

5.4.3.1 Computation of parameter estimates

Using the method by Liang and Zeger [1], the following variables were significant at p<0.05 significance level: (i) main effects - BMI, health professional diagnosed food allergy, other kinds of allergy, chronic bronchitis/emphysema, stomach or intestinal problems, region of residing, immigration status in the main effect; (ii) interaction terms: location * smoking status, location * socio-economic status, second hand exposure to smoke * repeat/time, smoking status * age group and age group * socio-economic status.

For the design-based marginal modeling approach, the Survey GEE proposed by Rao [183] was used. This method accounts for the longitudinal nature of the survey data as well as the clustering, stratification and unequal probability of selection. Following variables were significant at p<0.05 level: (i) main effects: health professional diagnosed food allergy, other allergy, chronic bronchitis /emphysema, and stomach or intestinal problems and immigrant status in the main effects model; (ii) interaction terms or effect modifiers: location * smoking status, location * socio-economic status and age group * socio-economic status.

Next, the Bootstrap method modified by Professor Lam of Queen's University was used. The BOOTVAR macro was modified to account for the repeated observation, The following variables were significant at p < 0.05: (i) main effects: BMI, health professional diagnosed food allergy, other allergies, chronic bronchitis/ emphysema and stomach/intestinal problems, immigration status; and (ii) interaction terms or effect modifiers: location * smoking status, location * smoking status, second hand exposure to smoke and repeat/time variable and age group * socio-economic status.

5.4.3.2 Interpretation of results

5.4.3.2.1 Interpretation of the main effects odds ratios

In the main effects model, the risk or odds of developing asthma was lower in females who were under weight, 1.2 times higher in overweight females and 1.7 times higher in obese females compared to normal weight females. Females diagnosed with food allergies were 1.5 times more likely to be diagnosed with asthma compared to females with no food allergies. Females reporting allergies other than food allergies were 1.8 times more likely to be diagnosed with asthma compared with females with no other allergies. The odds of being diagnosed with asthma were 2.2 times more likely in females who were diagnosed with chronic bronchitis or emphysema compared to females with no chronic bronchitis or emphysema. Finally, the odds of being diagnosed with asthma were 1.3 times higher in females with stomach or intestinal problems compared to females with no stomach or intestinal problems.

The odds of being diagnosed with asthma decreased for females residing in the Atlantic region (25%), Quebec region (17%), and in the Prairies region (21%). The odds of asthma increased by 1.2 times for females residing in the British Columbia region compared to females residing in the Ontario region. The odds of developing asthma was 56% less in females who were not Canadian citizen compared to the females who were Canadian citizen.

5.4.3.2.2 Interpretation of interaction terms

Rural females who were current smokers were 2.6 times more likely to be diagnosed with asthma when compared to urban non-smoking females. For rural females who were ex-smokers, the risk was about 1.5 times higher compared to the non-smoking urban females.

Rural females belonging to a higher socio-economic status were 1.8 times more likely to develop asthma compared to urban females belonging to lower socio-economic status. The same was true for rural females in the middle socio-economic status, the risk was about 1.3 times higher compared with urban females with lower socio-economic group.

Caucasian females belonging to higher socio-economic status were 51% less likely to be diagnosed with asthma compared to females belonging to non Caucasian lower socio-economic group females. However, Caucasian females in the middle socio-economic status were 1.7 times more likely to be diagnosed with asthma compared to the lower socio-economic status non Caucasian females.

The risk of being diagnosed with asthma was 1.1 times higher in females exposed to second hand smoke at Cycle 2 and the risk increased was higher for Cycle 5 compared to females who were not exposed to second hand smoke at baseline i.e. Cycle 1.

The interaction of smoking with age indicated that the risk of asthma was 2.5 times higher in 18 to 29 years age group female smokers, and 1.5 times higher in female ex-smokers in the same age range when compared with the 65 to 72 years age group non-smoker females. The odds of developing asthma were about 1.5 times higher in female smokers in the 30 to 49 years age group and 1.4 times higher in ex-smokers in the same age group when compared with non-smokers in the 65 to 72 years age group. Female smokers aged 50 to 64 were 1.7 times more likely and ex-smokers were 1.5 times more likely to be diagnosed with asthma compared to 65 to 72 years non-smoking females. The odds of developing asthma was highest amongst smokers and ex-smoker females in the age range 18 to 29 years, followed by 30 to 49 years, and finally, 50 to 64 years age group.

The interaction between age and socio-economic status interaction was significant, and indicated that the odds of being diagnosed with asthma was lower (55%) in 18 to 29 years females belonging to higher socio-economic status and about 26% lower in the middle socio-economic status when compared to 65 to 72 years females in the lower socio-economic status. The same was true for 30 to 49 years age group females, the odds decreased by 62% in higher income group and 34% in middle income group females. For the 50 to 64 years age group asthma decreased by about 49% in higher and 27% in middle socio-economic status when compared to lower socio-economic status females in 65 to 72 years age group category.

The final model-based on the significant main effects and interaction terms, modeling the probability of asthma and its various risk factors can be summarized as:

logit [Pr(Asthma)$_{ij}$=1] = -3.23 -0.42*(underweight)$_{i}$ + 0.19*(overweight)$_{i}$ + 0.53*(obese)$_{i}$ + 0.32*(food allergy)$_{ij}$ + 0.51*(other allergy)$_{ij}$ + (0.69)*(bronchitis)$_{ij}$ + 0.24*(intestinal problems)$_{ij}$ + 1.29*(high income)$_{ij}$ -0.31*(middle income)$_{ij}$ – 0.59*(rural)$_{ij}$ + 0.38*(18-29 years)$_{ij}$ + 0.42*(30-49 years)$_{ij}$ + 0.04*(50-64 years)$_{ij}$ - 0.29*(Atlantic)$_{ij}$ -0.18*(Quebec)$_{ij}$ – 0.24*(Prairie)$_{ij}$ + 0.10*(British Columbia)$_{ij}$ - 0.81*(immigrants)$_{ij}$ + 0.19*(white)$_{ij}$ – 0.48*(smokers)$_{ij}$ – 0.34*(ex-smoker)$_{ij}$ – 0.04*(exposure to second hand smoke)$_{ij}$ + 0.38*(Cycle 5)$_{ij}$ + 0.40*(Cycle 4)$_{ij}$ + 0.32*(Cycle 3)$_{ij}$ + 0.11*(Cycle 2)$_{ij}$ + 0.43*(rural smokers)$_{ij}$ +0.36*(rural ex-smokers)$_{ij}$

+ 0.56*(high income rural)$_{ij}$ + 0.28*(middle income rural)$_{ij}$ – 0.72*(high income white)$_{ij}$ + 0.46*(middle income white)$_{ij}$ + 0.06*(exposure to smoke in Cycle 2)$_{ij}$ + 0.12*(exposure to smoke in Cycle 3)$_{ij}$ + 0.11*(exposure to smoke in Cycle 4)$_{ij}$ + 0.27*(exposure to smoke in Cycle 5)$_{ij}$ + 0.80*(18-29 years smokers)$_{ij}$ + 0.44*(18-29 years ex-smokers)$_{ij}$ + 0.29*(30-49 years smokers)$_{ij}$ + 0.37*(30-49 years ex-smokers)$_{ij}$ + 0.46*(50-64 years smokers)$_{ij}$ + 0.38*(50-64 years ex-smokers)$_{ij}$ – 0.79*(18-29 years high income)$_{ij}$ – 0.30*(18-29 years middle income)$_{ij}$ – 0.97*(30-49 years high income)$_{ij}$ – 0.41*(30-49 years middle income)$_{ij}$ – 0.68*(50-64 years high income)$_{ij}$ – 0.19*(50-64 years middle income)$_{ij}$

Table 5.8 Estimates (Standard Errors) and Odds Ratio (95% Confidence Interval) with Exchangeable correlation matrix

Covariates	**Liang and Zeger (1986)**		**Rao (1998)**		**Bootstrap Method**	
	Estimate (S.E.)	**Odds Ratio (95% C.I.)**	**Estimate (S.E.)**	**Odds Ratio (95% C.I.)**	**Estimate (S.E.)**	**Odds Ratio (95% C.I.)**
Intercept	-3.23***	0.04	-3.36***	0.03	-3.23***	0.04
	(0.40)	(0.02-0.09)	(0.43)	(0.01-0.08)	(0.46)	(0.02-0.10)
BMI (Normal weight)						
Under weight	-0.42	0.67	-0.42	0.66	-0.42	0.66
	(0.30)	(0.36-1.18)	(0.27)	(0.38-1.12)	(0.36)	(0.33-1.32)
Over weight	0.19	1.21	0.21	1.23	0.19	1.21
	(0.14)	(0.92-1.57)	(0.13)	(0.95-1.59)	(0.14)	(0.91-1.60)
Obese	0.53	1.69**	0.55	1.74	0.53	1.70**
	(0.14)	(1.28-2.25)	(0.29)	(0.98-3.07)	(0.16)	(1.25-2.30)
Food Allergy (No)						
Yes	0.32	1.38**	0.40	1.48**	0.32	1.38***
	(0.09)	(1.16-1.65)	(0.11)	(1.21-1.83)	(0.08)	(1.19-1.60)
Other Allergy (No)						
Yes	0.51	1.66***	0.60	1.83***	0.51	1.66***
	(0.06)	(1.47-1.87)	(0.14)	(1.40-2.40)	(0.07)	(1.44-1.92)
Bronchitis (No)						
Yes	0.69	2.00***	0.80	2.23*	0.69	2.00***
	(0.14)	(1.51-2.65)	(0.31)	(1.23-4.06)	(0.11)	(1.62-2.47)
Intestinal Problem (No)						
Yes	0.24	1.27*	0.28	1.32	0.24	1.28*
	(0.12)	(1.00-1.62)	(0.16)	(1.00-1.79)	(0.12)	(1.02-1.60)
Socio-economic status (Low SES)						

Table 5.8 (Cont’d)

Covariates	**Liang and Zeger (1986)**		**Rao (1998)**		**Bootstrap Method**	
	Estimate	**Odds Ratio**	**Estimate**	**Odds Ratio**	**Estimate**	**Odds Ratio**
	(S.E.)	**(95% C.I.)**	**(S.E.)**	**(95% C.I.)**	**(S.E.)**	**(95% C.I.)**
High SES	1.29	3.63	1.31	3.72	1.29	3.64
	(0.58)	(1.17-11.27)	(0.53)	(1.31-10.56)	(0.68)	(0.96-13.80)
Middle SES	-0.31	0.73	-0.37	0.69	-0.32	0.73
	(0.27)	(0.43-1.25)	(0.40)	(0.32-1.52)	(0.29)	(0.41-1.29)
Location (Urban)						
Rural	-0.59	0.55	-0.66	0.52	-0.59	0.55
	(0.21)	(0.37-0.83)	(0.25)	(0.31-0.85)	(0.22)	(0.36-0.86)
Age Group (65-72 years)						
18-29	0.38	1.46	0.43	1.54	0.38	1.46
years	(0.33)	(0.77-2.76)	(0.44)	(0.65-3.63)	(0.33)	(0.76-2.81)
30-49	0.42	1.51	0.46	1.58	0.42	1.51
years	(0.28)	(0.87-2.63)	(0.40)	(0.73-3.42)	(0.29)	(0.85-2.70)
50-64	0.04	1.04	0.04	1.04	0.04	1.04
years	(0.25)	(0.64-1.69)	(0.31)	(0.57-1.90)	(0.25)	(0.63-1.71)
Region (Ontario)						
Atlantic	-0.29	0.75*	-0.31	0.73	-0.29	0.75
	(0.14)	(0.57-0.98)	(0.32)	(0.39-1.36)	(0.16)	(0.55-1.03)
Quebec	-0.18	0.83	-0.16	0.85	-0.18	0.83
	(0.14)	(0.64-1.09)	(0,18)	(0.60-1.20)	(0.16)	(0.61-1.13)
Prairies	-0.24	0.79	-0.24	0.79	-0.24	0.79
	(0.13)	(0.61-1.02)	(0.20)	(0.53-1.17)	(0.14)	(0.60-1.04)
British	0.10	1.11	0.15	1.16	0.10	1.11
Columbia	(0.16)	(0.81-1.52)	(0.19)	(0.81-1.67)	(0.17)	(0.79-1.56)
Immigration (Citizen)						

Table 5.8 (Cont'd)

Covariates	Liang and Zeger (1986)		Rao (1998)		Bootstrap Method	
	Estimate (S.E.)	**Odds Ratio (95% C.I.)**	**Estimate (S.E.)**	**Odds Ratio (95% C.I.)**	**Estimate (S.E.)**	**Odds Ratio (95% C.I.)**
Immigrants	-0.81	0.44***	-0.76	0.47*	-0.81	0.44***
	(0.20)	(0.30-0.65)	(0.30)	(0.26-0.84)	(0.21)	(0.29-0.67)
Ethnicity (Non-Caucasian)						
Caucasian	0.19	1.21	0.22	1.25	0.19	1.21
	(0.30)	(0.67-2.19)	(0.36)	(0.62-2.53)	(0.36)	(0.60-2.47)
Smoking Status (Non-Smokers)						
Current	-0.48	0.62	-0.57	0.57	-0.48	0.62
Smokers	(0.31)	(0.34-1.12)	(0.69)	(0.15-2.21)	(0.39)	(0.29-1.33)
Ex-	-0.34	0.71	-0.33	0.72	-0.34	0.71
Smokers	(0.27)	(0.41-1.22)	(0.36)	(0.36-1.45)	(0.30)	(0.40-1.28)
Second hand smoke (No)						
Yes	-0.04	0.96	-0.03	0.97	-0.05	0.96
	(0.12)	(0.76-1.20)	(0.20)	(0.66-1.42)	(0.12)	(0.76-1.21)
Time (Cycle 1)						
Cycle 5	0.38	1.46	0.37	1.45	0.37	1.45
	(0.08)	(1.24-1.72)	(0.14)	(1.10-1.90)	(0.08)	(1.23-1.71)
Cycle 4	0.40	1.49	0.39	1.48	0.40	1.49
	(0.07)	(1.29-1.72)	(0.15)	(1.11-1.98)	(0.08)	(1.27-1.74)
Cycle 3	0.32	1.38	0.32	1.38	0.32	1.38
	(0.08)	(1.19-1.60)	(0.15)	(1.04-1.84)	(0.08)	(1.18-1.60)
Cycle 2	0.11	1.11	0.10	1.11	0.11	1.11
	(0.06)	(0.99-1.26)	(0.10)	(0.92-1.34)	(0.07)	(0.98-1.27)

Table 5.8 (Cont'd)

Covariates	**Liang and Zeger (1986)**		**Rao (1998)**		**Bootstrap Method**	
	Estimate	**Odds Ratio**	**Estimate**	**Odds Ratio**	**Estimate**	**Odds Ratio**
	(S.E.)	**(95% C.I.)**	**(S.E.)**	**(95% C.I.)**	**(S.E.)**	**(95% C.I.)**
Location * Smoking						
Rural	0.43	1.54*	0.48	1.61*	0.43	1.54*
Smokers	(0.16)	(1.12-2.12)	(0.23)	(1.04-2.51)	(0.19)	(1.05-2.25)
Rural	0.36	1.44*	0.42	1.52*	0.36	1.43
Ex-Smokers	(0.18)	(1.01-2.04)	(0.20)	(1.04-2.23)	(0.20)	(0.96-2.13)
Location * SES						
High SES*	0.56	1.75*	0.60	1.83*	0.56	1.75*
Rural	(0.24)	(1.10-2.77)	(0.28)	(1.06-3.13)	(0.23)	(1.12-2.74)
Middle SES *	0.28	1.33	0.30	1.35	0.28	1.33
Rural	(0.18)	(0.93-1.88)	(0.23)	(0.86-2.10)	(0.19)	(0.92-1.93)
Ethnicity * Income						
Caucasian*	-0.72	0.49	-0.73	0.48	-0.72	0.49
High SES	(0.44)	(0.21-1.15)	(0.42)	(0.21-1.10)	(0.52)	(0.18-1.35)
Caucasian *	0.46	1.59*	0.51	1.67*	0.47	1.59
Middle SES	(0.23)	(1.01-2.52)	(0.26)	(1.00-2.80)	(0.28)	(0.92-2.75)
Second Hand Smoke *						
Time						
Exposure * Cycle 2	0.06	1.06	0.06	1.06	0.07	1.07
	(0.15)	(0.79-1.42)	(0.34)	(0.55-2.06)	(0.15)	(0.80-1.42)
Exposure * Cycle 3	0.12	1.12	0.11	1.11	0.12	1.12
	(0.13)	(0.87-1.45)	(0.30)	(0.62-2.00)	(0.13)	(0.87-1.45)
Exposure * Cycle 4	0.11	1.12	0.10	1.11	0.11	1.12
	(0.13)	(0.87-1.43)	(0.25)	(0.68-1.80)	(0.11)	(0.86-1.45)

Table 5.8 (Cont'd)

Covariates	Liang and Zeger (1986)		Rao (1998)		Bootstrap Method	
	Estimate (S.E.)	**Odds Ratio (95% C.I.)**	**Estimate (S.E.)**	**Odds Ratio (95% C.I.)**	**Estimate (S.E.)**	**Odds Ratio (95% C.I.)**
Exposure * Cycle 5	0.27	1.13*	0.27	1.31	0.27	1.31*
	(0.35)	(1.06-1.62)	(0.16)	(0.95-1.80)	(0.11)	(1.07-1.61)
Smoking * Age Group						
Smoker * 18-29	0.80	2.23*	0.92	2.51	0.80	2.23
years	(0.35)	(1.13-4.41)	(0.83)	(0.50-12.70)	(0.42)	(0.99-5.04)
Ex-Smoker *	0.44	1.55	0.42	1.52	0.44	1.55
18-29 years	(0.31)	(0.85-2.85)	(0.41)	(0.68-3.39)	(0.33)	(0.82-2.95)
Smoker * 30-49	0.29	1.34	0.40	1.50	0.29	1.34
years	(0.32)	(0.71-2.53)	(0.69)	(0.39-5.81)	(0.39)	(0.63-2.86)
Ex-Smoker *	0.37	1.44	0.37	1.44	0.37	1.44
30-49 years	(0.29)	(0.81-2.56)	(0.38)	(0.69-3.03)	(0.32)	(0.77-2.68)
Smoker *	0.46	1.58	0.57	1.77	0.46	1.59
50-64 years	(0.28)	(0.92-2.74)	(0.71)	(0.44-7.17)	(0.37)	(0.77-3.28)
Ex-Smoker *	0.38	1.46	0.42	1.52	0.38	1.46
50-64 years	(0.26)	(0.88-2.42)	(0.39)	(0.71-3.23)	(0.26)	(0.88-2.44)
Age Group * Income						
18-29 years *	-0.79	0.45*	-0.85	0.43*	-0.79	0.45*
High SES	(0.34)	(0.23-0.88)	(0.38)	(0.20-0.90)	(0.35)	(0.23-0.91)
18-29 years *	-0.30	0.74	-0.31	0.73	-0.30	0.74
Middle SES	(0.22)	(0.48-1.13)	(0.43)	(0.31-1.71)	(0.20)	(0.50-1.09)
30-49 years *	-0.97	0.38*	-1.02	0.36*	-0.97	0.38*
High SES	(0.31)	(0.21-0.69)	(0.34)	(0.18-0.70)	(0.33)	(0.20-0.72)
30-49 years *	-0.41	0.66*	-0.45	0.64	-0.41	0.66*
Middle SES	(0.18)	(0.46-0.95)	(0.36)	(0.31-1.31)	(0.17)	(0.48-0.93)

Table 5.8 (Cont'd)

Covariates	Liang and Zeger (1986)		Rao (1998)		Bootstrap Method	
	Estimate (S.E.)	**Odds Ratio (95% C.I.)**	**Estimate (S.E.)**	**Odds Ratio (95% C.I.)**	**Estimate (S.E.)**	**Odds Ratio (95% C.I.)**
50-64 years * High SES	-0.68 (0.28)	0.51* (0.29-0.88)	-0.72 (0.36)	0.49* (0.24-0.99)	-0.68 (0.30)	0.51* (0.28-0.90)
50-64 years * Middle SES	-0.19 (0.19)	0.83 (0.57-1.19)	-0.22 (0.30)	0.81 (0.45-1.45)	-0.19 (0.18)	0.83 (0.58-1.17)

Reference categories are provided in parentheses
*** p < 0.001
** p < 0.01
* p < 0.05

5.4.3.3 Predicted probability calculated for the significant effect modifiers

Mean predicted probabilities were calculated for significant interaction terms. Figure 5.2 provides the predicted probability of asthma status (yes/no) stratified by rural/urban location. The predicted probability of asthma is higher in females residing in urban area compared to rural females. At Cycle 3 (1998/99) and Cycle 5 (2001/03) the predicted probability is almost similar.

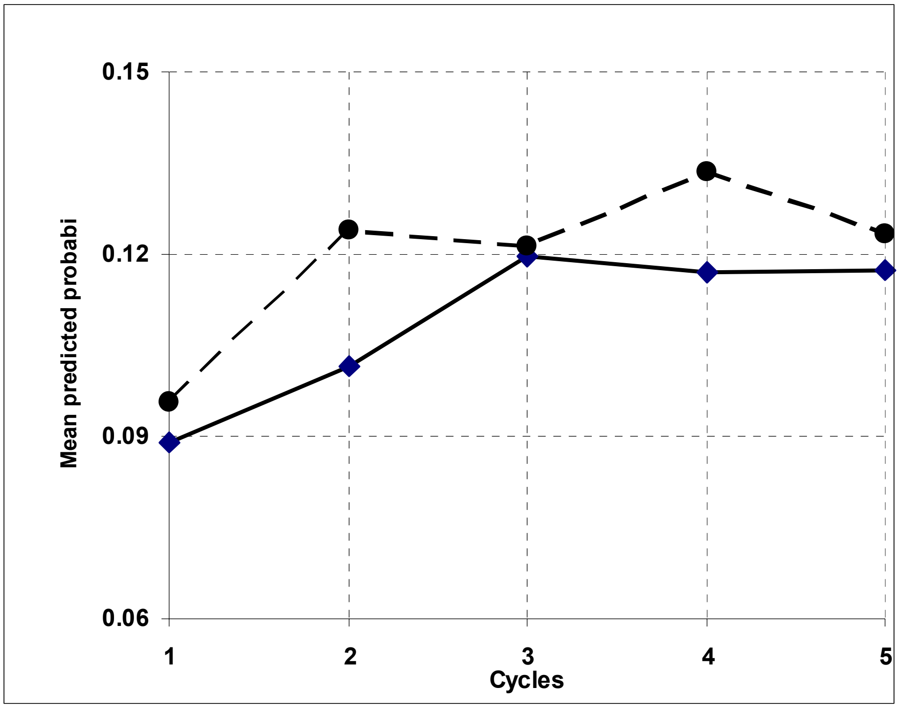


Figure 5.2 Mean predicted probability of asthma stratified by location (—— = rural; ---- = urban)

The predicted probabilities of asthma for females exposed to second hand smoke stratified by each cycle are provided in Figure 5.3. The risk of developing asthma was higher for females exposed to second hand smoke, and the risk increased from Cycle 1 to Cycle 4 and then dropped for Cycle 5. The risk of asthma was lower for the non-exposure group but it increased from Cycle 1 to Cycle 4 and then dropped slightly for Cycle 5. The increase in the mean predicted probability indicates a higher risk of asthma for females exposed to second hand smoke, and the risk increase with time.

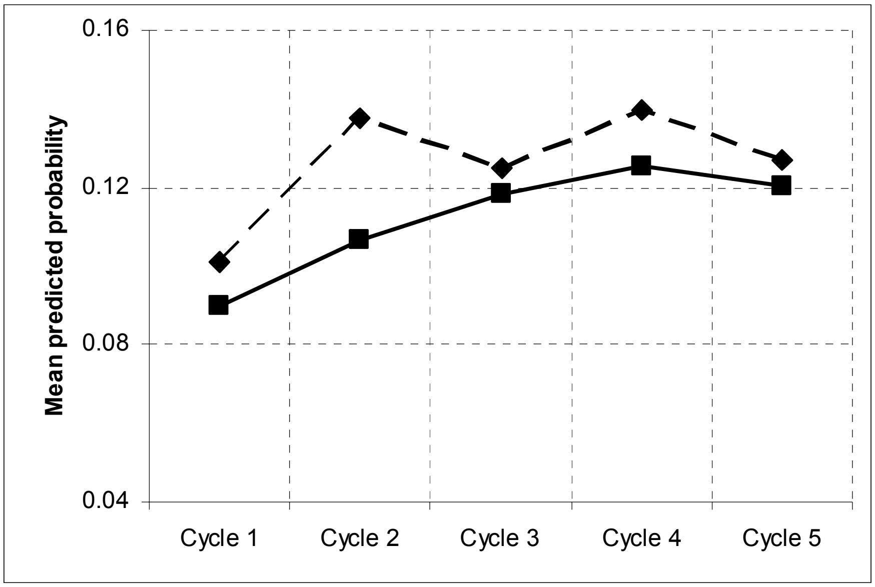


Figure 5.3 Mean predicted probability of asthma stratified by exposure to second hand smoke (---- = exposure to second hand smoke; ——= no exposure to second hand smoke)

Figure 5.4 shows the predicted probability on stratifying asthmatics females by smoking status and rural/urban location. The risk of developing asthma was highest among urban smokers compared to other categories, and it increased over time. For the ex-smoker group, the mean predicted probabilities were almost similar, and it increased steadily over time. Rural non-smokers females were at lower risk compared to the urban females for all the other categories of smoking, but the risk increased over the five study Cycles. However, the mean probability of rural non-smokers increased steadily over the study period. By the end of Cycle 5, the mean predicted probability was the same for urban smokers, rural and urban smokers, and ex-smokers.

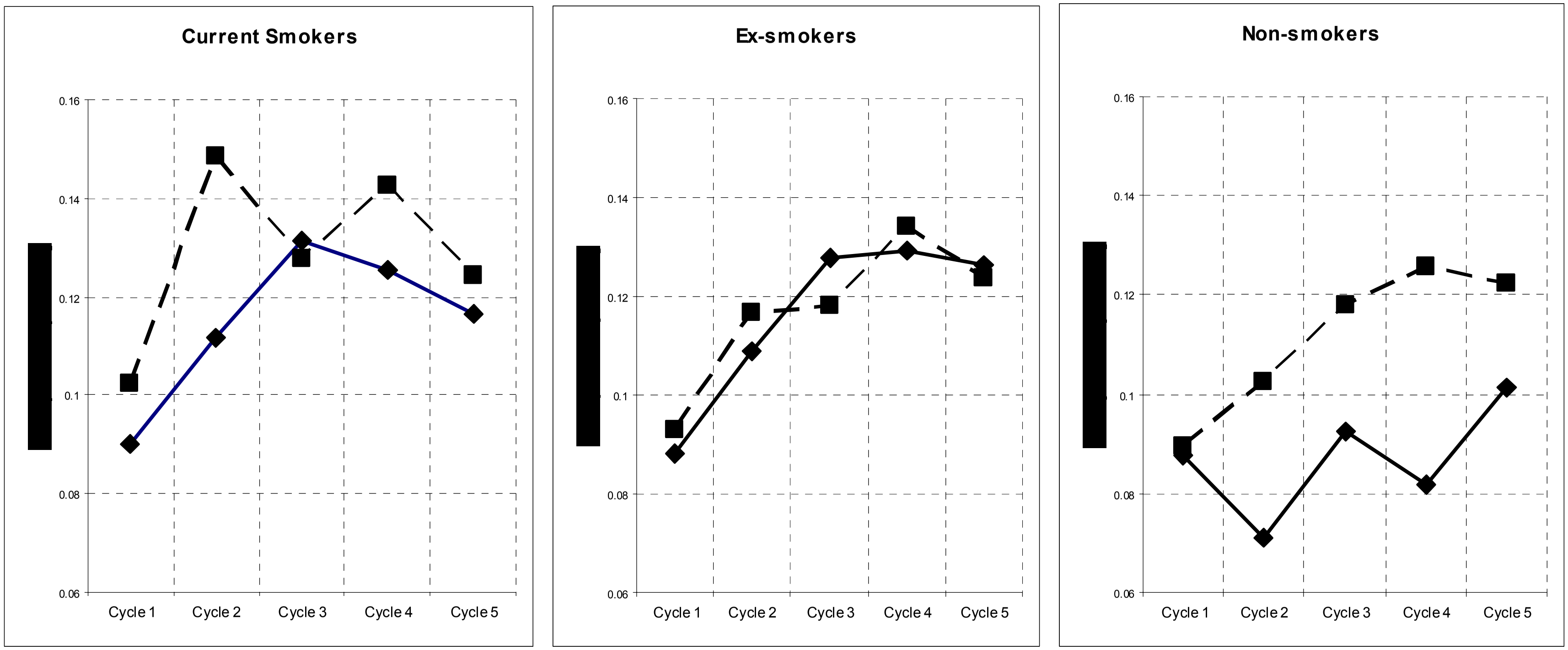


Figure 5.4 Mean predicted probability of asthma stratified by rural/urban location and smoking status (—— = rural; ------- = urban)

Predicted probabilities of socio-economic status stratified by location (rural/urban) for the five Cycles are provided in Figure 5.5. The risk of developing asthma was higher for rural females belonging to the higher socio-economic status and among urban females in the lower socio-economic status, followed by rural and urban females in the middle socio-economic status. The risk was lowest in rural females belonging to the lower socio-economic status in Cycle 1, then increasing in Cycle 2 and 3, and dropping again in Cycle 5. The risk of developing asthma increased from Cycle 1 to 4 and then decreased for Cycle 5 for high socio-economic status rural females and middle and low income females residing in urban areas.

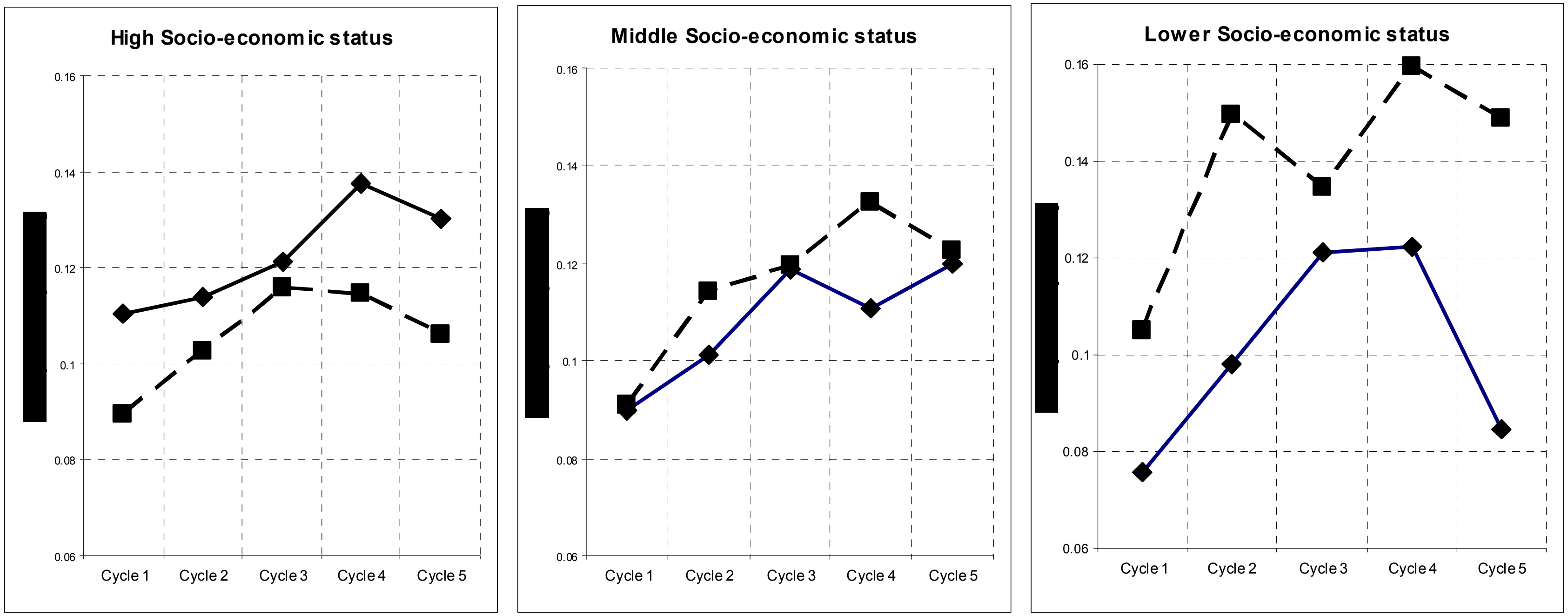


Figure 5.5 Mean predicted probability of asthma stratified by rural/urban location and socio-economic status (——= rural; ---- = urban)

The predicted probability of asthma by socio-economic status and ethnicity for each cycle is provided in Figure 5.6. Non-Caucasian females for all the three categories of income level were at lower risk of developing asthma compared to the Caucasian females, especially in the middle socio-economic status. Caucasian females belonging to the low income category were at higher risk of developing asthma, followed by middle and higher socio-economic status females, and the risk increased over time. Non-Caucasian females belonging to higher socio-economic group were at higher risk of asthma at the start of Cycle 1, but decreased over time. The risk of developing asthma increased for Caucasian females from Cycle 1 to Cycle 5 belonging to all three categories of socio-economic status.

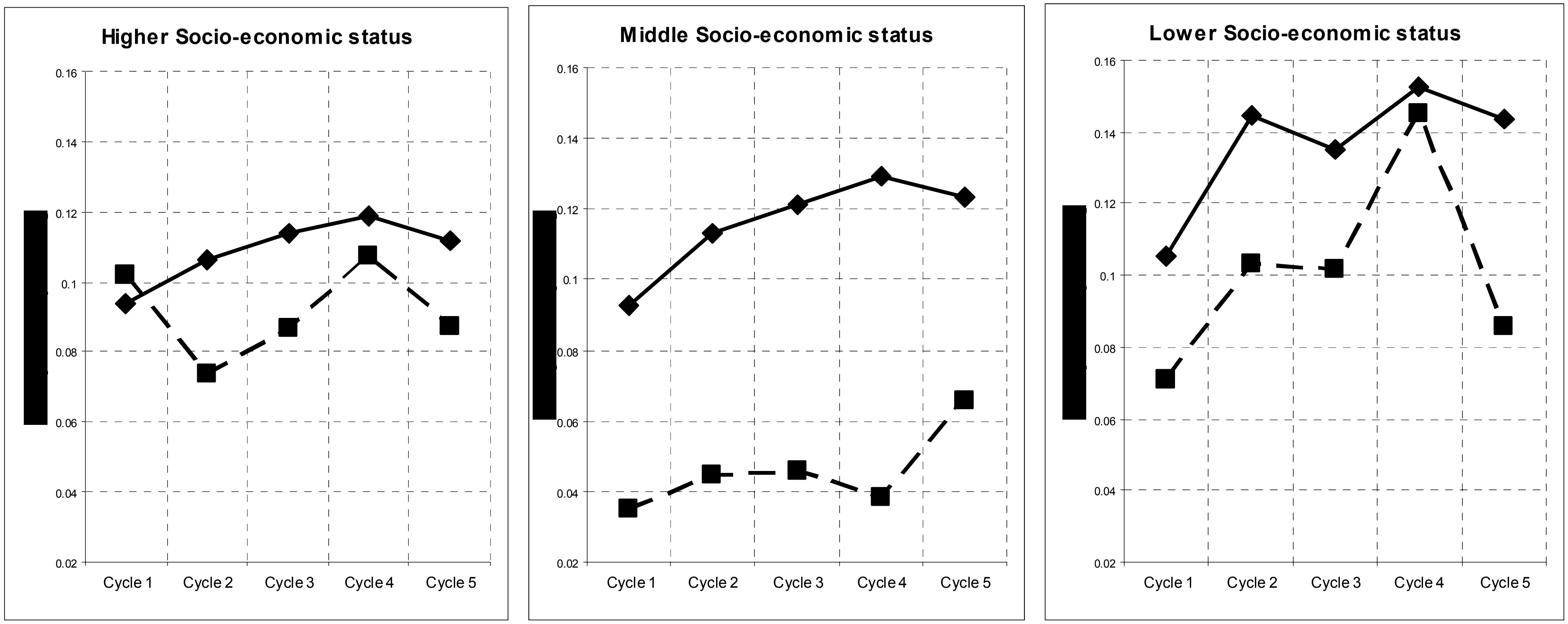


Figure 5.6 Mean predicted probability of asthma stratified by ethnicity (Caucasian/non-Caucasian) and socio-economic status (—— = Caucasian; ----=non-Caucasian)

The predicted probabilities of asthma by smoking status stratified by age groups for all the five cycles are provided in Table 5.7. Females in 18-29 years age group were at higher risk of developing asthma and this was true for all the three smoking categories. The risk among 18 to 29 years smokers increased from Cycle 1 to Cycle 4 and then decreased for Cycle 5. The mean predicted probability at the end of Cycle 5 was similar for smokers and ex-smokers in the age group 18 to 29 years, 30 to 49 years and 50 to 64 years. This was true for non-smokers in the age group 30 to 49 years and 65 to 72 years. The mean predicted probabilities increased slightly over time for non-smoker females in the age range 18 to 29 years and 50 to 64 years. These age groups, besides 65 to 72 years smokers, were at the lowest risk of having asthma. For Cycle 1, the mean predicted probability of asthma for females in the age group 65-72 years was not available as in baseline cycle all females were aged 18-64 years only.

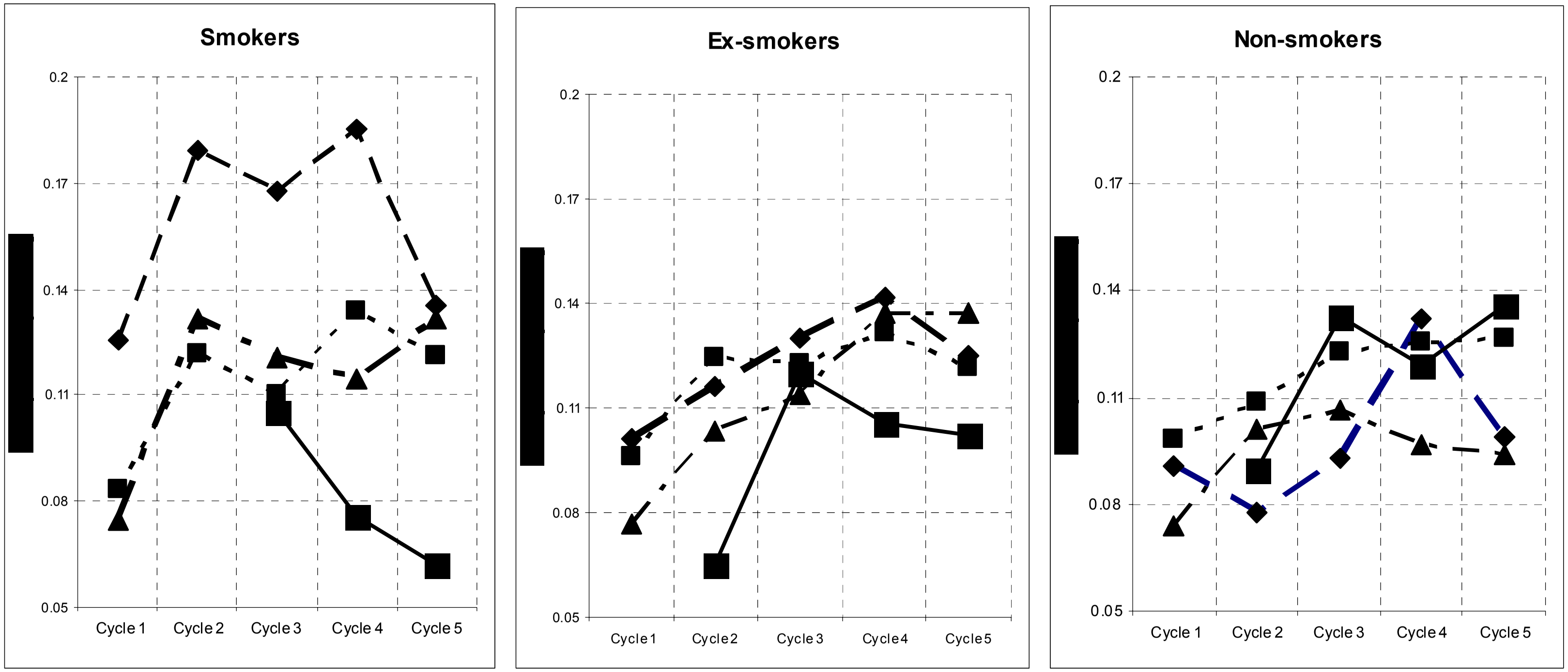


Figure 5.7 Mean predicted probability of asthma stratified by smoking status and age groups (--♦-- = 18-29 years; --■-- = 30-49 years; --▲-- = 50-64 years; ▬■▬ = 65-72 years)

The predicted probabilities of asthma by socio-economic status of different age groups are presented in Figure 5.8. Lower socio-economic status females in the age group 18 to 29 years, followed by 30-49 years and 50-64 years, were at higher risk of developing asthma. The risk, however, decreased for the 18 to 29 years age group females, but increased for 30 to 49 years and 50 to 64 years females. 65 to 72 years females belonging to a higher income level group were at a higher risk of developing asthma. Except for low and middle socio-economic status females in the age range 18 to 29 years, females in all other categories showed an increase in the risk over time. The risk of developing asthma increased from Cycle 1 to Cycle 5 for all the three income level for females aged 50-64 years.

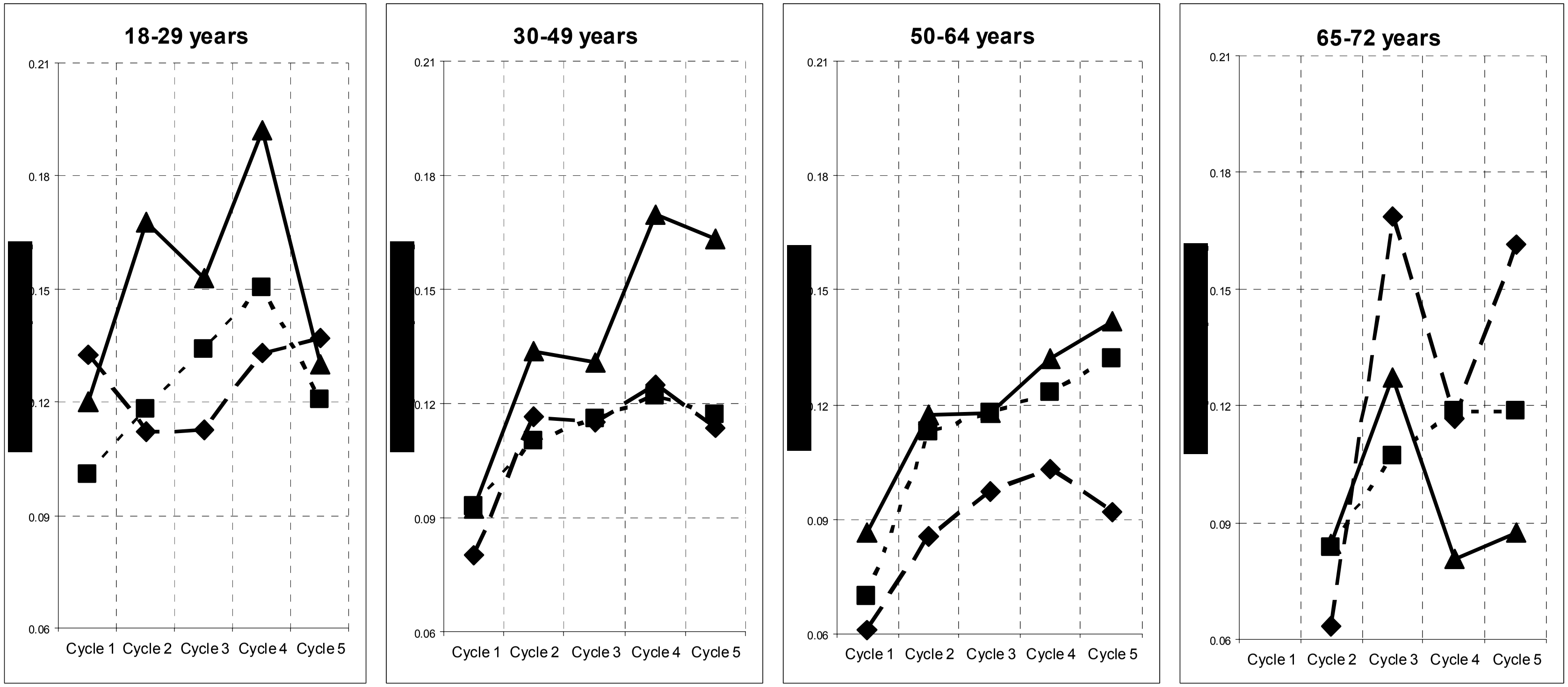


Figure 5.8 Mean predicted probability of asthma stratified by socio-economic status and age group (--♦-- = high income; --■-- = middle income; —▲— = low income)

5.5 Objective 2: Incidence analysis

5.5.1 Crude incidence rate calculation

The crude incidence rate was calculated using two methods: incidence density rate and cumulative incidence rate. In the incidence analysis, the focus was on self reported newly diagnosed health professionals who diagnosed asthma cases over the ten year study period. For the current analysis, asthma free females at the start of Cycle 1 were selected. Another reason for focusing on only asthma free individuals was that no prior information was available for those individuals who had already reported asthma in Cycle 1. Hence, the subset chosen for the purpose of analysis of the dataset contains only asthma free individuals at Cycle 1 (1994-95).

Table 5.9 provides the incident cases of asthma stratified by each cycle. The results show that in this closed population there was a decrease in the incidence of asthma over time. At the end of cycle 5, there were 3649 censored cases.

Table 5.9 New asthma cases stratified by Cycles

Cycles/waves	Event/ new cases	Censored cases	Total
Cycle 2 (1996-97)	128	3849	3977
Cycle 3 (1998-99)	90	3759	3849
Cycle 4 (2000-01)	62	3697	3759
Cycle 5 (2002-03)	48	3649	3697
Total	328	14954	15282

5.5.1.1 Incidence density rate

Table 5.10 provides the weighted and unweighted incidence rates per 1000 for all the covariates included in the final model. The overall incidence rate is also reported in this table. The weighted and unweighted incidence rates were very similar, except for the categories of underweight and obese category in the BMI covariate and the category of chronic bronchitis/emphysema. The 95% confidence intervals for the weighted analysis were slightly wider than the unweighted analysis. The results stratified by cycles could not be presented as the cell counts were very small and could not be reproduced for publication[22].

The incidence density rate of asthma decreased from 16/1000/year in Cycle 2 to 6.4/1000/year at the end of Cycle 5, and the overall incidence rate was 10.5/1000/year. Obese females had the highest incidence rate which was about 14/1000/year, followed by over weight (11/1000/year) and normal weight (10/1000/year) females. The incidence density rate was very high for food allergy, other kinds of allergies, chronic bronchitis and stomach/intestinal problems. The incidence density rate of asthma was about 69/1000/year for females diagnosed with chronic bronchitis or emphysema.

Females belonging to lower socio-economic groups had the highest incidence density rate (13/1000/year), followed by middle socio-economic group (10/1000/year). The incidence density rate of asthma stratified by location was 10% per 1000 per person years for both rural and urban females. The incidence rate of asthma was highest among young females who were in the 18 to 29 years age group and was 16/1000/year, followed by 50 to 64 years and 65 to 72 years old females (10/1000/year).

[22] Please refer to Appendix B (8.2.1)

The region of Quebec had the highest incidence density rate of asthma of about 12/1000/year, followed by Atlantic, British Columbia and Ontario region. When stratifying by immigration status, females who were Canadian citizens had the highest incidence rate of asthma, which was about 11.4/1000/year compared to others.

Caucasian females had the higher asthma incidence rate (11/1000/year) compared to non- Caucasian. Smokers and ex-smokers females had almost similar asthma incidence rate which was about 11/1000/year, and in non-smokers females the rate was about 8.6/1000/year. The incidence density rate of asthma was 14/1000/year among the females who reported exposure to second hand smoke and in the non-exposed group the incidence rate was 9.0/1000/year.

Table 5.10 Weighted and unweighted analysis of Incidence density rates (per 1000 person years) of asthma stratified by Cycle and each categorical covariate

Covariates	Weighted Analysis		Unweighted analysis	
	Rate	**95% C.I.**	**Rate**	**95% C.I.**
Time				
Cycle 2 (1996-97)	16.0	13.1-19.9	16.1	13.5-19.1
Cycle 3 (1998-99)	11.4	8.7-15.1	11.7	9.5-14.4
Cycle 4 (2000-01)	7.8	5.9-10.7	8.2	6.4-10.6
Cycle 5 (2002-03)	6.4	4.6-9.1	6.5	4.9-8.6
BMI				
Underweight	5.5	2.2-17.0	8.9	4.5-17.9
Normal weight	9.9	8.3-12.1	9.4	8.1-11.0
Over weight	10.9	8.5-14.2	11.4	9.3-14.0
Obese	13.8	10.2-19.1	15.0	11.7-19.3
Food Allergy				
Yes	24.2	18.2-32.9	24.5	19.2-31.3
No	9.3	8.0-10.8	9.4	8.4-10.7
Other Allergy				
Yes	21.2	17.9-25.4	20.6	17.8-23.8
No	6.3	5.1-7.7	6.8	5.8-8.0
Bronchitis				
Yes	68.9	49.1-99.9	62.1	45.5-84.7
No	9.4	8.1-10.8	9.6	8.6-10.8
Intestinal Problems				
Yes	24.8	14.9-44.4	23.1	15.2-35.1
No	10.1	8.8-11.6	10.3	9.2-11.6
Socio-economic status				
Low Income	13.2	9.4-19.2	14.6	11.2-19.0
Middle Income	10.1	8.6-12.1	10.2	8.9-11.8
High Income	9.0	6.7-12.6	8.5	6.5-11.2
Location (Rural/Urban)				
Rural	10.1	7.5-13.9	9.3	7.3-11.7
Urban	10.6	9.2-12.3	11.2	9.9-12.7
Age Group (years)				
18-29 years	14.2	11.1-18.4	14.7	11.9-18.2
30-49 years	9.0	6.5-12.9	8.9	6.8-11.7
50-64 years	9.8	7.7-12.5	10.4	8.6-12.6
65-72 years	10.0	7.8-13.2	9.7	7.9-11.9
Region				
Atlantic	10.6	8.2-13.9	9.9	7.9-12.4
Quebec	11.7	8.8-15.7	10.8	8.4-14.0
Prairie	9.8	7.6-12.9	10.5	8.4-13.2
British Columbia	10.0	6.9-15.0	11.3	8.0-15.9
Ontario	10.1	8.0-13.0	11.3	9.2-14.1

Table 5.10 Cont'd

Covariates	Weighted Analysis		Unweighted analysis	
	Rate	**95% C.I.**	**Rate**	**95% C.I.**
Immigration status				
Immigrants	6.4	4.1-10.6	6.5	4.4-9.7
Citizen	11.4	9.9-13.1	11.3	10.1-12.6
Ethnicity				
White	10.9	9.6-12.5	10.8	9.7-12.1
Non-white	6.6	3.6-13.4	10.0	6.2-16.0
Smoking Status				
Current Smokers	11.9	9.4-15.3	12.9	10.6-15.7
Ex-Smokers	11.8	9.5-14.7	11.3	9.5-13.5
Non-Smokers	8.6	6.8-11.1	8.7	7.1-10.6
Second Hand Smoke				
Exposure	14.4	11.7-17.9	14.8	12.5-17.5
No Exposure	9.0	7.6-10.7	9.1	7.9-10.4
Overall	10.5	9.2-12.1	10.7	9.6-12.0

5.5.1.2 Crude rate ratio using STMH command

The ratio of the rates also mentioned as crude rate ratio between the two groups was calculated using the STMH command in STATA software. The rate ratio was calculated for all the important risk factors or covariates with respect to the reference category. Both weighted and unweighted rate ratio and their corresponding 95% confidence interval are provided in Table 5.11.

The rate ratio obtained from the weighted and unweighted analysis, were different from each other. For the weighted analysis the survey weights were used. In STMH command when the sampling weights are included, the 95% confidence intervals are calculated using the jackknife method. The results using the two methods were different, especially for some covariates. These variables included body mass index, other allergies, emphysema, intestinal problems, region and ethnicity. The 95%

confidence intervals for the weighted analysis were very tight causing in higher significance level for all covariates in the model.

The results show that there was a strong positive association incidence of asthma in females with the covariates obesity, food allergies, other types of allergies, chronic bronchitis, intestinal problems, females in 18-29 years age group, current smokers and exposure to second hand smoke when considered separately. A negative association of asthma incidence was observed for the covariates socio-economic status and females who were non Canadian citizens.

Table 5.11 Crude stratified rate ratio of asthma incidence for covariates/risk factor using the STMH command in STATA

Covariates	Weighted Analysis		Unweighted Analysis	
	Rate Ratio	**95% C.I.**	**Rate Ratio**	**95% C.I.**
BMI (Normal weight)				
Under weight	0.55***	0.54-0.56	0.95	0.47-1.93
Over weight	1.09***	1.09-1.10	1.21	0.94-1.57
Obese	1.39***	1.38-1.40	1.59**	1.19-2.14
Food Allergy (No)				
Yes	2.60***	2.58-2.62	2.60***	1.97-3.41
Other Allergy (No)				
Yes	3.39***	3.37-3.41	3.00***	2.42-3.73
Bronchitis (No)				
Yes	7.35***	7.28-7.41	6.45***	4.63-8.98
Intestinal Problem (No)				
Yes	2.46***	2.43-2.48	2.23***	1.45-3.44
Socio-economic status (Low Income)				
Middle Income	0.68***	0.68-0.69	0.58**	0.40-0.85
High Income	0.77***	0.76-0.77	0.70*	0.52-0.94
Location (Urban)				
Rural	0.95***	0.95-0.96	0.83	0.64-1.08
Age Group (65-72 years)				
18-29 years	1.41***	1.40-1.42	1.52**	1.13-2.04
30-49 years	0.90***	0.89-0.91	0.92	0.65-1.29
50-64 years	0.97***	0.97-0.98	1.07	0.80-1.42
Region (Ontario)				
Atlantic	1.04***	1.03-1.05	0.88	0.64-1.19
Quebec	1.15***	1.14-1.16	0.95	0.68-1.33
Prairie	0.97***	0.96-0.98	0.92	0.68-1.26
British Columbia	0.98**	0.97-0.99	0.99	0.67-1.49
Immigration (Citizen)				
Others	0.56***	0.55-0.56	0.58**	0.38-0.88
Ethnicity (Non-white)				
White	1.65***	1.63-1.67	1.08	0.66-1.76
Smoking Status (Non-Smokers)				
Current Smokers	1.38***	1.37-1.39	1.49**	1.13-1.96
Ex-Smokers	1.37***	1.36-1.37	1.30	0.99-1.69
Second hand smoke (No)				
Yes	1.61***	1.60-1.62	1.63***	1.30-2.03

Reference categories are specified in parentheses
*** p<0.001
**p<0.01
*p<0.05

5.5.2 Proportional hazard regression models

To examine the effect of risk factors or covariates on incidence of asthma discrete version of the proportional hazard regression model was used. Table 5.12 summarizes the different methods and STATA commands were used to fit the discrete and Cox proportional hazard model. Various STATA commands used for calculating the incidence density and the stratified rate ratio are also summarized in this table.

Table 5.12 Methods and the STATA command used to achieve objective 2

Methods	**Parameter estimates and standard errors**	**STATA Command**	**Tables**
Incidence Density	Weighted	STPTIME	5.10
	Unweighted	STPTIME	5.10
Crude Rate ratio	Weighted	STMH	5.11
	Unweighted	STMH	5.11
Discrete Proportional Hazard Model	Weighted	GLM	5.13*, 5.15**
	Robust	RGLM	5.13*, 5.15**
	Unweighted	G LM	5.14*, 5.16**
Cox's proportional hazard model	Weighted	STCOX	5.13*, 5.15**
	Robust	Robust option	5.13*, 5.15**
	Unweighted	STCOX	5.14*, 5.16**

* Unadjusted hazard rate
** Adjusted hazard rate

Table 5.13 provides the weighted and robust standard error unadjusted hazard rate (rate ratio) and standard errors for discrete and Cox proportional hazard model. At the bivariate level, the proportionality hazard assumption was satisfied for all the covariates. The weighted and robust hazard ratios, as well as the standard errors for the Cox proportional hazard model were different, especially for the covariates BMI, other allergies, bronchitis, region and ethnicity. The standard errors for the weighted analysis were larger than the robust analysis.

For the Cox proportional hazard model, the weighted and robust hazard ratio and the corresponding standard errors were different. The standard errors for the weighted analysis were larger than the robust analysis.

On comparing the weighted (robust) discrete and Cox proportional hazard model, the results were similar. The standard error obtained using the weighted discrete proportional hazard models were larger than the Cox proportional hazard model. All the covariates provided in Table 5.13 were significant at p<0.25 level, hence in the final model all these covariates were included.

Table 5.13 Discrete and Cox's proportional hazard model (Robust standard error), unadjusted hazard ratio of covariates/risk factors

Covariates	Discrete Proportional Hazard Model		Cox's Proportional Hazard Model	
	Hazard Ratio (Weighted S.E.)	**Hazard Ratio (Robust S.E.)**	**Hazard Ratio (Weighted S.E.)**	**Hazard Ratio (Robust S.E.)**
BMI (Normal weight)				
Under weight	0.54 (0.25)	0.95 (0.35)	0.55 (0.25)	0.95 (0.34)
Over weight	1.09 (0.18)	1.22 (0.16)	1.09 (0.18)	1.21 (0.16)
Obese	1.40 (0.26)	1.61 (0.24)**	1.38 (0.25)	1.59 (0.23)**
Food Allergy (No)				
Yes	2.51 (0.43)***	2.52 (0.36)***	2.67 (0.44)***	2.67 (0.36)***
Other Allergy (No)				
Yes	3.35 (0.47)***	2.97 (0.33)***	3.44 (0.47)***	3.05 (0.33)***
Bronchitis (No)				
Yes	8.55 (1.81)***	7.21 (1.28)***	6.84 (1.33)***	6.16 (0.98)***
Intestinal Problem (No)				
Yes	2.52 (0.71)**	2.31 (0.52)***	2.43 (0.65)**	2.20 (0.47)***
Socio-economic status (Low Income)				
Middle Income	0.56 (0.13)*	0.47 (0.09)***	0.81 (0.19)	0.69 (0.13)
High Income	0.71 (0.14)	0.64 (0.10)**	0.80 (0.16)	0.74 (0.11)*
Location (Urban)				
Rural	0.92 (0.16)	0.81 (0.11)	0.98 (0.17)	0.84 (0.11)
Age Group (65-72 years)				
18-29 years	1.72 (0.32)**	1.86 (0.28)***	1.22 (0.23)	1.32 (0.20)
30-49 years	1.03 (0.23)	1.03 (0.18)	0.81 (0.18)	0.84 (0.14)
50-64 years	1.00 (0.18)	1.11 (0.16)	0.95 (0.17)	1.04 (0.15)
Region (Ontario)				
Atlantic	1.05 (0.19)	0.88 (0.14)	1.04 (0.19)	0.87 (0.14)
Quebec	1.16 (0.22)	0.95 (0.16)	1.15 (0.22)	0.95 (0.16)
Prairie	0.96 (0.17)	0.92 (0.15)	0.97 (0.18)	0.93 (0.14)

Table 5.13 (Cont'd)

Covariates	Discrete Proportional Hazard Model		Cox's Proportional Hazard Model	
	Hazard Ratio (Weighted S.E.)	**Hazard Ratio (Robust S.E.)**	**Hazard Ratio (Weighted S.E.)**	**Hazard Ratio (Robust S.E.)**
British Columbia	0.99 (0.23)	1.01 (0.21)	0.98 (0.22)	0.99 (0.20)
Immigration (Citizen)				
Immigrants	0.55 (0.14)*	0.57 (0.12)**	0.56 (0.14)*	0.58 (0.12)*
Ethnicity (Non-white)				
White	1.69 (0.54)	1.11 (0.28)	1.62 (0.52)	1.06 (0.26)
Smoking Status (Non-Smokers)				
Current Smokers	1.40 (0.24)	1.52 (0.21)**	1.37 (0.24)	1.47 (0.20)**
Ex-Smokers	1.28 (0.21)	1.22 (0.16)	1.44 (0.24)*	1.37 (0.18)*
Second hand smoke (No)				
Yes	1.79 (0.25)***	1.81 (0.21)***	1.49 (0.20)**	1.52 (0.17)***

Reference categories are provided in parentheses
*** p<0.001
**p<0.01
*p<0.05

Table 5.14 provides the model-based or unweighted unadjusted hazard ratios and standard errors for the discrete and Cox's proportional hazard model. The proportionality hazard assumption for all the covariates at a bivariate level was satisfied. The hazard ratio and the standard errors were very similar using these two methods, the hazard ratio and standard error of the unweighted analysis were very similar to the unadjusted robust analysis (Table 5.13). For the model-based case, the discrete and Cox proportional hazard model were similar, with slightly large standard errors obtained using the first method. All the covariates (Table 5.14) for the model-based analysis were highly significant.

Table 5.14 Model-based Discrete and Cox's proportional hazard model; unadjusted hazard ratio of covariates/risk factors

Covariates	Discrete Proportional Hazard Model	Cox's Proportional Hazard Model
	Hazard Ratio (S.E.)	**Hazard Ratio (S.E.)**
BMI (Normal weight)		
Under weight	0.95 (0.34)	0.95 (0.34)
Over weight	1.22 (0.16)	1.21 (0.16)
Obese	1.61 (0.24)**	1.59 (0.24)**
Food Allergy (No)		
Yes	2.52 (0.35)***	2.67 (0.37)***
Other Allergy (No)		
Yes	2.97 (0.33)***	3.05 (0.34)***
Bronchitis (No)		
Yes	7.21 (1.22)***	6.16 (1.04)***
Intestinal Problem (No)		
Yes	2.31 (0.51)***	2.20 (0.48)***
Socio-economic status (Low Income)		
Middle Income	0.47 (0.09)***	0.69 (0.13)
High Income	0.64 (0.10)**	0.74 (0.11)
Location (Urban)		
Rural	0.81 (0.11)	0.84 (0.11)
Age Group (65-72 years)		
18-29 years	1.86 (0.28)***	1.32 (0.20)
30-49 years	1.03 (0.18)	0.84 (0.15)
50-64 years	1.11 (0.16)	1.04 (0.15)
Region (Ontario)		
Atlantic	0.88 (0.14)	0.87 (0.14)
Quebec	0.96 (0.16)	0.95 (0.16)
Prairie	0.92 (0.15)	0.93 (0.15)
British Columbia	1.01 (0.21)	0.99 (0.20)
Immigration (Citizen)		
Others	0.57 (0.12)**	0.58 (0.12)*
Ethnicity (Non-Caucasian)		
Caucasian	1.11 (0.27)	1.06 (0.26)
Smoking Status (Non-Smokers)		
Current Smokers	1.52 (0.21)**	1.47 (0.21)**
Ex-Smokers	1.22 (0.16)	1.37 (0.18)*
Second hand smoke (No)		
Yes	1.81 (0.20)***	1.52 (0.17)***

Reference categories are provided in parentheses
*** p<0.001
**p<0.01; *p<0.05

The adjusted hazard ratios and 95% confidence interval for the weighted and robust analysis using discrete and Cox's proportional model are provided in Table 5.15. The proportionality hazard assumption of covariates included in the final model was satisfied for weighted, unweighted and the robust analysis. The weighted and robust analyses for discrete and Cox proportional hazard model were very different from each other, with weighted analysis providing larger standard errors.

The hazard ratio and the corresponding standard errors were similar for the weighted (robust) analysis for discrete and Cox proportional hazard models, with the exception of some of the covariates. The standard errors for the discrete proportional hazard model were larger than the Cox's model. The significance level of the covariates was also differed based on the standard errors.

Table 5.15 Discrete and Cox's proportional hazard model (Robust standard error), adjusted hazard ratio of covariates/risk factors

Covariates	**Discrete Proportional Hazard Model**		**Cox's Proportional Hazard Model**	
	Hazard Ratio (Weighted S.E.)	**Hazard Ratio (Robust S.E.)**	**Hazard Ratio (Weighted S.E.)**	**Hazard Ratio (Robust S.E.)**
BMI (Normal weight)				
Under weight	0.51 (0.26)	0.83 (0.33)	0.53 (0.25)	0.85 (0.33)
Over weight	1.37 (0.25)	1.43 (0.21)*	1.26 (0.22)	1.34 (0.19)*
Obese	1.40 (0.29)	1.65 (0.28)**	1.39 (0.27)	1.64 (0.26)**
Food Allergy (No)				
Yes	1.66 (0.35)*	1.72 (0.28)**	1.82 (0.34)**	1.78 (0.27)***
Other Allergy (No)				
Yes	3.04 (0.47)***	2.49 (0.31)***	3.09 (0.47)***	2.51 (0.30)***
Bronchitis (No)				
Yes	7.25 (1.68)***	5.87 (1.20) ***	5.90 (1.18)***	5.13 (0.88)***
Intestinal Problem (No)				
Yes	1.79 (0.58)	1.80 (0.46)*	1.95 (0.58)*	1.84 (0.42)**
Socio-economic status (Low Income)				
Middle Income	0.67 (0.18)	0.58 (0.12)*	0.97 (0.24)	0.83 (0.17)
High Income	0.87 (0.18)	0.79 (0.13)	0.96 (0.19)	0.90 (0.14)
Location (Urban)				
Rural	0.96 (0.19)	0.79 (0.12)	1.04 (0.19)	0.85 (0.12)
Age Group (65-72 years)				
18-29 years	2.11 (0.45)***	2.24 (0.39)***	1.47 (0.30)	1.53 (0.25)**
30-49 years	1.18 (0.29)	1.23 (0.24)	0.94 (0.22)	1.00 (0.18)
50-64 years	1.09 (0.23)	1.20 (0.20)	1.01 (0.20)	1.11 (0.17)

Table 5.15 (Cont'd)

Covariates	**Discrete Proportional Hazard Model**		**Cox's Proportional Hazard Model**	
	Hazard Ratio (Weighted S.E.)	**Hazard Ratio (Robust S.E.)**	**Hazard Ratio (Weighted S.E.)**	**Hazard Ratio (Robust S.E.)**
Region (Ontario)				
Atlantic	0.76 (0.16)	0.68 (0.12)*	0.81 (0.16)	0.71 (0.12)
Quebec	0.91 (0.20)	0.80 (0.16)	0.99 (0.20)	0.87 (0.16)
Prairie	0.74 (0.15)	0.74 (0.13)	0.78 (0.15)	0.78 (0.13)
British Columbia	1.15 (0.28)	1.11 (0.24)	1.12 (0.27)	1.10 (0.22)
Immigration (Citizen)				
Immigrants	0.62 (0.17)	0.61 (0.16)	0.61 (0.17)	0.58 (0.15)*
Ethnicity (Non-white)				
White	1.21 (0.45)	1.01 (0.32)	1.03 (0.36)	0.85 (0.25)
Smoking Status (Non-Smokers)				
Current Smokers	0.60 (0.14)*	0.68 (0.13)	0.73 (0.16)	0.79 (0.15)
Ex-Smokers	1.04 (0.18)	1.03 (0.15)	1.19 (0.20)	1.14 (0.16)
Second hand smoke (No)				
Yes	2.20 (0.45)***	2.20 (0.39)***	1.73 (0.34)**	1.78 (0.30)**

Reference categories are provided in parentheses
*** p<0.001
**p<0.01
*p<0.05

Table 5.16 presents the model-based (unweighted) hazard ratio and standard errors using discrete and Cox's proportional hazard model when all the covariates or risk factors are included in the model. As previously noted, the model-based hazard ratio and standard errors using discrete and Cox proportional hazard was similar to the robust analysis (Table 5.15), with standard errors slightly larger than the robust analysis.

Table 5.16 Model-based adjusted hazard ratio Discrete and Cox's proportional hazard model of covariates/risk factors

Covariates	**Discrete Proportional Hazard Model**	**Cox's Proportional Hazard Model**
	Rate (S.E.)	**Rate (S.E.)**
BMI (Normal weight)		
Under weight	0.83 (0.32)	0.85 (0.33)
Over weight	1.43 (0.20)*	1.34 (0.19)*
Obese	1.65 (0.27)**	1.64 (0.26)**
Food Allergy (No)		
Yes	1.72 (0.27)***	1.78 (0.28)***
Other Allergy (No)		
Yes	2.49 (0.31)***	2.51 (0.31)***
Bronchitis (No)		
Yes	5.87 (1.06)***	5.13 (0.93)***
Intestinal Problem (No)		
Yes	1.80 (0.42)*	1.84 (0.43)*
Socio-economic status (Low Income)		
Middle Income	0.58 (0.12)**	0.83 (0.17)
High Income	0.79 (0.12)	0.90 (0.14)
Location (Urban)		
Rural	0.79 (0.12)	0.85 (0.13)
Age Group (65-72 years)		
18-29 years	2.24 (0.38)***	1.53 (0.26)*
30-49 years	1.23 (0.23)	1.00 (0.19)
50-64 years	1.20 (0.19)	1.11 (0.18)
Region (Ontario)		
Atlantic	0.68 (0.12)*	0.71 (0.12)
Quebec	0.80 (0.15)	0.87 (0.16)
Prairie	0.74 (0.13)	0.78 (0.13)
British Columbia	1.11 (0.23)	1.09 (0.23)
Immigration (Citizen)		
Others	0.61 (0.15)*	0.56 (0.14)*
Ethnicity (Non-Caucasian)		
Caucasian	1.01 (0.29)	0.85 (0.24)
Smoking Status (Non-Smokers)		
Current Smokers	0.68 (0.13)	0.79 (0.16)
Ex-Smokers	1.03 (0.15)	1.14 (0.16)
Second hand smoke (No)		
Yes	2.20 (0.37)***	1.78 (0.30)**

Reference categories are provided in parentheses
*** p<0.001
**p<0.01
*p<0.05

Since a complex survey data set was used and it is recommended that the weight variable should be used in order to get proper estimates and standard errors, hence the weighted discrete and Cox's proportional hazard model was interpreted (Table 5.15).

When adjusted for other covariates in the model, the hazard ratio of asthma incidence decreased for underweight females by 49%, increased by 1.4 times in over weight and obese females compared to normal weight females. However, BMI was not a significant predictor of asthma incidence.

The hazard ratio of asthma was 1.8 times higher in females who had food allergies compared to those who did not. The hazard ratio was 3 times higher in females diagnosed with any other kind of allergy and 7 times higher in females diagnosed with chronic bronchitis or emphysema, compared to undiagnosed ($p<0.05$). Asthma incidence was 2 times higher in females diagnosed with intestinal problems compared to females with no intestinal problems. However, the increased risk was not statistically significant.

Asthma incidence decreased by 33% in the middle socioeconomic group and by 13% in highest socioeconomic group, compared to the lowest socioeconomic group. For rural females, the risk of asthma was almost equal to 1, showing that there was no difference in the hazard ratio of rural or urban females.

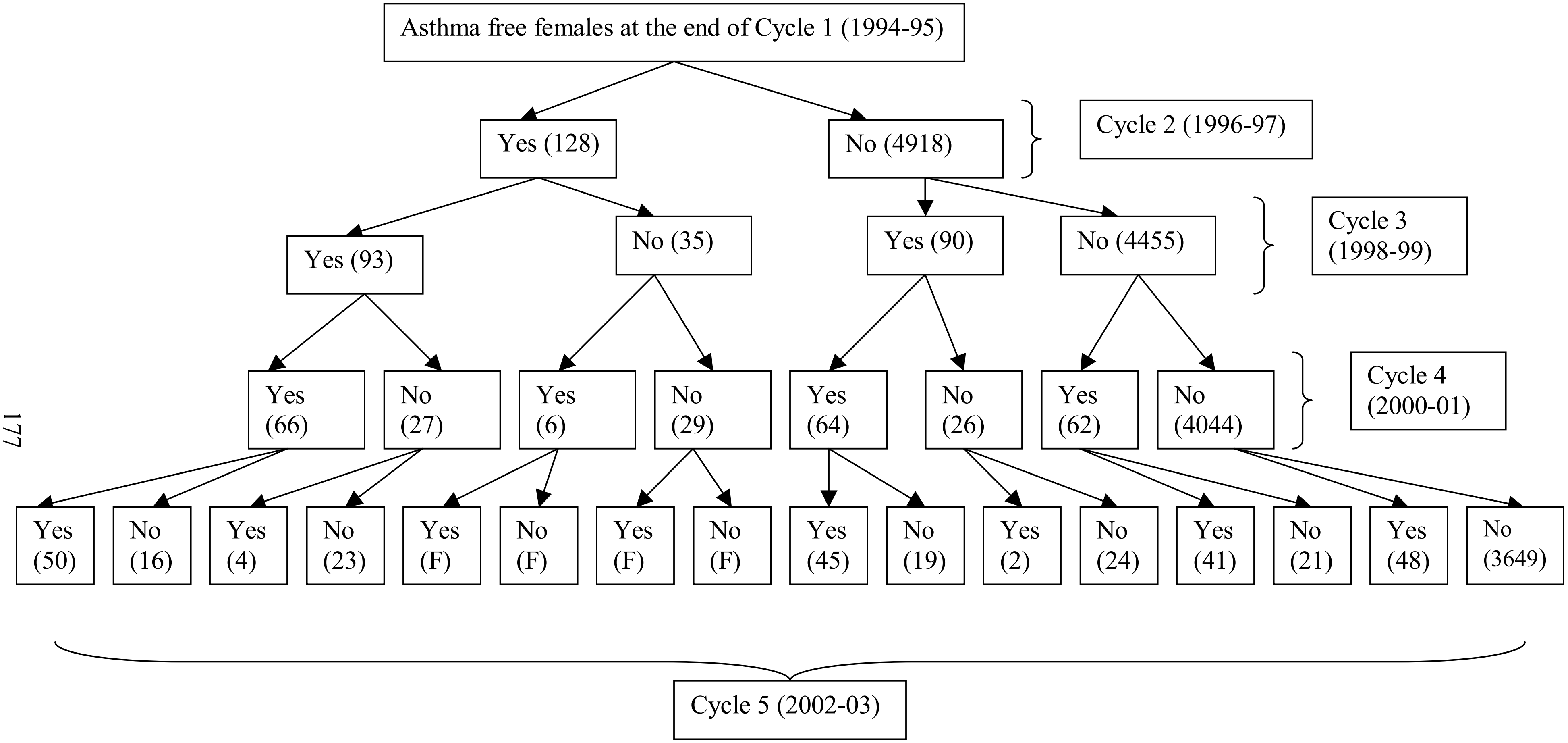
When studied by age group, the risk of asthma was 2 times higher in the 18 to 29 year age group, 1.2 times higher in the 30 to 49 year age group, and 1.1 times higher in the 50 to 64 year age group, compared to the 65 to 72 year age group. The increase in the risk was statistically significant, except for the 50 to 64 years age group.

Current smokers showed a significant decrease of 40% in the risk of asthma incidence, compared to non-smokers. Among ex-smokers, the risk was unity indicating that there was no risk associated between asthma incidences and being an ex-smoker. The risk of asthma was 2.2 times higher in females exposed to second hand smoke compared to the non-exposed females, and this increase was statistically significant at $p<0.0001$. There were no statistically significant findings between asthma incidence and region of residence or ethnicity.

5.6 Objective 3: Variance corrected and frailty models

The primary aim of the third objective was to compare the variance corrected and frailty models for recurrent event data. To perform the survival analysis, the data set were modified so that variance corrected and frailty modeling approach could be fitted. The asthma definition used was "Do you have asthma diagnosed by a physician?" All those females were included in the study who had answered 'no' to the above question in Cycle 1. Females who had answered yes to the above question were not included in the study as information was not available regarding whether this was recurrent asthma attack they had, or if they were experiencing asthma for the first time.

Descriptive analysis was conducted to study the recurrence of asthma over the ten year study period. Figure 5.9 shows the frequency distribution of asthma cases for each cycle and provides the number of individuals who experienced asthma episodes and individuals who reported no asthma. At the end of Cycle 2, it was further sub-divided into two groups, one who experienced asthma episodes and other who did not. By the end of Cycle 3 those who experienced asthma episodes were further subdivided into those who experienced asthma recurrence and those who did not experience recurrence in Cycle 3. Those without asthma were also subdivided into two categories. Similar sub-division was conducted for Cycles 4 and 5. The diagrammatic representation is provided in Figure 5.9.



F- Results were flagged, as the cell counts were very small

Figure 5.9 Frequency distribution of asthma recurrence in females from Cycle 2 to Cycle 5

5.6.1 Fitting variance corrected models

Table 5.17 provides the recurrent episodes of asthma for each cycle. There were 83 first episodes of recurrence, 69 cases of second recurrence, followed by 62 cases of third recurrent episodes of asthma and 56 fourth episodes of asthma.

Table 5.17 Distribution of first and subsequent episodes of asthma and censoring during the follow-up time

Follow-up	Event	Censored cases	Total
Cycle 1-2	83	4582	4665
Cycle 1-3	69	4596	4665
Cycle 1-4	62	4603	4665
Cycle 1-5	56	4609	4665
Total	270	18390	18660

The covariates for the final model were chosen based on the standard model building strategy and included BMI, food allergies, other allergies, bronchitis, socio-economic status, location, age, region, immigration status, race, smoking and exposure to second hand smoke. All the covariates significant at p<0.25 level in the bivariate analysis with the outcome variable which in this case was recurrent events of asthma were included in the final model.

Table 5.18 provides the weighted and unweighted hazard ratio and 95% confidence interval for recurrent data using Anderson Gill (AG) approach. Weighted and unweighted hazard ratios were close for some of the variables, but for the variables obese category of BMI, age and ethnicity the hazard ratio were slightly different. The standard errors obtained when using the sampling weight were very small, resulting in very tight confidence intervals, resulting in high significance of all covariates at

$p<0.0001$ level. The standard errors obtained when ignoring the sampling weights were larger and resulted in less significant covariates. The hazard ratio for the weighted and unweighted analysis for some covariates like BMI, age group, ethnicity, smoking status and exposure to second hand smoke provided very different results. BMI, self reported health professional diagnosed food allergies, other allergies and chronic bronchitis, age group, region, immigrant status and smoking category were the significant variables.

Table 5.18 Weighted and unweighted hazard ratio (HR) and 95% confidence interval using Anderson Gill (AG) approach

Variables	**Weighted**		**Unweighted**	
	HR	**95% CI**	**HR**	**95% CI**
BMI (Normal weight)				
Under weight	1.21***	1.19-1.23	1.44	0.77-2.69
Over weight	1.37***	1.36-1.38	1.60**	1.18-2.17
Obese	2.05***	2.67-2.73	3.44***	2.55-4.64
Food Allergy (No)				
Yes	2.41***	2.38-2.43	2.34***	1.69-3.25
Other Allergy (No)				
Yes	2.54***	2.52-2.56	2.21***	1.70-2.87
Bronchitis (No)				
Yes	2.24***	2.21-2.26	2.45***	1.57-3.83
Socio-economic status (Low Income)				
Middle Income	1.66***	1.64-1.67	1.41	0.91-2.18
High Income	1.12***	1.11-1.13	1.16	0.85-1.58
Location (Urban)				
Rural	0.85***	0.84-0.86	0.76	0.55-1.05
Age Group (65-72 years)				
18-29 years	1.45***	1.43-1.46	2.29***	1.57-3.34
30-49 years	1.06***	1.05-1.07	1.45	0.98-2.13
50-64 years	1.10***	1.09-1.11	1.57*	1.07-2.28
Region (Ontario)				
Atlantic	0.62***	0.61-0.63	0.51***	0.35-0.72
Quebec	0.63***	0.63-0.64	0.55**	0.36-0.82
Prairie	0.69***	0.69-0.70	0.69**	0.50-0.96
British Columbia	0.92***	0.91-0.93	0.86*	0.56-1.32
Immigration (Citizen)				
Immigrants	0.60***	0.59-0.61	0.58*	0.36-0.94
Ethnicity (Non-white)				
White	4.35***	4.24-4.47	1.39	0.74-2.63
Smoking Status (Non-Smokers)				
Current Smokers	2.70***	2.67-2.73	1.73**	1.17-2.56
Ex-Smokers	1.51***	1.49-1.52	1.38*	1.00-1.91
Second hand smoke (No)				
Yes	0.78***	0.78-0.79	1.07	0.76-1.52

*** p<0.001
**p<0.01
*p<0.05

Table 5.19 provides the weighted and unweighted hazard ratio and the 95% confidence intervals for recurrent event data using the marginal modeling WLW approach. The weighted hazard ratio when using the WLW method were very similar to that of the weighted AG approach and the same was also true for unweighted result. However, the confidence interval obtained using the WLW approach was wider than the AG approach. The weighted and unweighted hazard ratios were different, and as noted previously, were very different for some of the covariates. The confidence intervals when using the sampling weight was larger compared to the unweighted standard errors.

Table 5.19 Weighted and unweighted hazard ratio (HR) and 95% confidence interval using Wei, Lin and Weissfeld (WLW) approach

Variables	**Weighted**		**Unweighted**	
	HR	**95% CI**	**HR**	**95% CI**
BMI (Normal weight)				
Under weight	1.25	0.60-2.61	1.48	0.80-2.75
Over weight	1.37**	0.94-1.99	1.57**	1.16-2.14
Obese	2.02**	1.41-2.89	3.39***	2.53-4.54
Food Allergy (No)				
Yes	2.26**	1.48-3.45	2.22***	1.59-3.11
Other Allergy (No)				
Yes	2.53***	1.78-3.60	2.19***	1.67-2.87
Bronchitis (No)				
Yes	2.14**	1.21-3.77	2.38***	1.49-3.81
Socio-economic status (Low Income)				
Middle Income	1.65	0.98-2.79	1.41	0.91-2.18
High Income	1.12	0.79-1.60	1.17	0.87-1.58
Location (Urban)				
Rural	0.85	0.54-1.35	0.75	0.54-1.05
Age Group (65-72 years)				
18-29 years	1.51	0.94-2.44	2.37***	1.62-3.48
30-49 years	1.09	0.67-1.77	1.47	0.99-2.17
50-64 years	1.13	0.72-1.78	1.59*	1.09-2.32
Region (Ontario)				
Atlantic	0.61*	0.41-0.92	0.50***	0.36-.071
Quebec	0.63	0.38-1.05	0.55**	0.36-0.83
Prairie	0.69*	0.48-0.99	0.70*	0.51-0.96
British Columbia	0.91	0.55-1.52	0.86	0.56-1.32
Immigration (Citizen)				
Immigrants	0.60	0.33-1.10	0.58*	0.34-0.99
Ethnicity (Non-white)				
White	4.35**	2.06-9.19	1.40	0.73-2.69
Smoking Status (Non-Smokers)				
Current Smokers	2.61**	1.52-4.51	1.66*	1.10-2.49
Ex-Smokers	1.52*	1.04-2.24	1.39*	1.01-1.91
Second hand smoke (No)				
Yes	0.79	0.48-1.29	1.08	0.75-1.55

Reference categories are provided in parentheses
*** p<0.001
**p<0.01
*p<0.05

Table 5.20 provides the weighted and unweighted hazard ratio and 95% confidence interval using the PWP-gap time/total time approach for recurrent event data. Both the gap time and total time provided exactly identical result and one table was provided. The weighted and unweighted hazard ratio using the PWP gap time and total time approach were exactly the same as WLW approach.

The third objective of this thesis was aimed at comparing the three variance corrected models. Based on the result obtained, the AG model was not able to account for the complex survey design. The result of the WLW and the PWP model provided exactly the same result; hence for the purpose of interpretation the WLW weighted analysis results will be used.

Table 5.20 Weighted and unweighted hazard ratio (HR) and 95% confidence interval using gap time/total time Prentice, William and Peterson (PWP) approach

Variables	**Weighted**		**Unweighted**	
	HR	**95% CI**	**HR**	**95% CI**
BMI (Normal weight)				
Under weight	1.25	0.60-2.61	1.48	0.80-2.75
Over weight	1.37**	0.94-1.99	1.57**	1.16-2.14
Obese	2.02**	1.41-2.89	3.39***	2.53-4.54
Food Allergy (No)				
Yes	2.26**	1.48-3.45	2.22***	1.59-3.11
Other Allergy (No)				
Yes	2.53***	1.78-3.60	2.19***	1.67-2.87
Bronchitis (No)				
Yes	2.14**	1.21-3.77	2.38***	1.49-3.81
Socio-economic status (Low Income)				
Middle Income	1.65	0.98-2.79	1.41	0.91-2.18
High Income	1.12	0.79-1.60	1.17	0.87-1.58
Location (Urban)				
Rural	0.85	0.54-1.35	0.75	0.54-1.05
Age Group (65-72 years)				
18-29 years	1.51	0.94-2.44	2.37***	1.62-3.48
30-49 years	1.09	0.67-1.77	1.47	0.99-2.17
50-64 years	1.13	0.72-1.78	1.59*	1.09-2.32
Region (Ontario)				
Atlantic	0.61*	0.41-0.92	0.50***	0.36-.071
Quebec	0.63	0.38-1.05	0.55**	0.36-0.83
Prairie	0.69*	0.48-0.99	0.70*	0.51-0.96
British Columbia	0.91	0.55-1.52	0.86	0.56-1.32
Immigration (Citizen)				
Immigrants	0.60	0.33-1.10	0.58*	0.34-0.99
Ethnicity (Non-white)				
White	4.35**	2.06-9.19	1.40	0.73-2.69
Smoking Status (Non-Smokers)				
Current Smokers	2.61**	1.52-4.51	1.66*	1.10-2.49
Ex-Smokers	1.52*	1.04-2.24	1.39*	1.01-1.91
Second hand smoke (No)				
Yes	0.79	0.48-1.29	1.08	0.75-1.55

Reference categories are provided in parentheses
*** p<0.001
**p<0.01
*p<0.05

5.6.2 Interpretation of the WLW model

The hazard ratio increased for all the three categories of body mass index. The risk of recurrent asthma increased by 1.3 times for under weight females, by 1.4 times for over weight and 2 times for obese females when compared to the normal weight females. The risk of asthma recurrence was 2.3 times higher in females diagnosed with food allergy compared to the females with no food allergies. Risk of asthma recurrence also increased 2.5 times for females with other kind of allergies and 2 times for females with bronchitis compared to females with no allergies or bronchitis. Females in the middle socio-economic status showed 1.7 times increase in the risk of asthma recurrence compared to lower socio-economic status females. For the higher socio-economic status the risk was 1.1 times, however, this increase was not statistically significant.

Compared to the 65 to 72 year old group, the risk of asthma recurrence was 1.5 times higher for females in 18 to 29 year, 1.1 times higher in the 30 to 49 group. For 50 to 64 years, the hazard rate was similar to the 65 to 72 year old females. However, none of the increases were statistically significant.

Compared to the Ontario region, the hazard of asthma recurrence for females residing in the Atlantic region decreased by about 39%, in the Quebec region it decreased by 37%, in the Prairie region decreased by 31% and in the British Columbia region decreased by 9%. The decreased in the hazard rate were statistically significant at $p<0.05$ level.

Females who were not Canadian citizens were at 40% lower risk of asthma recurrence compared to females who were Canadian citizens. Females who were

Caucasian were at 4.4 times higher risk of asthma recurrence compared to the non-Caucasian females (p<0.01).

Females who were current smokers were at 2.6 times higher risk of asthma recurrence compared to the non-smoker females (p<0.01). The hazard rate for female ex-smokers was about 1.5 times higher compared to non-smoker females (p<0.05). For females who were exposed to second hand smoke, the risk decreased by about 21% compared to females who were not exposed to second hand smoke, but this decrease was not statistically significant.

5.7 Objective 4: Missing data analysis

The fourth objective focused on comparing the robustness of the data with completers versus incompleters, using a missing data approach. The approaches used were the weighted generalized estimating equation and the random effects modeling approach also known as generalized linear mixed models.

5.7.1 Marginal models

Final Model as obtained from Objective 1 is:

$$\begin{aligned}
&\mathit{logit}[\Pr(\text{asthma})_{ij}=1]=\beta_0+\beta_1*(\text{underweight})_i+\beta_2*(\text{overweight})_i+\beta_3*(\text{obese})_i \\
&+\beta_4*(\text{foodallergy})_{ij}+\beta_5*(\text{otherallergy})_{ij}+\beta_6*(\text{bronchitis})_{ij}+\beta_7*(\text{intestinalproblem})_{ij} \\
&+\beta_8*(\text{highincome})_{ij}+\beta_9*(\text{middleincome})_{ij}+\beta_{10}*(\text{rural})_{ij}+\beta_{11}*(\text{18-29years})_{ij}+ \\
&\beta_{12}*(\text{30-49years})_{ij}+\beta_{13}*(\text{50-64years})_{ij}+\beta_{14}*(\text{Atlantic})_{ij}+\beta_{15}*(\text{Quebec})_{ij} \\
&+\beta_{16}*(\text{Prairie})_{ij}+\beta_{17}*(\text{BritishColumbia})_{ij}+\beta_{18}*(\text{Immigrants})_{ij}+\beta_{19}*(\text{white})_{ij} \\
&+\beta_{20}*(\text{smokers})_{ij}+\beta_{21}*(\text{ex-smokers})_{ij}+\beta_{22}*(\text{secondHandSmoke})_{ij} \\
&+\beta_{23}*(\text{Cycle5})_{ij}+\beta_{24}*(\text{Cycle4})_{ij}+\beta_{25}*(\text{Cycle3})_{ij}+\beta_{26}*(\text{Cycle2})_{ij}+ \\
&\beta_{27}*(\text{rural*smokers})_{ij}+\beta_{28}*(\text{rural*ex-smokers})_{ij}+\beta_{29}*(\text{rural*highIncome})_{ij} \\
&+\beta_{30}*(\text{rural*middleIncome})_{ij}+\beta_{31}*(\text{white*highIncome})_{ij}+\beta_{32}*(\text{white*middleIncome})_{ij} \\
&+\beta_{33}*(\text{exposure*Cycle5})_{ij}+\beta_{34}*(\text{exposure*Cycle4})_{ij}+\beta_{35}*(\text{exposure*Cycle3})_{ij}+ \\
&\beta_{36}*(\text{exposure*Cycle2})_{ij}+\beta_{37}*(\text{smoker*18-29years})_{ij}+\beta_{38}*(\text{smoker*30-49years})_{ij} \\
&+\beta_{39}*(\text{smoker*50-64years})_{ij}+\beta_{40}*(\text{ex-smoker*18-29years})_{ij}+ \\
&\beta_{41}*(\text{ex-smoker*30-49years})_{ij}+\beta_{42}*(\text{ex-smoker*50-64years})_{ij}+ \\
&\beta_{43}*(\text{highIncome*18-29years})_{ij}+\beta_{44}*(\text{highIncome*30-49years})_{ij} \\
&+\beta_{45}*(\text{highIncome*50-64years})_{ij}+\beta_{46}*(\text{middleIncome*18-29years})_{ij}+ \\
&\beta_{47}*(\text{middleIncome*30-49years})_{ij}+\beta_{48}*(\text{middleIncome*50-64years})_{ij}
\end{aligned}$$

The modified final model for Objective 4 was obtained by adding a drop variable in the model as a main effect, and as an interaction term by multiplying all the variables in the final model by the drop variable. This approach is known as the pattern mixture model (PMM).

The GEE analysis using the SAS procedure GENMOD was used with the drop variable, as well as all possible interaction with the main effects, as well as interaction terms. The results indicated that the interaction terms with the drop variable and its interaction with the main effect variable or the interaction terms was not significant (result not presented). In the next step, the three way interaction terms were dropped from the final model and the analysis was re-run with just the main effects variables from the above equation, the drop variable and interaction of drop variable with the main effects variable. In this model, it was seen that the drop variable and the interaction of drop variable with location, ethnicity and socio-economic status variable were significant at $p<0.05$ level (result not presented). The following step included only the main effects variable, the drop variable and the significant drop and main effect interaction terms. In this model, the interaction terms (location, ethnicity and socio-economic status with drop variable) were not significant. Hence, the final model was chosen using the variables included in Objective 1 and keeping only the drop variable as a main effect term in the model. The final model was fitted using the exchangeable working correlation matrix as it was observed that with this correlation structure the model was stable. For the WGEE approach, special weight variable was created which accounts for missingness and the survey non-response. The empirically corrected standard errors, odds ratio and 95% confidence intervals are presented in Table 5.21.

The result obtained using the WGEE approach without the drop variable and PMM with the drop variable differed in their parameter estimates for some variables, whereas for some of the covariates the estimates were similar. Self reported health professional diagnosed bronchitis and intestinal problems, rural location, smoking status, time points or Cycles, interaction terms location and smoking as well as age group and income showed very similar point estimates. On comparing the standard errors using WGEE and PMM, the standard errors for WGEE without the drop variables were larger compared with the model with drop variable.

The drop variable was significant for the PMM marginal model. The significance of the drop variable indicates that there is a difference between completers and incompleters, there is some bias associated with the missing data. The odds of being diagnosed with asthma were 1.3 times higher among incompleters compared to completers.

The odds of being diagnosed with asthma was 1.7 times higher in obese females compared to the normal weight females ($p<0.0001$). The odds of asthma in females increased by 4 times in females who reported food allergies, 1.6 times higher in females with other allergies and 2 times higher in females diagnosed with bronchitis were significantly higher compared to their reference categories.

Females staying in the Atlantic region were at a lower risk of developing asthma compared to females staying in Ontario region and this was statistically significant at $p<0.05$ level. Females who were not Canadian citizens were at a lower risk of being diagnosed with asthma compared to females who were not immigrants and this was highly significant at $p<0.0001$ level.

Rural females who were current smokers were at 1.5 times more likely to be diagnosed with asthma compared to the urban non-smokers females. Females who lived in the rural areas and belonging to the higher socio-economic level were 1.7 times more likely of being diagnosed with asthma compared to urban females belonging to lower socio-economic status.

Younger female smokers (18-29 years) were 2.2 times more likely to be diagnosed with asthma compared to 65 to 72 years non-smoker females. The increase in the odds was significant. For various other age groups the odds of asthma prevalence increased, but this increase was not statistically significant. Interaction of socio-economic status with various categories of age group showed a decrease in the odds of being diagnosed with asthma. The odds of being diagnosed with asthma were lower for all the combination of age and socio-economic status.

Table 5.21 Parameter estimates (standard errors) and odds ratio (95% confidence interval) for GEE with survey weights and weighted generalized estimating equation (WGEE)

Covariates	**GEE-WT64LS**		**WGEE**	
	Estimate	**Odds Ratio**	**Estimate**	**Odds Ratio**
	(S.E.)	**(95% C.I.)**	**(S.E.)**	**(95% C.I.)**
Intercept	-3.33***	0.04	-4.84***	0.008
	(0.40)	(0.02-0.08)	(1.42)	(0.00-0.13)
Drop (Completers)				
Incompleters	0.29*	1.34		
	(0.12)	(1.05-1.70)		
BMI (Normal weight)				
Under weight	-0.45	0.64	-1.12*	0.33
	(0.30)	(0.35-1.16)	(0.48)	(0.13-0.84)
Over weight	0.19	1.21	-0.47	0.62
	(0.14)	(0.92-1.58)	(0.38)	(0.30-1.31)
Obese	0.53**	1.69	-0.18	0.84
	(0.14)	(1.27-2.25)	(0.34)	(0.42-1.64)
Food Allergy (No)				
Yes	0.31***	1.37	0.06	1.07
	(0.09)	(1.14-1.64)	(0.17)	(0.76-1.49)
Other Allergy (No)				
Yes	0.50***	1.64	0.98*	2.66
	(0.06)	(1.45-1.86)	(0.44)	(1.13-6.26)
Bronchitis (No)				
Yes	0.67***	1.96	0.64**	1.89
	(0.15)	(1.47-2.61)	(0.22)	(1.22-2.94)
Intestinal Problem (No)				
Yes	0.23	1.26	0.22	1.25
	(0.13)	(0.98-1.62)	(0.22)	(0.80-1.94)
Socio-economic status (Low Income)				
High Income	1.33	3.78	3.79	44.33
	(0.59)	(1.18-12.07)	(1.44)	(2.65-742.6)
Middle Income	-0.30	0.74	0.41	1.50
	(0.28)	(0.43-1.28)	(1.15)	(0.17-13.34)
Location (Urban)				
Rural	-0.58	0.56	-0.51	0.60
	(0.21)	(0.37-0.84)	(0.33)	(0.31-1.14)
Age Group (65-72 years)				
18-29 years	0.36	1.44	0.40	1.49
	(0.33)	(0.75-2.74)	(0.48)	(0.60-3.81)

Table 5.21 (Cont'd)

Covariates	GEE-WT64LS		WGEE	
	Estimate (S.E.)	**Odds Ratio (95% C.I.)**	**Estimate (S.E.)**	**Odds Ratio (95% C.I.)**
30-49 years	0.40 (0.28)	1.50 (0.86-2.62)	0.66 (0.47)	1.94 (0.77-4.87)
50-64 years	0.04 (0.25)	1.05 (0.64-1.70)	0.0004 (0.43)	1.00 (0.43-2.32)
Region (Ontario)				
Atlantic	-0.27* (0.14)	0.76 (0.58-0.99)	-0.92** (0.33)	0.40 (0.21-0.76)
Quebec	-0.19 (0.14)	0.83 (0.63-1.09)	-0.82* (0.36)	0.44 (0.22-0.90)
Prairies	-0.22 (0.13)	0.80 (0.62-1.04)	-1.07** (0.37)	0.34 (0.16-0.71)
British Columbia	0.09 (0.16)	1.10 (0.80-1.51)	-0.80 (0.44)	0.45 (0.19-1.07)
Immigration (Citizen)				
Immigrants	-0.83*** (0.20)	0.43 (0.29-0.64)	-1.81** (0.61)	0.16 (0.05-0.54)
Ethnicity (Non-white)				
White	0.23 (0.30)	1.26 (0.70-2.27)	1.85 (1.42)	6.34 (0.39-102.0)
Smoking Status (Non-Smokers)				
Current Smokers	-0.50 (0.31)	0.61 (0.33-1.12)	-0.84 (0.57)	0.43 (0.14-1.32)
Ex-Smokers	-0.35 (0.28)	0.71 (0.41-1.22)	-0.37 (0.52)	0.69 (0.25-1.89)
Second hand smoke (No)				
Yes	-0.05 (0.12)	0.95 (0.76-1.20)	0.11 (0.29)	1.12 (0.63-1.99)
Time (Cycle 1)				
Cycle 5	0.39 (0.08)	1.48 (1.25-1.75)	0.54 (0.18)	1.72 (1.21-2.45)
Cycle 4	0.41 (0.08)	1.51 (1.30-1.75)	0.76 (0.29)	2.15 (1.22-3.79)
Cycle 3	0.33 (0.08)	1.39 (1.19-1.62)	0.80 (0.40)	2.23 (1.03-4.86)
Cycle 2	0.11 (0.06)	1.12 (0.99-1.26)	0.10 (0.09)	1.11 (0.92-1.33)
Location * Smoking				
Rural Smokers	0.43** (0.17)	1.54 (1.11-2.14)	0.59* (0.28)	1.81 (1.04-3.13)

Table 5.21 (Cont'd)

Covariates	**GEE-WT64LS**		**WGEE**	
	Estimate (S.E.)	**Odds Ratio (95% C.I.)**	**Estimate (S.E.)**	**Odds Ratio (95% C.I.)**
Rural Ex-Smokers	0.35	1.42	0.30	1.34
	(0.18)	(0.99-2.04)	(0.29)	(0.76-2.37)
Location * Income				
High Income Rural	0.56*	1.75	0.15	1.16
	(0.24)	(1.09-2.79)	(0.38)	(0.56-2.43)
Middle Income Rural	0.28	1.32	0.005	1.01
	(0.18)	(0.93-1.89)	(0.26)	(0.59-1.69)
Ethnicity * Income				
White* High SES	-0.74	0.48	-2.74*	0.06
	(0.45)	(0.20-1.17)	(1.34)	(0.004-0.89)
White * Middle SES	0.46	1.58	-0.17	0.84
	(0.24)	(0.99-2.53)	(1.16)	(0.09-8.15)
Second Hand Smoke * Time				
Exposure * Cycle 2	0.06	1.07	-0.20	0.82
	(0.15)	(0.79-1.44)	(0.31)	(0.44-1.52)
Exposure * Cycle 3	0.12	1.12	-0.20	0.81
	(0.13)	(0.87-1.45)	(0.38)	(0.39-1.71)
Exposure * Cycle 4	0.11	1.12	-0.37	0.69
	(0.13)	(0.87-1.44)	(0.49)	(0.26-1.79)
Exposure * Cycle 5	0.27*	1.31	0.29	1.34
	(0.11)	(1.06-1.62)	(0.17)	(0.95-1.89)
Smoking * Age Group				
Smoker * 18-29 years	0.79*	2.21	1.04	2.83
	(0.35)	(1.11-4.40)	(0.61)	(0.85-9.47)
Ex-Smoker * 18-29 years	0.44	1.56	0.39	1.48
	(0.32)	(0.84-2.90)	(0.55)	(0.50-4.39)
Smoker * 30-49 years	0.28	1.32	0.54	1.71
	(0.33)	(0.70-2.52)	(0.59)	(0.53-5348)
Ex-Smoker * 30-49 years	0.37	1.45	0.26	1.29
	(0.30)	(0.80-2.61)	(0.54)	(0.45-3.71)
Smoker * 50-64 years	0.45	1.58	0.68	1.97
	(0.28)	(0.91-2.75)	(0.54)	(0.68-5.71)
Ex-Smoker * 50-64 years	0.37	1.45	0.84	2.32
	(0.27)	(0.86-2.44)	(0.54)	(0.80-6.72)
Age Group * Income				
18-29 years * High SES	-0.80*	0.45	-1.36*	0.25
	(0.34)	(0.23-0.88)	(0.61)	(0.08-0.84)
18-29 years * Middle SES	-0.30	0.74	-0.28	0.75
	(0.22)	(0.48-1.13)	(0.38)	(0.36-1.58)

Table 5.21 (Cont'd)

Covariates	GEE-WT64LS		WGEE	
	Estimate (S.E.)	**Odds Ratio (95% C.I.)**	**Estimate (S.E.)**	**Odds Ratio (95% C.I.)**
30-49 years * High SES	-0.98** (0.31)	0.37 (0.20-0.69)	-1.51* (0.59)	0.22 (0.07-0.70)
30-49 years * Middle SES	-0.40* (0.18)	0.67 (0.46-0.96)	-0.50 (0.37)	0.61 (0.29-1.25)
50-64 years * High SES	-0.70* (0.29)	0.50 (0.28-0.88)	-0.29 (0.52)	0.75 (0.27-2.08)
50-64 years * Middle SES	-0.19 (0.19)	0.82 (0.57-1.20)	-0.02 (0.37)	0.98 (0.47-2.04)

Reference categories are provided in parentheses
*** p<0.001
** p<0.01
* p<0.05

5.7.2 Random Effect Models

Random effect models were also fitted using the SAS procedure GLIMMIX. PQL method under the restricted maximum likelihood and maximum likelihood approach with and without drop variables were used. Table 5.22 provides the PQL results with/without drop variable. The PQL method with restricted maximum likelihood as well as with maximum likelihood provided similar estimates and standard errors, only the difference was with the random intercept term and the deviance. For the PQL-REML method with the drop variable in the model, a total of 33 iterations were used in order to satisfy the convergence criterion. With the PQL-ML approach a total of 23 iterations were used to reach convergence. When the drop variable was removed from the model, the PQL-REML method required a total of 36 iterations to reach convergence and for the PQL-ML method a total of 31 iteration was needed to satisfy convergence. On comparing the PQL model with and without the drop variable, it was seen that the model with drop variable in the model required lesser iterations to satisfy the convergence criterion. The drop variable's parameter estimate and the standard error using the random effect model were higher than the marginal model. The difference is expected with binary outcome for the marginal and the random effects model. Both these models are direct extensions of the generalized linear model, but they produce very different results.

Comparing the PQL-REML with drop variable with PQL-REML without the drop variable, results in likelihood ratio statistics of 3203899-3203135 = 764, df = 1, p<0.0001 (Table 5.22). The results indicate that the model terms do vary by missing patterns. However, this was not a test if missing at random (MAR) criterion was satisfied, but it does specify that the model with the drop variable fits the data better than without the drop variable. The PQL-ML with the drop variable was compared to the PQL-ML without the drop variable. The resulting likelihood ratio test statistics, 3203574-3202815 = 759, df = 1 and p<0.0001. This result also indicates the same that model terms do vary with the missing pattern.

In terms of the interpretation of the parameter estimates, we see that all the variables are highly significant at p<0.001 for all the four models. Highly significant results were mainly due to smaller standard errors. All the covariates among the completers, except for the middle income level, rural location, residing in Quebec, Prairies and British Columbia region, non Canadian citizens, Caucasian, current smoker or ex-smoker females, exposure to second hand smoke, and the age group and income interaction increased compared to their reference category. The negative parameter estimate indicates that the females who completed the study were at lower risk of being diagnosed with asthma. The positive parameter estimates indicates that the risk is higher of being diagnosed with asthma compared to the reference category.

Table 5.22 Parameter estimates (standard errors) for a generalized linear mixed model (GLMM) assuming Penalized Quasi Likelihood (PQL) restricted maximum likelihood and maximum likelihood approach with and without drop variable in the model

Covariates	**With Drop variable**		**Without drop variable**	
	PQL-REML	**PQL-ML**	**PQL-REML**	**PQL-ML**
Intercept	-9.87*** (0.55)	-9.87*** (0.55)	-9.07*** (0.54)	-9.07*** (0.54)
Drop (Completers)				
Incompleters-Intercept of drop variable	1.75*** (0.26)	1.75*** (0.26)		
BMI (Normal weight)				
Under weight	0.23 (0.64)	0.23 (0.64)	0.40 (0.65)	0.40 (0.65)
Over weight	0.21 (0.27)	0.21 (0.27)	0.20 (0.28)	0.20 (0.28)
Obese	1.66*** (0.32)	1.66*** (0.32)	1.61*** (0.33)	1.61*** (0.33)
Food Allergy (No)				
Yes	0.30*** (0.007)	0.30*** (0.007)	0.30*** (0.007)	0.30*** (0.007)
Other Allergy (No)				
Yes	0.89*** (0.005)	0.89*** (0.005)	0.89*** (0.005)	0.89*** (0.005)
Bronchitis (No)				
Yes	1.30*** (0.008)	1.30*** (0.008)	1.30*** (0.008)	1.30*** (0.008)
Intestinal Problem (No)				
Yes	1.22*** (0.01)	1.22*** (0.01)	1.22*** (0.01)	1.22*** (0.01)
Socio-economic status (Low Income)				
High Income	5.92*** (0.36)	5.92*** (0.36)	5.89*** (0.35)	5.89*** (0.35)
Middle Income	-3.18*** (0.05)	-3.18*** (0.05)	-3.18*** (0.05)	-3.18*** (0.05)
Location (Urban)				
Rural	-2.05*** (0.02)	-2.05*** (0.02)	-2.05*** (0.02)	-2.05*** (0.02)
Age Group (65-72 years)				
18-29 years	0.18*** (0.04)	0.18*** (0.04)	0.18*** (0.04)	0.18*** (0.04)
30-49 years	0.58*** (0.04)	0.58*** (0.04)	0.58*** (0.04)	0.58*** (0.04)

Table 5.22 (Cont'd)

Covariates	**With Drop variable**		**Without drop variable**	
	PQL-REML	**PQL-ML**	**PQL-REML**	**PQL-ML**
50-64 years	0.20*** (0.03)	0.20*** (0.03)	0.20*** (0.03)	0.20*** (0.03)
Region (Ontario)				
Atlantic	2.86*** (0.09)	2.86*** (0.09)	2.87*** (0.09)	2.87*** (0.09)
Quebec	-1.33*** (0.04)	-1.33*** (0.04)	-1.33*** (0.04)	-1.33*** (0.04)
Prairies	-0.83*** (0.03)	-0.83*** (0.03)	-0.83*** (0.03)	-0.83*** (0.03)
British Columbia	-1.48*** (0.03)	-1.48*** (0.03)	-1.48*** (0.03)	-1.48*** (0.03)
Immigration (Citizen)				
Immigrants	-1.36*** (0.41)	-1.36*** (0.41)	-1.32*** (0.41)	-1.32*** (0.41)
Ethnicity (Non-white)				
White	-1.76*** (0.52)	-1.76*** (0.52)	-2.16*** (0.53)	-2.16*** (0.53)
Smoking Status (Non-Smokers)				
Current Smokers	-2.60*** (0.04)	-2.60*** (0.04)	-2.60*** (0.04)	-2.60*** (0.04)
Ex-Smokers	-2.44*** (0.03)	-2.44*** (0.03)	-2.43*** (0.03)	-2.43*** (0.03)
Second hand smoke (No)				
Yes	-0.33*** (0.01)	-0.33*** (0.01)	-0.33*** (0.01)	-0.33*** (0.01)
Time (Cycle 1)				
Cycle 5	2.09*** (0.01)	2.09*** (0.01)	2.09*** (0.008)	2.09*** (0.008)
Cycle 4	2.17*** (0.01)	2.17*** (0.01)	2.17*** (0.008)	2.17*** (0.008)
Cycle 3	1.62*** (0.01)	1.62*** (0.01)	1.62*** (0.007)	1.62*** (0.007)
Cycle 2	0.62*** (0.01)	0.62*** (0.01)	0.62*** (0.007)	0.62*** (0.007)
Location * Smoking				
Rural Smokers	1.60*** (0.02)	1.60*** (0.02)	1.60*** (0.02)	1.60*** (0.02)
Rural Ex-Smokers	0.49*** (0.02)	0.49*** (0.02)	0.49*** (0.02)	0.49*** (0.02)

Table 5.22 (Cont'd)

Covariates	With Drop variable		Without drop variable	
	PQL-REML	PQL-ML	PQL-REML	PQL-ML
Location * Income				
High Income Rural	1.89***	1.89***	1.89***	1.89***
	(0.02)	(0.02)	(0.02)	(0.02)
Middle Income Rural	1.34***	1.34***	1.34***	1.34***
	(0.02)	(0.02)	(0.02)	(0.02)
Ethnicity * Income				
White* High SES	1.23***	1.23***	1.23***	1.23***
	(0.04)	(0.04)	(0.04)	(0.04)
White * Middle SES	4.58***	4.58***	4.58***	4.58***
	(0.04)	(0.04)	(0.04)	(0.04)
Second Hand Smoke * Time				
Exposure * Cycle 2	0.33***	0.33***	0.33***	0.33***
	(0.01)	(0.01)	(0.01)	(0.01)
Exposure * Cycle 3	0.71***	0.71***	0.71***	0.71***
	(0.01)	(0.01)	(0.01)	(0.01)
Exposure * Cycle 4	0.84***	0.84***	0.84***	0.84***
	(0.01)	(0.01)	(0.01)	(0.01)
Exposure * Cycle 5	1.44***	1.44***	1.44***	1.44***
	(0.01)	(0.01)	(0.01)	(0.01)
Smoking * Age Group				
Smoker * 18-29 years	2.87***	2.87***	2.87***	2.87***
	(0.05)	(0.05)	(0.05)	(0.05)
Ex-Smoker * 18-29 years	2.70***	2.70***	2.69***	2.69***
	(0.03)	(0.03)	(0.03)	(0.03)
Smoker * 30-49 years	0.39***	0.39***	0.39***	0.39***
	(0.04)	(0.04)	(0.04)	(0.04)
Ex-Smoker * 30-49 years	1.88***	1.88***	1.88***	1.88***
	(0.03)	(0.03)	(0.03)	(0.03)
Smoker * 50-64 years	0.89***	0.89***	0.89***	0.89***
	(0.04)	(0.04)	(0.04)	(0.04)
Ex-Smoker * 50-64 years	1.04***	1.04***	1.04***	1.04***
	(0.03)	(0.03)	(0.03)	(0.03)
Age Group * Income				
18-29 years * High SES	-7.60***	-7.60***	-7.57***	-7.57***
	(0.36)	(0.36)	(0.35)	(0.35)
18-29 years * Middle SES	-2.10***	-2.10***	-2.10***	-2.10***
	(0.03)	(0.03)	(0.03)	(0.03)
30-49 years * High SES	-8.44***	-8.44***	-8.40***	-8.40***
	(0.36)	(0.36)	(0.35)	(0.35)
30-49 years * Middle SES	-2.25***	-2.25***	-2.25***	-2.25***
	(0.03)	(0.03)	(0.03)	(0.03)

Table 5.22 (Cont'd)

Covariates	With Drop variable		Without drop variable	
	PQL-REML	PQL-ML	PQL-REML	PQL-ML
50-64 years * High SES	-7.91***	-7.91***	-7.88***	-7.88***
	(0.36)	(0.36)	(0.35)	(0.35)
50-64 years * Middle SES	-1.36***	-1.36***	-1.36***	-1.36***
	(0.03)	(0.03)	(0.03)	(0.03)
Random intercept	47.82	47.74	48.76	48.69
	(1.07)	(1.07)	(1.10)	(1.09)
Deviance	3203899	3203574	3203135	3202815

Reference categories are provided in parentheses
*** p<0.001
** p<0.01
* p<0.05

5.8 Conclusion

The final model for the four objectives is summarized in tabular form in Table 5.23.

Table 5.23 Summarizing the final model selected for interpretation

Objective 1	**Methods for parameter estimation**	**Methods for S.E. estimation**	**Important Findings**	**Section, page # (Chapter 4)**
Crude Prevalence	P individuals in population with disease at a given time/ Population		All three methods produced similar parameter estimates. The S.E. produced using Survey	4.2.1.1, page 66
Adjusted Prevalence	Generalized Estimating Equation [1]	Sandwich Estimator	GEE was larger than compared to other two	4.2.2.1, page 70
	Survey GEE [3]	Taylor Linearization Bootstrap method	methods. Design-based method better than model-based method	4.2.1.2, page 68 4.2.2.2, page 72
Objective 2				
Crude Incidence	Cumulative Incidence Give equation number Incidence Density give equation number	Weighted Unweighted	Unweighted method produced conservative results	4.3.4.2, page 86 4.3.1, page 78
Adjusted Incidence	Cox's proportional Hazard Model Discrete proportional hazard model	Partial likelihood Weighted Sandwich estimator	Unweighted and Robust methods produced similar results	4.3.2, page 79 4.3.3, page 81
Objective 3				
Recurrent survival Analysis	Anderson Gill (AG) model [58]	Unweighted Robust sandwich covariance	AG model produced the most conservative results.	4.4.1.1, page 92
	Wei Lin Weissfeld (WLW) model [63]	Robust sandwich	WLW produced the most stable results.	4.4.1.2, page 94

	Prentice William Peterson (PWP) model [65]	covariance		4.4.1.3, page 94
Objective 4 Missing data approach	Marginal Models: Pattern Mixture Model (PMM) and Weighted GEE [93]	Sandwich estimator Sandwich estimator	PMM produced results similar to survey GEE. These results were preferred over weighted GEE.	4.5.1, page 101 4.5.2, page 104
	Random Effect model: Penalized Quasi Likelihood (PQL) REML (Restricted Maximum Likelihood) ML (Maximum Likelihood)	Numerical approximations	Random effect model was not able to account for the complex survey design and produced conservative results	4.5.3, page 105

CHAPTER 6 - DISCUSSION

6.1 Introduction

Multi-stage sampling is a common approach to gather information from large scale complex surveys, which can be either cross-sectional or longitudinal in nature. The statistical methodologies for analyzing data obtained from complex longitudinal surveys are still in the developmental stage, mainly because the methods must address the longitudinal nature of the data, as well as the complexity of the survey design. Several statistical approaches have been proposed in literature, and this dissertation examined the two most commonly used methods, design-based and model-based. Comparisons of weighted, unweighted and robust variance estimation methods for the event history and recurrent survival data were also assessed. Missing data analyses were conducted using marginal and random effects modeling approaches. The NPHS dataset was used to achieve the above objectives with asthma in adult females as the outcome of interest. The associated risk factors for asthma prevalence and incidence among females was also examined.

6.2 Objective 1: To compare the design-based and model-based methods for the marginal modeling approach

The focus of this objective was to compare the model-based approach (GEE- Liang and Zeger [1]) with the design-based approach (Survey GEE- Rao [3]) for longitudinal survey data. With the exception of a few variables, the parameter estimates obtained using the model-based and design-based approaches provided very similar results. However, the standard errors obtained for the two GEE methods were different, with the standard errors using the design-based approach being larger. Robust standard errors were used to compare the design-based and model-based methods. A difference of 0.15 to 0.01 standard errors was considered to assess the best approach between model-based and design-based methods. The differences in the standard errors of these two methods can be explained by the fact that additional sources of uncertainty, which can arise due to the complexity of the survey design, were taken into account by the survey GEE method. Also accounting for the complexity of the survey design results in larger variance estimate.

The results were also compared with another method referred to as BOOTVAR GEE, which used Bootstrap method to account for the complexity of longitudinal survey data. The standard errors obtained using this method were larger than the model-based GEE but were smaller compared to the survey GEE proposed by Rao [3].

There may be several reasons for the differences in the standard errors between the model-based and design-based methods. One difference could be because of the large variation of weights used with a complex survey design, which can result in larger standard errors for the weighted estimates compared to the unweighted estimates [103].

The larger standard errors may also be a result of using only a subset of the NPHS (i.e., 18-64 year old women) which could have resulted in the larger variability of weights [201]. Including the sampling weights in the analysis increases the variance of estimates, although it removes bias.

An additional way of accounting for complex survey data is to include design or auxiliary variables in the model [103]. Design variables, such as sex, age, and socioeconomic status, are important components of a multi-stage survey. In this study, the design variables of age and socio-economic status were used.

If analyses were conducted ignoring the three features of complex survey design (i.e., stratification, clustering and unequal inclusion probabilities), the parameter estimates and their corresponding standard errors would be quite different [212]. When we account for the sampling weights, it protects against model misspecification but it also increases the variances of estimates [201]. Hence, ignoring the sample design will result in biased estimates of standard errors.

Since the true variance of the population cannot be determined (only an approximation can be obtained), it is hard to know which of these methods (model-based or design-based) produced consistent estimates of standard errors. To summarize, for marginal modeling approaches, the design-based method should be preferred, as this method provided unbiased estimates.

6.3 Objective 2: To compare the design-based and model-based methods for event history data.

The incidence rate and hazard rate of asthma was determined using Cox's proportional hazard model and the discrete proportional hazard model. Weighted, unweighted and robust variance estimation methods were compared using the proportional hazard models.

Robust standard errors were used to compare the model-based and design-based approaches. Also measures of confidence interval length were used to assess the relative efficiency of design-based and model-based methods for Mantel-Haenszel statistics. The 95% confidence intervals for the weighted incidence rates were wider than those for the unweighted incidence density rates. The sampling weights in the analysis can cause extra variability resulting in wider confidence intervals. The weighted standard errors obtained using STMH (STATA command to calculate rate ratios using a Mantel-Haenszel method) produced very tight confidence intervals, resulting in highly significant p-values. This indicates that the STMH method was unable to account for the complexities of the survey design and produced biased results.

The adjusted and unadjusted weighted analysis using Cox's proportional hazard model and the discrete proportional hazard model provided similar hazard ratios for most covariates. The confidence intervals were wider and the standard errors were slightly larger (a difference of about 0.01 to 0.12 was observed) for the discrete model as compared to Cox's proportional hazard model. The robust generalized method suggested by Lin and Wei [112] was used to obtain robust variance estimates. The robust hazard ratios and corresponding 95% confidence intervals were similar to those obtained in the unweighted analysis. In the absence of a standard method, it becomes very difficult to compare the model-based and the design-based approaches for longitudinal survey data. It cannot be concluded from the results which method would best account for the complexities of survey design.

Other studies of longitudinal data with binary outcome using different methods and software have been conducted. Boudreau and Lawless [116] used a stratified semi-parametric Cox's proportional hazard modeling approach to account for the longitudinal survey data and associated issues. Although SPlus and SUDAAN allow for the application of the stratified semi-parametric Cox's proportional hazard model, however, this software is not available when using remote data access.

Binder [111] prefers design-based approaches as they produce valid estimates with minimal efficiency loss. Boudreau and Lawless [116] suggest the use of the robust variance estimation method, though sampling weights are needed to account for the non-ignorable sampling or losses to follow- up.

6.4 Objective 3: To compare the variance corrected and frailty models for recurrent survival data using both the design-based and model-based approach.

The focus of the third objective was to compare the variance corrected models for recurrent survival data and to test for heterogeneity using a frailty model approach. The frailty model could not be fitted due to technical problems with the software. SAS macro 'gamfrail' was used to fit the gamma frailty model, but the problems with the macro could not be resolved using remote data access. STATA software was also used to fit the gamma frailty model. However, the gamma frailty model was not able to iterate and went into a loop so this method was also not used. Using the SAS procedure PHREG with the WEIGHT option, AG, WLW and PWP-total time and PWP-gap time model were applied to the survey data. The hazard ratios obtained for the AG and WLW models (accounting for the survey weights) were similar. The 95% confidence intervals were very tight for AG model, resulting in highly significant p-values. This indicated that the AG model was not able to account for the recurrent events in the survey data. Using the robust variance estimation method and ignoring the sampling design completely resulted in similar hazard ratios and their corresponding 95% confidence intervals for the AG and WLW models. The PWP-gap time and total time produced exactly the same results as the WLW approach. When the survey weights were specified, the confidence intervals of the WLW model were wider than the unweighted or the robust analysis. The difference in the confidence intervals could be due to extra variability arising from the complexity of the data. Although the WLW method provided the most stable results, the lack of any standard method makes it difficult to assess which method is the most suitable to analyze recurrent event history data.

There are several reasons for the similar results between the WLW and the PWP approaches used in the current study. First, the similarity could be due to the absence of an exact follow-up time. In absence of this information, age at the start of the risk period and age when the event occurred was used, resulting in a two year gap for each individual at a particular time point. Hence, it was difficult to distinguish between risks sets at the time of censoring. Second, in this particular analysis, the number of censored cases was larger than the number of events. The reason for so many censored cases was due to the fact that the NPHS focuses on the overall health of the Canadian population. Thus, the population at risk included not only subjects who were at risk for asthma, but also, for other diseases. Third, the reason for such results could be due to ignoring the intermittent missing data or the loss to follow up [116]. Fourth, similar results could be due to the fact that clustering due to the sampling design was not taken into account. Indeed, some researchers suggest that clustering should not be ignored [110]. In absence of the exact follow-up time, the risk sets which distinguish between the AG, WLW and PWP models [61] were all the same, and could have been responsible for the similar results. Sampling weights in survey data assist in the calculation of the estimates of hazard ratios. To obtain unbiased and correct estimates and their standard errors, stratification and clustering should also be taken into account, along with survey weights [202].

The unweighted results of all three models (AG, WLW and PWP) were similar. The three features of the sampling design were completely ignored. All three methods used the robust variance estimation method to account for interdependence due to repeated events. However, the results suggest that robustness alone is not sufficient to account for the complexity of the survey design. Other features of the sampling design should also be considered while analyzing such data sets. As mentioned previously, the sampling weights only account for the unequal probability of selection . Methods should account for clustering and stratification to calculate the correct estimates and unbiased standard errors in multi-stage sampling design. Most researchers emphasize accounting for the clustering effect [6, 110] rather than the other issues of survey design.

To summarize, it is recommended that an analysis examining prevalence and incidence should be conducted accounting for the complexity of the survey design. The results also suggest that if the above methods are used, they should be interpreted with caution. The design-based approach should be used to obtain correct and unbiased estimates. Other complexities of longitudinal survey design, such as intermittent missing observations, loss to follow- up and recurrent event data, should be considered so that the estimates obtained are unbiased. Further research is needed to extend the current statistical methods used in standard longitudinal (non-survey) studies to longitudinal complex surveys.

6.5 Objective 4: To compare the robustness of data for completers versus incompleters using missing data analysis.

The focus of this objective was to study the bias associated with missing data by comparing the results of completers versus incompleters. Marginal (WGEE and PMM) and random effect modeling approaches were compared. There was a difference in the standard errors of the regression parameter estimates (a difference of 0.10 – 1.04 in standard errors was noted), with larger standard errors for the PMM than the WGEE method. The confidence intervals of PMM model were tighter as compared to the WGEE model. This difference in the standard errors and the measures of confidence interval length suggests that the PMM accounts for additional sources of uncertainty mainly arising from missing observations and non-response [43]. Thus, the results of the PMM suggest that there was bias associated with the missing data and that this should be accounted for in the analysis. The standard errors obtained for the random effect modeling using both the PQL-REML or PQL-ML approach were very small, resulting in highly significant point estimates. These highly significant results suggest that the weighted random effect modeling approach does not sufficiently account for the sampling design. Stratification and clustering effects should also be considered to obtain the correct standard errors [2].

A possible solution for fitting random effects models for the survey data is to use the four stage multilevel modeling approach. In this method, the primary sampling unit can be treated as level 4, the secondary sampling unit as level 3, the tertiary sampling unit as level 2, and the repeated observation as level 1. This method can then account for both the multi-stage sampling design and the longitudinal nature of the data. Unfortunately, for the present study, this approach was not available using remote data access. In the current analysis, only two-stage multi-level modeling was used, with subjects as Level 2 and repeated observations as Level 1. The results indicated that this approach was not able to account for the sampling design. The sampling weights specially calculated for the NPHS dataset should be recalculated for the multi-level model.[203]. Pfeffermann et al. [204] have shown that for two-level or two-stage sampling, the inclusion probability for Level 2 is Π_i and for Level 1 the inclusion probability $\Pi_{t|i}$ is conditional on Level 2. The sampling weights which should be created are W_i for Level 2 and for Level 1 $W_{t|i} = \frac{W_{it}}{W_{i1}}$, where t = 1, ….., T and $W_i = W_{i1}$, i.e. the weight for the first time point. These newly created weights can be used with a modified iterative generalized least square (IGLS) estimation approach [203]. This approach has been applied to data with a continuous outcome but can be used for discrete outcomes. The method proposed by Pfeffermann could not be applied in the present analysis, as these weights were not available to the researcher.

In short, the conservative results obtained when using random effect modeling suggested that the weight variable alone was not able to account for the two levels in the model and that the special weights discussed above are needed to obtain unbiased estimates and standard errors.

In conclusion, the marginal model approach using PMM provided the most stable results and is therefore recommended for missing data analysis. The proposed probability weighted Iterative Generalized Least Square (PWIGLS) algorithm protects against informative sampling and should be used if there are indications that the design is informative and should not be ignored [7]. Future analysis should consider extending the PWIGLS model for binary outcomes in the NPHS [6].

6.6 Prevalence and incidence estimation of asthma in the adult Canadian female population

Based on the results of the marginal model and event history analysis, the risk factors for asthma prevalence and incidence among adult Canadian women were studied. The results showed an increase in the overall prevalence of asthma during the ten year study period, from 6.2% (5.0-7.5) in Cycle 1 to 6.9% (6.1-7.7) in Cycle 5. When stratified by smoking status, asthma prevalence showed a significant increase among ex-smokers, from 5.8% (4.4-7.2) in Cycle 1 to 10.5 (8.9-12.2) in Cycle 5. The prevalence of asthma also increased among females who were not exposed to second hand smoke.

The statistically significant predictors of asthma prevalence were: obesity, allergies (food and other kind), bronchitis, intestinal problems, residing in the Atlantic region and immigration status. The significant interaction variables were: location and smoking status, location and socioeconomic status, ethnicity and socioeconomic status, exposure to second hand smoke and time, smoking status and age, and socioeconomic status and age.

The overall incidence rate showed a decrease from 16% in Cycle 2 to 6.4% in Cycle 5. The decrease in the incidence of asthma over the study period could be because a closed population was studied. The significant predictors of asthma incidence were allergies, bronchitis, current smoking and exposure to second hand smoke.

The relationship between asthma and body mass index among females has been studied extensively. In this study, the prevalence and incidence of asthma was highest among obese women followed by overweight women. Compared to women of normal weight, the risk of asthma was significantly lower for underweight women. The results of this study are similar to other studies which have also reported a positive association between asthma and body mass index [13, 14, 16, 161, 205, 206]. The reason for the higher asthma prevalence and incidence of asthma in obese and overweight women could be because weight gain can lead to decreases in lung volumes and increasing airflow obstruction [14, 207, 208]. Other researchers have suggested that the observed relationship between asthma and body mass index may be partly due to the fact that asthma is over-diagnosed in obese individuals and/or that more obese people are seen by health care providers and thus have a higher chance of receiving an asthma diagnosis [160]. Several studies have also shown that increasing obesity rates have not resulted in the rising trend in asthma prevalence [209, 210].

Women 18 to 29 years of age were at a higher risk of both asthma prevalence and incidence, followed 30 to 49 year old women. These results were similar to several other studies which reported that younger females were at higher risk of asthma compared to older females and that the risk of asthma decreased with age [16, 17, 206, 209, 211]. In contrast to these findings, two studies found no statistically significant association between asthma and age [212].

The relationship between smoking and asthma was also assessed in the present study. Compared to non-smokers, the incidence of asthma showed a statistically significant decrease over time among smokers and a non-statistically significant increase among ex-smokers. Compared to those not exposed to second hand smoke, the risk of asthma was 2.2 times higher amongst females who were exposed to second hand smoke. Some research has shown active smoking to be associated with increased respiratory symptoms among those diagnosed with asthma [168, 169], while other studies report a higher risk among ex-smokers [213]. Similar to the results obtained in this study, other research has reported a decreased risk of asthma in smokers and ex-smokers compared to non-smokers [159, 209]. The decreased risk of asthma among smokers found in this study and others may be due to the fact that individuals with sensitive airways are less likely to become smokers and are more likely to quit smoking [165, 209]. Another possibility is that there is a tendency to label asthma-like disorders as asthma in non-smokers, but not in smokers . Several studies have shown that there is no association between asthma and smoking [164, 165], while others have found that smoking is an independent risk factor f asthma [166, 205].

The relationship between asthma prevalence and exposure to second hand smoke was also studied and the results showed that the prevalence was higher in the exposed category and that it increased over time. Asthma incidence was also higher among those women exposed to second hand smoke. However, several studies have failed to find an association between asthma and second hand exposure to smoke among non-smokers [13]. Other research among adults with asthma has found second hand exposure to smoke to be associated with decreased lung function, greater asthma severity, worse health status, and increased health care utilization [172].

The interaction effect between smoking and rural/urban residence was also examined in the present study. Smokers and ex-smokers residing in rural areas were at higher risk of developing asthma compared to non-smokers residing in urban areas. Several studies have shown an association between a higher prevalence of asthma and asthma-like symptoms and smoking, after adjusting for place of residence [149]. However, location has not been studied as an effect modifier in the relationship between asthma prevalence and smoking. Rural living, particularly in farming environments, has been associated with a higher prevalence of asthma, allergies and respiratory symptoms in adults. [156]. In this study, the positive interaction observed between smoking and rural living   cannot be more fully explored since information on outdoor environmental exposures that could modify the relationship between smoking and asthma were not available [15, 214]. The irritating effects of smoking on the lungs may explain why smokers and ex-smokers were at a higher risk of asthma than non-smokers

[214]. However, further research is needed to identify why rural female smokers and ex-smokers may be more susceptible to asthma than their urban counterparts.

There was a significant increase in the risk of asthma prevalence among young female smokers in the 18 to 29 years age group. The risk also increased for smokers and ex-smokers in the 30 to 64 years age groups; however, this risk was not statistically significant. These results are similar to several other studies (studying adult population-18 years and older) where the increase was observed among smokers compared to the non-smokers [16-18, 173, 211].

Previous research has found the prevalence and incidence of asthma to be higher among lower socioeconomic groups [16-18, 159, 173, 206]. In the present study, a statistically significant interaction emerged between location and socioeconomic status. More specifically, there was an increase in the prevalence of asthma among rural females in the higher and middle socioeconomic groups compared to urban females with lower socioeconomic status. These findings, though interesting, were not supported in other studies.

The association of asthma with ethnicity and immigrant status was also examined in this study. Similar to previous research [16-18, 206], the prevalence and incidence of asthma was higher among Canadian citizens than non-Canadian citizens. In addition, Caucasian women had a higher prevalence and incidence of asthma compared to non-Caucasian women.

Similar to previous research [16-18, 159], allergies were positively associated with both the incidence and prevalence of asthma in the present study . Asthma prevalence and incidence was also higher among women diagnosed with chronic bronchitis/emphysema, consistent with the results of a previous study [138].

6.7 Limitations and advantages of using the NPHS data

There are several advantages of analyzing data from large national databases such as the NPHS. The longitudinal NPHS data provided a large sample size and enhanced statistical power due to repeated observations on the same individual when compared to other similar kinds of cross-sectional surveys. Some of the other advantages of longitudinal studies over cross-sectional studies are that fewer subjects are needed and repeated observations on the same individual adds more information, as each subject acts like their own control [35]. In Canada, most of the studies that have been conducted to investigate the prevalence of asthma among adults were cross-sectional [20, 22, 131, 132, 215]. The NPHS is unique in that a cohort has been studied cross-sectionally over a period of time providing useful data to determine both the prevalence and incidence of asthma in a population.

To reduce bias in the NPHS, quality assurance measures were implemented. Interviews were conducted by experienced and trained interviewers to reduce potential bias. Non-response bias was minimized by implementing many strategies designed to enhance the response rate [216]. Another advantage of using such large national databases are that the results generated from the analysis will help policy makers to make decisions regarding the most needed areas of attention that can help to reduce the burden of disease.

There are also limitations to the present study. The diagnostic criteria used in the NPHS was self-reported, health professional diagnosed asthma. The sensitivity and specificity of self-reported asthma has been evaluated in numerous studies. In one study, the mean sensitivity and specificity of "health professional diagnosed asthma" was 64.3 % and 94.3%, respectively [217]. Thus, there may have been some subjects with asthma in the present study misclassified as not having asthma. Another limitation of using the NPHS was that no objective measures of asthma were included, such as pulmonary function tests, methacholine challenge tests, or allergy skin prick tests. This data set was not developed for asthma studies alone but as a study of general health and chronic disease. Consequently, very limited information related to asthma was available. Some of the results on associated risk factors could not be presented due to low cell counts [216]. Another limitation of the study was the reliance on self-report of smoking, height and weight for calculation of body mass index, which could have also resulted in measurement or misclassification error.

Finally, there were several limitations in using the NPHS for event history analysis. First, the NPHS data did not focus on a specific event of interest as required for survival analysis. Second, information on time to an event, a key feature of survival analysis, was not collected. Hence, the time to an event had to be calculated as the two year time gap between any two consecutive cycles. However, this data set provides valuable new information on the incidence of asthma in Canadian women. If additional information is made available on the exact date of asthma diagnosis in future surveys, this would provide more reliable information on asthma incidence in Canada. Apart from these limitations, the other major limitation was the use of remote data access.

Generalizability of conclusions about efficiency and unbiasedness can be achieved with a simulation study that systematically varies parameters such as the proportion of missing observations, correlation structure of repeated measurements, magnitude of the effect size, and various others. The consistency of the model-based and design-based methods could not be assessed using simulation studies due to the use of remote data access.

6.8 Conclusion and future studies

In conclusion, the design- based methods should be preferred over the model-based methods. The design- based methods provide unbiased results for complex survey designs. Results considering only the sampling weights produced biased results and should be avoided. Comparative studies using different statistical methods are needed to determine which method(s) can best handle the complexities of survey design.

The overall crude asthma prevalence increased among adult Canadian women from Cycle 1 to Cycle 5 and the incidence of decreased over the eight year period. The present study was not able to find any rural-urban differences for asthma incidence. However, for the prevalence of asthma, there was significant interaction for rural/urban living and smoking status, as well as for rural/urban living and socioeconomic status. As well, the risk of asthma was higher for those females who were either smokers or ex-smokers. Further research is needed to identify the characteristics of rural environments that could contribute to the results reported in this thesis.

The application of recent developments in statistical theories to the analysis of the NPHS data set to determine the risk factors related to asthma prevalence and incidence in adult female population was novel. The limited use of large scale surveys may be due to the fact that the required analyses are complex and researchers may not be trained to apply these methods. Continuing to train researchers in the use of these techniques is warranted.

Some of the areas in the field of survey methodology which need attention are missing data analysis, recurrent survival data, hybrid frailty models and joint modeling of longitudinal data with survival analysis. Some of these areas, like missing data analysis and recurrent survival data analysis are well developed for non-survey studies, but have received very little consideration for survey data.

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APPENDIX A

A.1 Notation of matrices and vector

Let us consider a longitudinal study with m subjects, and n_i observation on i^{th} subject, where i = 1,…….., m subjects, j = 1,…….., n_i responses for the i^{th} subject recorded at times $t_{i1} < t_{i2} <$……..$<t_i\ n_i$

$\mathbf{Y}_{ij}$ is the observed response for subject i at time t_{ij}

So $\begin{bmatrix} y_{i1} \\ y_{i2} \\ \cdots \\ y_{in_i} \end{bmatrix}$ is a n_ix1 column vector for subject i

For all the subjects ($\sum n_i$) x1 column vector is given as

$$\begin{bmatrix} y_{11} \\ \ldots \\ y_{1n1} \\ y_{21} \\ \ldots \\ y_{2n2} \\ \ldots \\ y_{m1} \\ \ldots \\ y_{mn_m} \end{bmatrix}$$

$\mathbf{X}_{ij} = \begin{bmatrix} X_{ij1} \\ X_{ij2} \\ \ldots \\ X_{ijp} \end{bmatrix}$ is the px1 column vector of covariate value for the i^{th} subject at time t_{ij}

and $\mathbf{X}_i^{'} = \begin{bmatrix} X_{i1}^{'} \\ X_{i2}^{'} \\ \ldots \\ X_{in_i}^{'} \end{bmatrix} = \begin{bmatrix} X_{i11} X_{i12} \ldots X_{i1p} \\ X_{i21} X_{i22} \ldots X_{i2p} \\ \ldots \\ X_{in_i 1} X_{in_i 2} \ldots X_{in_i p} \end{bmatrix}$ is the $n_i$xp matrix of covariate values for the ith subject

A. 2 Glossary of statistical terms used for survival analysis

Heterogeneity across individuals -: The variance across individuals are not equal, and there exists within subject correlation.

Event Dependence -: The occurrence of one event may make further disruption more or less likely. The dependence violates the independent assumption of the Cox model.

Independent Increment -: The number of event in non-overlapping time intervals are independent, given the covariates.

Coverage probabilities -: When we have a set of ensembles (a group of elements) of experiments and each member of which is associated with a fixed value of the parameter to be measured θ. For a given ensemble, the fraction of experiments with intervals containing the θ value associated with that ensemble is called the coverage probabilities. The interval $\theta \pm 1.96 * \text{S.E.}$ covers the true value θ with a probability of approximately 95%.

Multiple level of association -: is also known as clustering, intra (within) family association, between and within household association.

Maximum likelihood estimation-: An estimation procedure involving maximization of the likelihood or the log-likelihood with respect to the parameters.

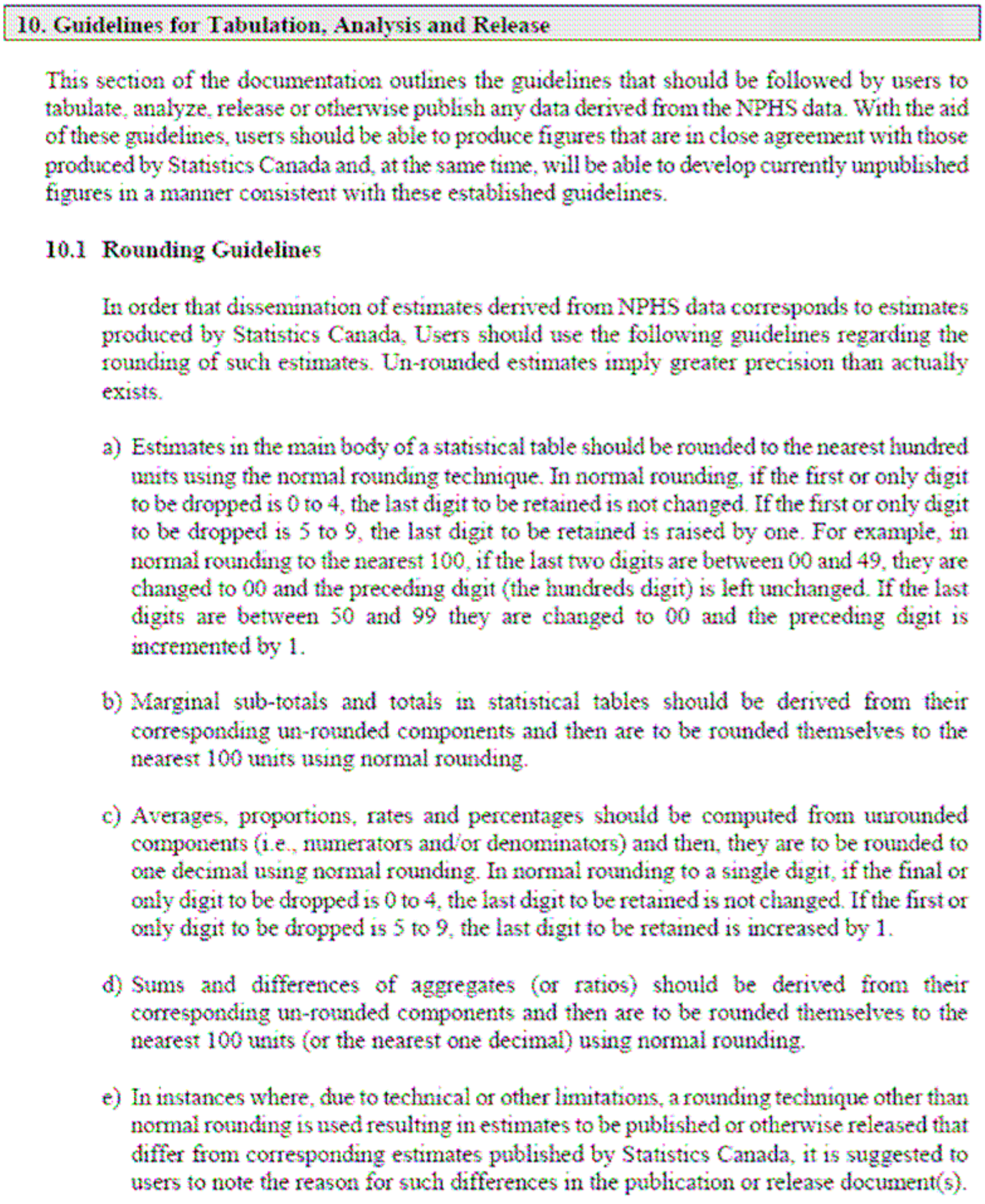
Partial Likelihood -: This is used to estimate the β coefficients (parameter estimates) in proportional hazard models. It is obtained by comparing the risk given x_j to the risk given all other x_is in the risk set at time t.

$$L_j \propto \frac{\text{risk for failed subject at time t}}{\text{average risk in the risk set at time t}}$$

Pseudo Likelihood -: A function of the data and parameters that has properties similar to the usual likelihood function; frequently arises as an estimate of the observed likelihood based on incomplete data.

APPENDIX B

B. 1 Guidelines of Statistics Canada for result publication



10. Guidelines for Tabulation, Analysis and Release

This section of the documentation outlines the guidelines that should be followed by users to tabulate, analyze, release or otherwise publish any data derived from the NPHS data. With the aid of these guidelines, users should be able to produce figures that are in close agreement with those produced by Statistics Canada and, at the same time, will be able to develop currently unpublished figures in a manner consistent with these established guidelines.

10.1 Rounding Guidelines

In order that dissemination of estimates derived from NPHS data corresponds to estimates produced by Statistics Canada, Users should use the following guidelines regarding the rounding of such estimates. Un-rounded estimates imply greater precision than actually exists.

a) Estimates in the main body of a statistical table should be rounded to the nearest hundred units using the normal rounding technique. In normal rounding, if the first or only digit to be dropped is 0 to 4, the last digit to be retained is not changed. If the first or only digit to be dropped is 5 to 9, the last digit to be retained is raised by one. For example, in normal rounding to the nearest 100, if the last two digits are between 00 and 49, they are changed to 00 and the preceding digit (the hundreds digit) is left unchanged. If the last digits are between 50 and 99 they are changed to 00 and the preceding digit is incremented by 1.

b) Marginal sub-totals and totals in statistical tables should be derived from their corresponding un-rounded components and then are to be rounded themselves to the nearest 100 units using normal rounding.

c) Averages, proportions, rates and percentages should be computed from unrounded components (i.e., numerators and/or denominators) and then, they are to be rounded to one decimal using normal rounding. In normal rounding to a single digit, if the final or only digit to be dropped is 0 to 4, the last digit to be retained is not changed. If the first or only digit to be dropped is 5 to 9, the last digit to be retained is increased by 1.

d) Sums and differences of aggregates (or ratios) should be derived from their corresponding un-rounded components and then are to be rounded themselves to the nearest 100 units (or the nearest one decimal) using normal rounding.

e) In instances where, due to technical or other limitations, a rounding technique other than normal rounding is used resulting in estimates to be published or otherwise released that differ from corresponding estimates published by Statistics Canada, it is suggested to users to note the reason for such differences in the publication or release document(s).

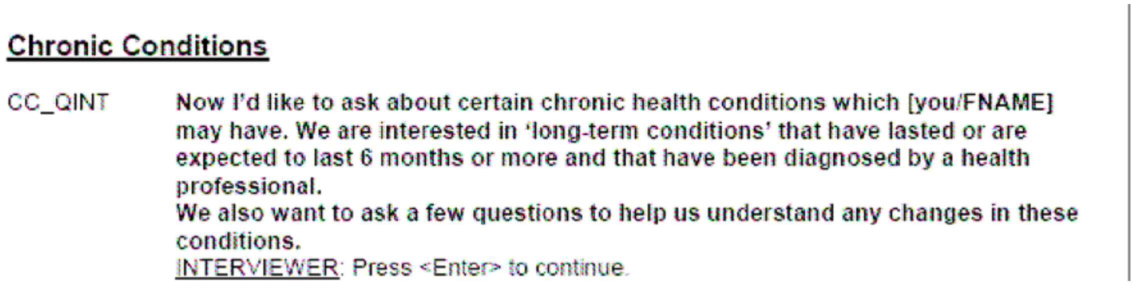
10.4 Release Guidelines

Before releasing or publishing any total or proportion estimates from the master files, users must first determine the number of sampled respondents having the characteristic of interest (for example, the number of respondents who smoke when interested in the proportion of smokers for a given population). If this number is less than 10, the weighted estimate should not be released regardless of the value of the coefficient of variation for this estimate. This is due to the fact that the possibility of obtaining an artificially low variance is greater with a sample size less than 10. For weighted estimates based on sample sizes of 10 or more, users should determine the coefficient of variation of the estimate and follow the guidelines described in Table 10.A.

Table 10.A: Sampling Variability Guideline

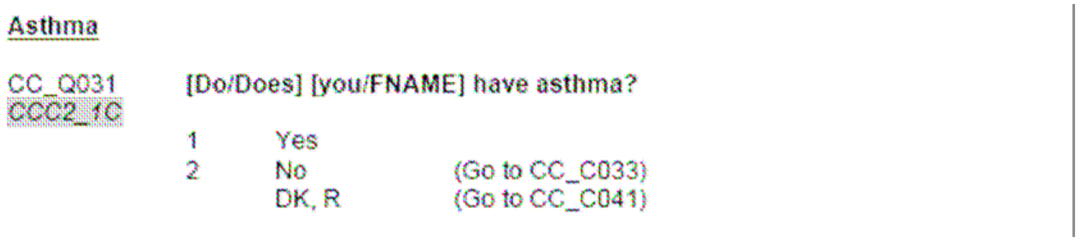
Type of Estimate	C.V. (in %)	Guidelines
Acceptable	0.0 - 16.5	Estimates can be considered for general unrestricted release. Requires no special notation.
Marginal	16.6 - 33.3	Estimates can be considered for general unrestricted release but should be accompanied by a warning cautioning subsequent users of the high sampling variability associated with the estimates. Such estimates should be identified by the letter E (or in some other similar fashion).
Unacceptable	greater than 33.3	Statistics Canada recommends not to release estimates of unacceptable quality. However, if the user chooses to do so then estimates should be flagged with the letter F (or in some other fashion) and the following warning should accompany the estimates: "The user is advised that . . .(specify the data) . . . do not meet Statistics Canada's quality standards for this statistical program. Conclusions based on these data will be unreliable and most likely invalid. These data and any consequent findings should not be published. If the user chooses to publish these data or findings, then this disclaimer must be published with the data."

B.2 NPHS selected questionnaires



Chronic Conditions

CC_QINT Now I'd like to ask about certain chronic health conditions which [you/FNAME] may have. We are interested in 'long-term conditions' that have lasted or are expected to last 6 months or more and that have been diagnosed by a health professional.
We also want to ask a few questions to help us understand any changes in these conditions.
INTERVIEWER: Press <Enter> to continue.

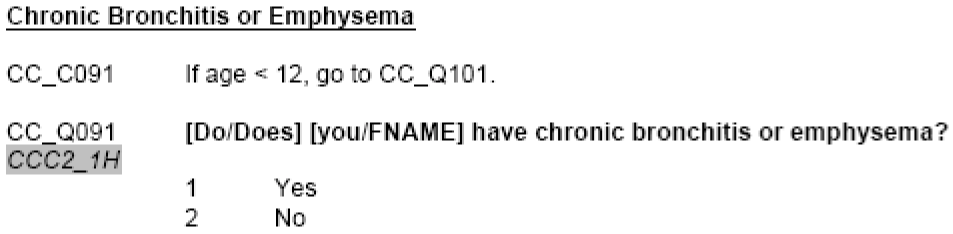


Asthma

CC_Q031
CCC2_1C

[Do/Does] [you/FNAME] have asthma?

1 Yes
2 No (Go to CC_C033)
DK, R (Go to CC_C041)



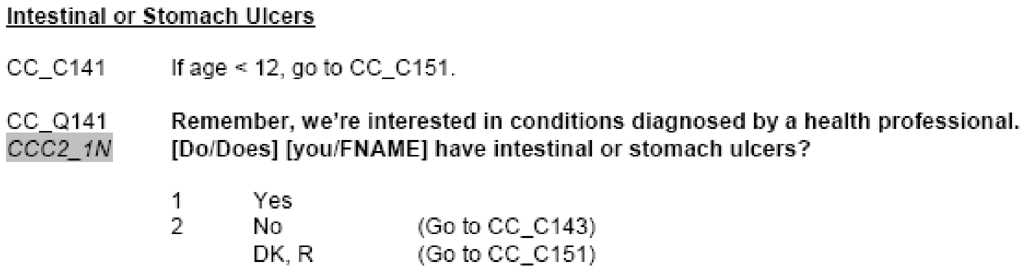
Chronic Bronchitis or Emphysema

CC_C091 If age < 12, go to CC_Q101.

CC_Q091
CCC2_1H

[Do/Does] [you/FNAME] have chronic bronchitis or emphysema?

1 Yes
2 No



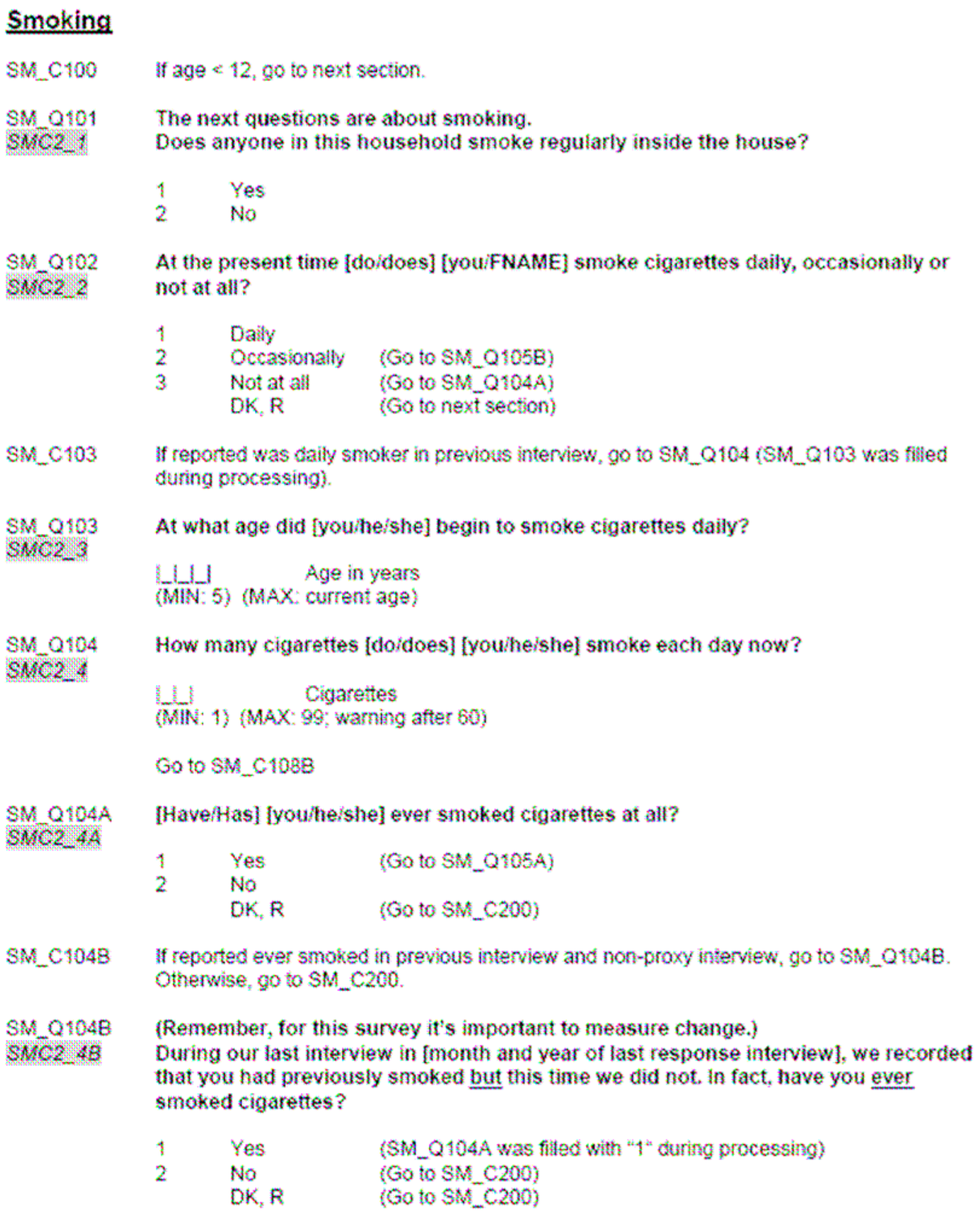
Intestinal or Stomach Ulcers

CC_C141 If age < 12, go to CC_C151.

CC_Q141
CCC2_1N

Remember, we're interested in conditions diagnosed by a health professional.
[Do/Does] [you/FNAME] have intestinal or stomach ulcers?

1 Yes
2 No (Go to CC_C143)
DK, R (Go to CC_C151)



Smoking

SM_C100 If age < 12, go to next section.

SM_Q101 **The next questions are about smoking.**
SMC2_1 **Does anyone in this household smoke regularly inside the house?**

1 Yes
2 No

SM_Q102 **At the present time [do/does] [you/FNAME] smoke cigarettes daily, occasionally or**
SMC2_2 **not at all?**

1 Daily
2 Occasionally (Go to SM_Q105B)
3 Not at all (Go to SM_Q104A)
DK, R (Go to next section)

SM_C103 If reported was daily smoker in previous interview, go to SM_Q104 (SM_Q103 was filled during processing).

SM_Q103 **At what age did [you/he/she] begin to smoke cigarettes daily?**
SMC2_3

|_|_|_| Age in years
(MIN: 5) (MAX: current age)

SM_Q104 **How many cigarettes [do/does] [you/he/she] smoke each day now?**
SMC2_4

|_|_| Cigarettes
(MIN: 1) (MAX: 99; warning after 60)

Go to SM_C108B

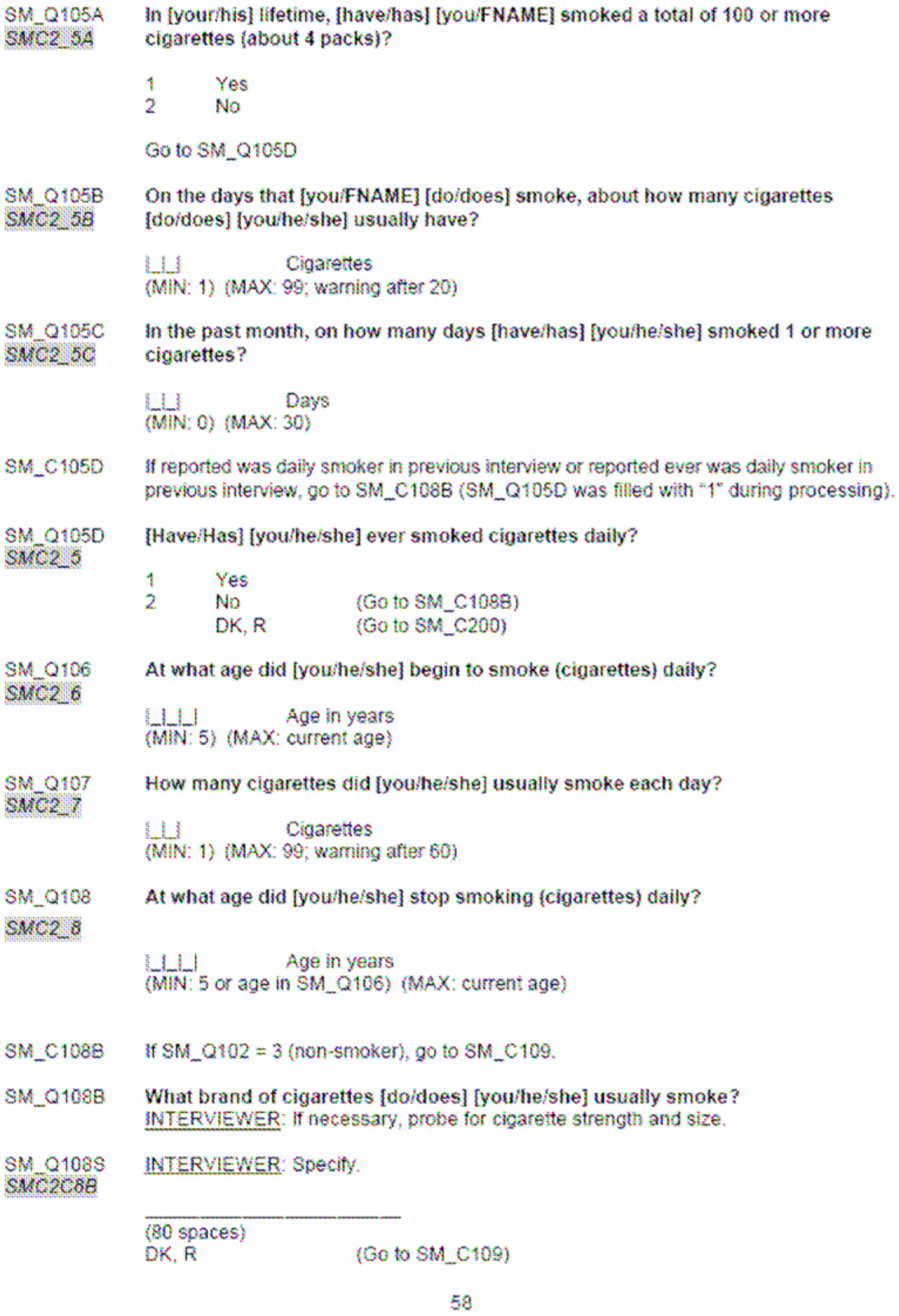
SM_Q104A **[Have/Has] [you/he/she] ever smoked cigarettes at all?**
SMC2_4A

1 Yes (Go to SM_Q105A)
2 No
DK, R (Go to SM_C200)

SM_C104B If reported ever smoked in previous interview and non-proxy interview, go to SM_Q104B. Otherwise, go to SM_C200.

SM_Q104B **(Remember, for this survey it's important to measure change.)**
SMC2_4B **During our last interview in [month and year of last response interview], we recorded that you had previously smoked <u>but</u> this time we did not. In fact, have you <u>ever</u> smoked cigarettes?**

1 Yes (SM_Q104A was filled with "1" during processing)
2 No (Go to SM_C200)
DK, R (Go to SM_C200)



SM_Q105A
SMC2_5A

In [your/his] lifetime, [have/has] [you/FNAME] smoked a total of 100 or more cigarettes (about 4 packs)?

1 Yes
2 No

Go to SM_Q105D

SM_Q105B
SMC2_5B

On the days that [you/FNAME] [do/does] smoke, about how many cigarettes [do/does] [you/he/she] usually have?

|_|_| Cigarettes
(MIN: 1) (MAX: 99; warning after 20)

SM_Q105C
SMC2_5C

In the past month, on how many days [have/has] [you/he/she] smoked 1 or more cigarettes?

|_|_| Days
(MIN: 0) (MAX: 30)

SM_C105D

If reported was daily smoker in previous interview or reported ever was daily smoker in previous interview, go to SM_C108B (SM_Q105D was filled with "1" during processing).

SM_Q105D
SMC2_5

[Have/Has] [you/he/she] ever smoked cigarettes daily?

1 Yes
2 No (Go to SM_C108B)
DK, R (Go to SM_C200)

SM_Q106
SMC2_6

At what age did [you/he/she] begin to smoke (cigarettes) daily?

|_|_|_| Age in years
(MIN: 5) (MAX: current age)

SM_Q107
SMC2_7

How many cigarettes did [you/he/she] usually smoke each day?

|_|_| Cigarettes
(MIN: 1) (MAX: 99; warning after 60)

SM_Q108
SMC2_8

At what age did [you/he/she] stop smoking (cigarettes) daily?

|_|_|_| Age in years
(MIN: 5 or age in SM_Q106) (MAX: current age)

SM_C108B

If SM_Q102 = 3 (non-smoker), go to SM_C109.

SM_Q108B

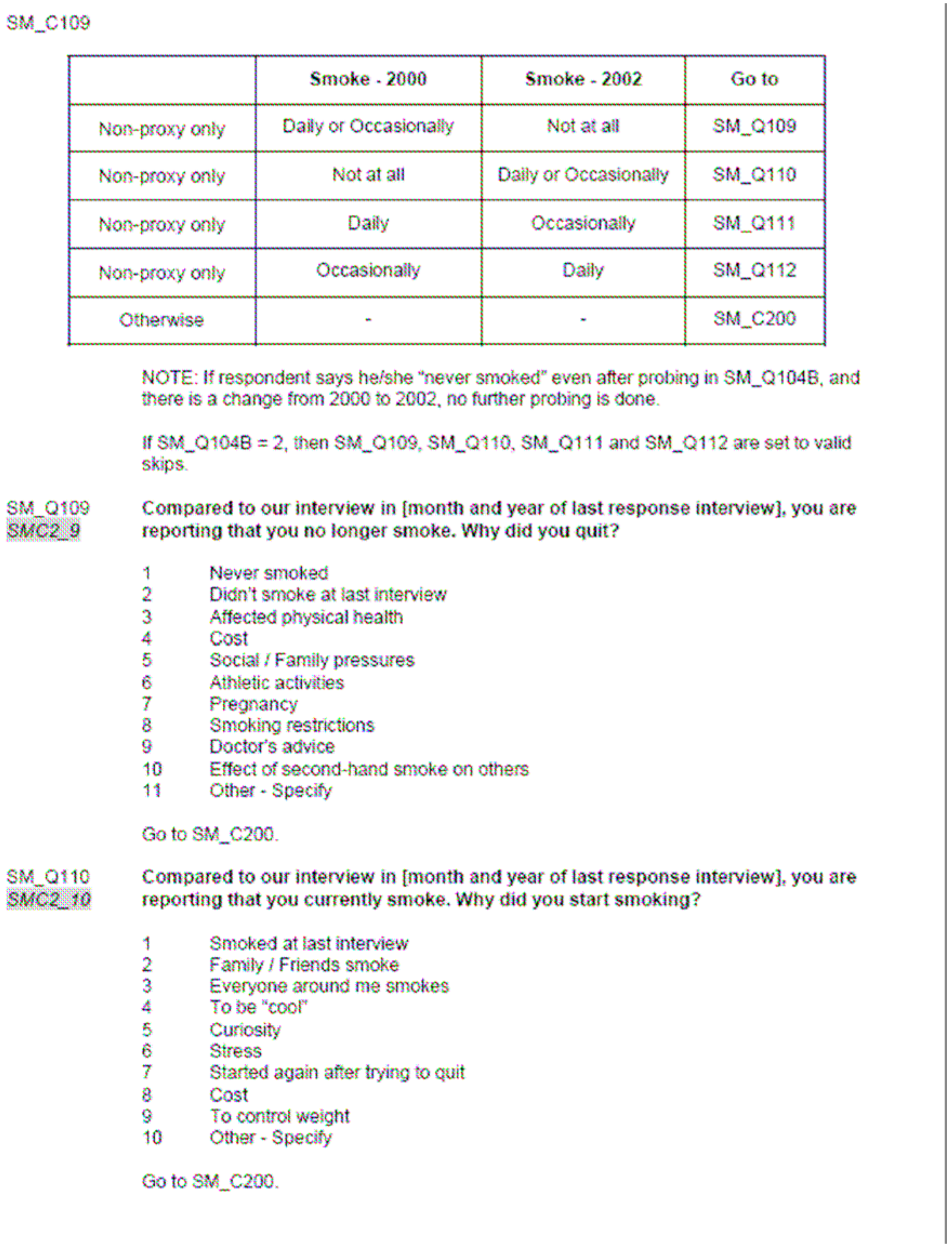
What brand of cigarettes [do/does] [you/he/she] usually smoke?
INTERVIEWER: If necessary, probe for cigarette strength and size.

SM_Q108S
SMC2C8B

INTERVIEWER: Specify.

____
(80 spaces)
DK, R (Go to SM_C109)

58



SM_C109

	Smoke - 2000	Smoke - 2002	Go to
Non-proxy only	Daily or Occasionally	Not at all	SM_Q109
Non-proxy only	Not at all	Daily or Occasionally	SM_Q110
Non-proxy only	Daily	Occasionally	SM_Q111
Non-proxy only	Occasionally	Daily	SM_Q112
Otherwise	-	-	SM_C200

NOTE: If respondent says he/she "never smoked" even after probing in SM_Q104B, and there is a change from 2000 to 2002, no further probing is done.

If SM_Q104B = 2, then SM_Q109, SM_Q110, SM_Q111 and SM_Q112 are set to valid skips.

SM_Q109
SMC2_9

Compared to our interview in [month and year of last response interview], you are reporting that you no longer smoke. Why did you quit?

1 Never smoked
2 Didn't smoke at last interview
3 Affected physical health
4 Cost
5 Social / Family pressures
6 Athletic activities
7 Pregnancy
8 Smoking restrictions
9 Doctor's advice
10 Effect of second-hand smoke on others
11 Other - Specify

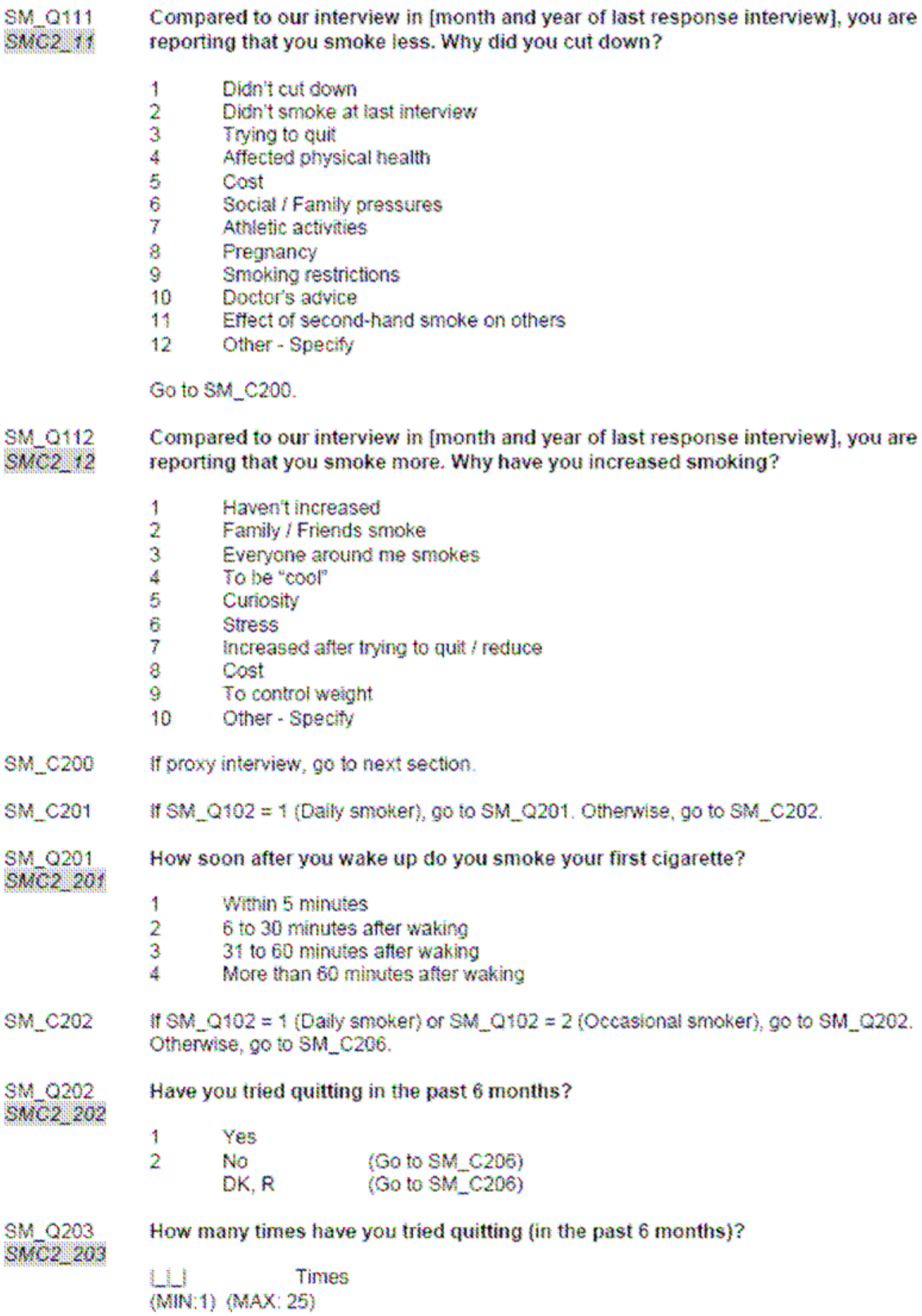
Go to SM_C200.

SM_Q110
SMC2_10

Compared to our interview in [month and year of last response interview], you are reporting that you currently smoke. Why did you start smoking?

1 Smoked at last interview
2 Family / Friends smoke
3 Everyone around me smokes
4 To be "cool"
5 Curiosity
6 Stress
7 Started again after trying to quit
8 Cost
9 To control weight
10 Other - Specify

Go to SM_C200.



SM_Q111
SMC2_11

Compared to our interview in [month and year of last response interview], you are reporting that you smoke less. Why did you cut down?

1 Didn't cut down
2 Didn't smoke at last interview
3 Trying to quit
4 Affected physical health
5 Cost
6 Social / Family pressures
7 Athletic activities
8 Pregnancy
9 Smoking restrictions
10 Doctor's advice
11 Effect of second-hand smoke on others
12 Other - Specify

Go to SM_C200.

SM_Q112
SMC2_12

Compared to our interview in [month and year of last response interview], you are reporting that you smoke more. Why have you increased smoking?

1 Haven't increased
2 Family / Friends smoke
3 Everyone around me smokes
4 To be "cool"
5 Curiosity
6 Stress
7 Increased after trying to quit / reduce
8 Cost
9 To control weight
10 Other - Specify

SM_C200 If proxy interview, go to next section.

SM_C201 If SM_Q102 = 1 (Daily smoker), go to SM_Q201. Otherwise, go to SM_C202.

SM_Q201
SMC2_201

How soon after you wake up do you smoke your first cigarette?

1 Within 5 minutes
2 6 to 30 minutes after waking
3 31 to 60 minutes after waking
4 More than 60 minutes after waking

SM_C202 If SM_Q102 = 1 (Daily smoker) or SM_Q102 = 2 (Occasional smoker), go to SM_Q202. Otherwise, go to SM_C206.

SM_Q202
SMC2_202

Have you tried quitting in the past 6 months?

1 Yes
2 No (Go to SM_C206)
DK, R (Go to SM_C206)

SM_Q203
SMC2_203

How many times have you tried quitting (in the past 6 months)?

|_|_| Times
(MIN:1) (MAX: 25)

SM_Q204 *SMC2_204* **Are you seriously considering quitting within the next 30 days?**

1 Yes (Go to SM_C206)
2 No

SM_Q205 *SMC2_205* **Are you seriously considering quitting within the next 6 months?**

1 Yes
2 No

SM_C206 If ST_Q400 = 1 (currently employed), go to SM_Q206. Otherwise, go to next section.

SM_Q206 *SMC2_206* **At your place of work what are the restrictions on smoking?**
INTERVIEWER: Read categories to respondent.

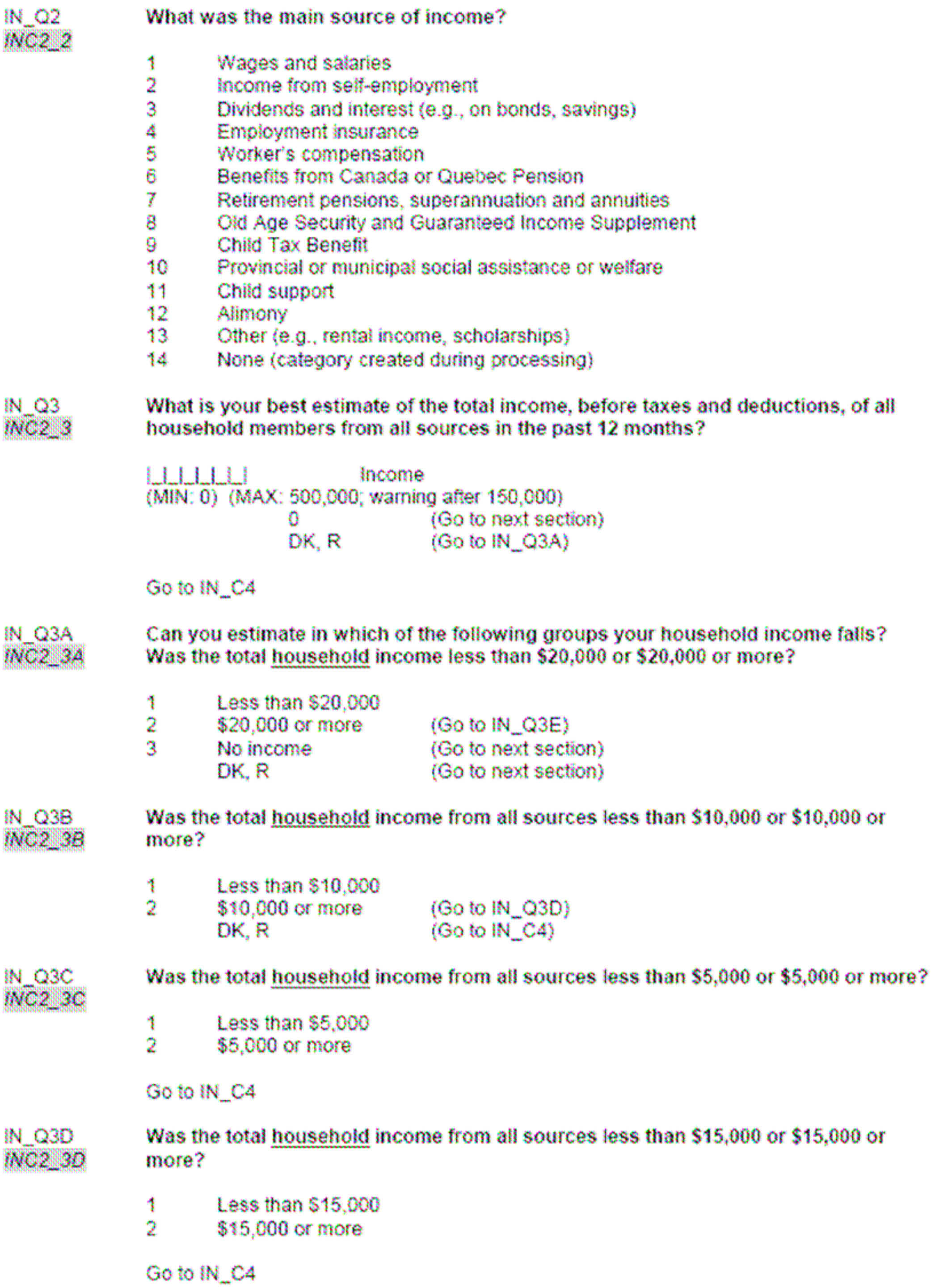
1 **Restricted completely**
2 **Allowed in designated areas**
3 **Restricted only in certain places**
4 **Not restricted at all**

Income

IN_Q1 **Thinking about the total income for all household members, from which of the following sources did your household receive any income in the past 12 months?**
INTERVIEWER: Read categories to respondent. Mark ALL that apply.

INC2_1A	1	**Wages and salaries**
INC2_1B	2	**Income from self-employment**
INC2_1C	3	**Dividends and interest (e.g., on bonds, savings)**
INC2_1D	4	**Employment insurance**
INC2_1E	5	**Worker's compensation**
INC2_1F	6	**Benefits from Canada or Quebec Pension Plan**
INC2_1G	7	**Retirement pensions, superannuation and annuities**
INC2_1H	8	**Old Age Security and Guaranteed Income Supplement**
INC2_1I	9	**Child Tax Benefit**
INC2_1J	10	**Provincial or municipal social assistance or welfare**
INC2_1K	11	**Child support**
INC2_1L	12	**Alimony**
INC2_1M	13	**Other (e.g., rental income, scholarships)**
INC2_1N	14	None (Go to IN_Q3)
		DK, R (Go to next section)

IN_C2 If more than one source of income is indicated, ask IN_Q2. Otherwise, ask IN_Q3. (IN_Q2 will be filled with IN_Q1 during processing.)



IN_Q2
INC2_2

What was the main source of income?

1	Wages and salaries
2	Income from self-employment
3	Dividends and interest (e.g., on bonds, savings)
4	Employment insurance
5	Worker's compensation
6	Benefits from Canada or Quebec Pension
7	Retirement pensions, superannuation and annuities
8	Old Age Security and Guaranteed Income Supplement
9	Child Tax Benefit
10	Provincial or municipal social assistance or welfare
11	Child support
12	Alimony
13	Other (e.g., rental income, scholarships)
14	None (category created during processing)

IN_Q3
INC2_3

What is your best estimate of the total income, before taxes and deductions, of all household members from all sources in the past 12 months?

|_|_|_|_|_|_| Income
(MIN: 0) (MAX: 500,000; warning after 150,000)

0	(Go to next section)
DK, R	(Go to IN_Q3A)

Go to IN_C4

IN_Q3A
INC2_3A

Can you estimate in which of the following groups your household income falls? Was the total household income less than $20,000 or $20,000 or more?

1	Less than $20,000	
2	$20,000 or more	(Go to IN_Q3E)
3	No income	(Go to next section)
	DK, R	(Go to next section)

IN_Q3B
INC2_3B

Was the total household income from all sources less than $10,000 or $10,000 or more?

1	Less than $10,000	
2	$10,000 or more	(Go to IN_Q3D)
	DK, R	(Go to IN_C4)

IN_Q3C
INC2_3C

Was the total household income from all sources less than $5,000 or $5,000 or more?

1	Less than $5,000
2	$5,000 or more

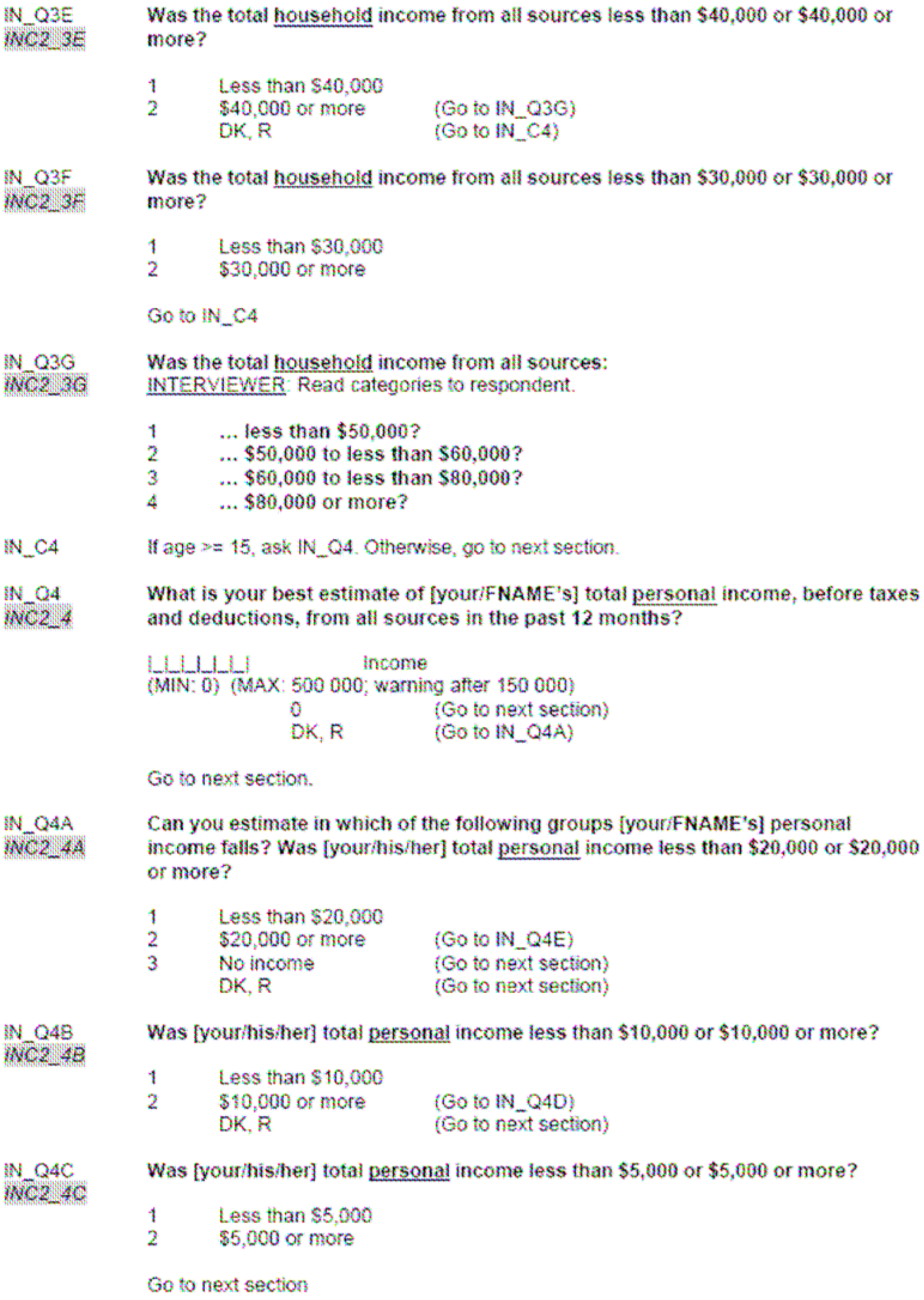
Go to IN_C4

IN_Q3D
INC2_3D

Was the total household income from all sources less than $15,000 or $15,000 or more?

1	Less than $15,000
2	$15,000 or more

Go to IN_C4



IN_Q3E
INC2_3E

Was the total household income from all sources less than $40,000 or $40,000 or more?

1	Less than $40,000	
2	$40,000 or more	(Go to IN_Q3G)
	DK, R	(Go to IN_C4)

IN_Q3F
INC2_3F

Was the total household income from all sources less than $30,000 or $30,000 or more?

1	Less than $30,000
2	$30,000 or more

Go to IN_C4

IN_Q3G
INC2_3G

Was the total household income from all sources:
INTERVIEWER: Read categories to respondent.

1	**... less than $50,000?**
2	**... $50,000 to less than $60,000?**
3	**... $60,000 to less than $80,000?**
4	**... $80,000 or more?**

IN_C4

If age >= 15, ask IN_Q4. Otherwise, go to next section.

IN_Q4
INC2_4

What is your best estimate of [your/FNAME's] total personal income, before taxes and deductions, from all sources in the past 12 months?

|_|_|_|_|_|_| Income
(MIN: 0) (MAX: 500 000; warning after 150 000)

0	(Go to next section)
DK, R	(Go to IN_Q4A)

Go to next section.

IN_Q4A
INC2_4A

Can you estimate in which of the following groups [your/FNAME's] personal income falls? Was [your/his/her] total personal income less than $20,000 or $20,000 or more?

1	Less than $20,000	
2	$20,000 or more	(Go to IN_Q4E)
3	No income	(Go to next section)
	DK, R	(Go to next section)

IN_Q4B
INC2_4B

Was [your/his/her] total personal income less than $10,000 or $10,000 or more?

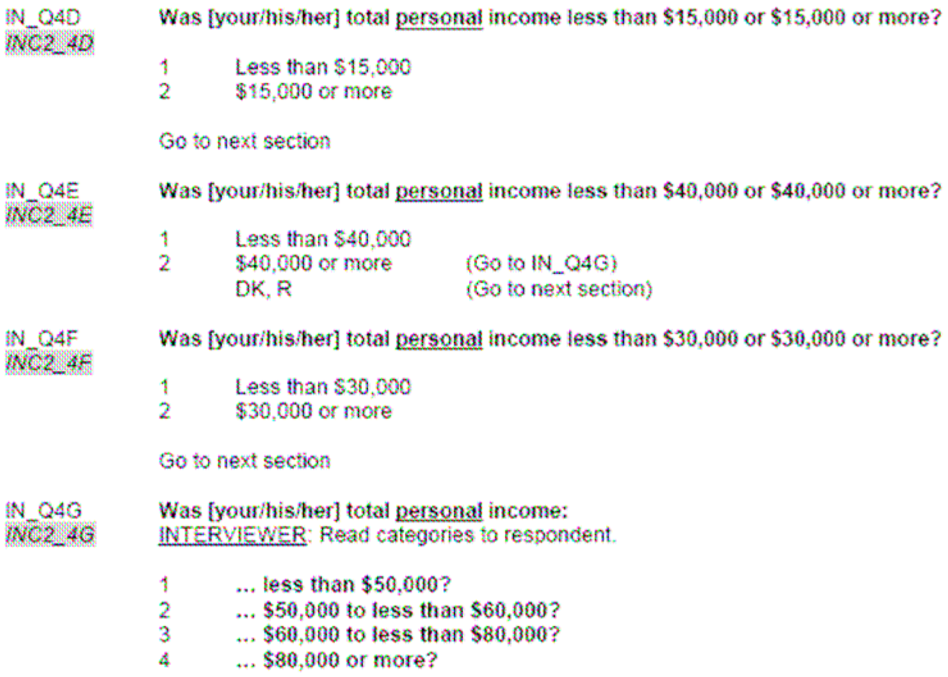
1	Less than $10,000	
2	$10,000 or more	(Go to IN_Q4D)
	DK, R	(Go to next section)

IN_Q4C
INC2_4C

Was [your/his/her] total personal income less than $5,000 or $5,000 or more?

1	Less than $5,000
2	$5,000 or more

Go to next section



IN_Q4D
INC2_4D

Was [your/his/her] total <u>personal</u> income less than $15,000 or $15,000 or more?

1 Less than $15,000
2 $15,000 or more

Go to next section

IN_Q4E
INC2_4E

Was [your/his/her] total <u>personal</u> income less than $40,000 or $40,000 or more?

1	Less than $40,000	
2	$40,000 or more	(Go to IN_Q4G)
	DK, R	(Go to next section)

IN_Q4F
INC2_4F

Was [your/his/her] total <u>personal</u> income less than $30,000 or $30,000 or more?

1 Less than $30,000
2 $30,000 or more

Go to next section

IN_Q4G
INC2_4G

Was [your/his/her] total <u>personal</u> income:
<u>INTERVIEWER</u>: Read categories to respondent.

1 **... less than $50,000?**
2 **... $50,000 to less than $60,000?**
3 **... $60,000 to less than $80,000?**
4 **... $80,000 or more?**

Appendix C

C.1 SAS Macro: Survey GEE

```
data bsamp ;
  set in2.bootwt;
  keep fwgt REALUKEY PERSONID bsw1-bsw500;
run;

 PROC SORT DATA=bsamp;BY REALUKEY PERSONID;RUN;
* Match the principal file and the weights bootstrap;
data clusters;
set in1.survival1;
 keep  REALUKEY PERSONID ;
run;

 PROC SORT DATA=clusters nodupkey;BY REALUKEY PERSONID;RUN;

     data in2.boot ;
       merge clusters (in=in1) bsamp (in=in2);
       by REALUKEY PERSONID;
       if in1;
           keep  REALUKEY PERSONID  bsw1-bsw500;
     run;
options nocenter linesize=80;

%macro c2(reg,num,name2);
  %do k=1 %to &num;
     %let covk=%scan(&reg,&k);
       &covk = &covk * &name2 ;
  %end;
%mend c2;

%macro contrast(c=);
do;
if contrast = 0 then goto bottom;

nc= ncol(contrast);

r= nrow(variable);

contrast=contrast[1,2:nc];

nr=(nc-1)/(r);
nr=round(nr);

contrast=shape(contrast,nr,r);

xsq=(contrast*estimate)`*inv(contrast*vb*contrast`)*
    (contrast*estimate);
cont_est = contrast*estimate;
var_cont = contrast*vb*contrast`;

df=nrow(contrast);

p=1-probchi(xsq,df);
```

```
&c=contrast;


%if &c=c1 %then %do;
print,  {"CONTRAST:   &title1"  };
%end;
%if &c=c2 %then %do;
print, {'                   '  };
print, {"CONTRAST:   &title2"  };
%end;
print , &c;
print, xsq df p;

%if &c1est^=no %then %do;
print, {'estimate of contrast is'  };
print, cont_est var_cont;
%end;
%if &c2est^=no %then %do;
print, {'estimate of contrast is'  };
print, cont_est var_cont;
%end;

bottom:
   stop;
end;
%mend contrast;

%macro delem(reg,num);
  %do k=1 %to &num;
    %let covk=%scan(&reg,&k);
    if &covk=. then delete;
  %end;
%mend delem;


%macro
gee(data=_last_,y=y,x=x,id=id,maxit=15,int=,print=yes,corr=ind,weight=
wt64ls,
           outbeta=,it_his=no,method=cond,crit=.000001,outrho=,

time=,k_j=,power=1,c1=,title1=,c1est=no,c2=,title2=,c2est=no,fmt=7.3,n
boot=);

%* id = 1 to n;
%* time = time of observation ;

%* ---- count the covariates;
%let p=0;
%do %while(%scan(&x,&p+1)^=); %let p=%eval(&p+1); %end;

data zzone;
   set &data;
 one=1;
  if &y=. then delete;
   %delem(&x,&p);
   yzzz=1-&y;
   intercep=1;
```

```
run;

proc sort data = zzone;
 by &id;
run;

data zzone;
  set zzone;
  by &id;
  if first.&id then idm+1;
  run;

proc sort data=zzone;
  by &id
%if &time^= %then %do;
    &time
%end;
  ;
run;

/*file of the identifiers of the clusters(individuals or households)*/
data name ( keep = realukey MENAGE personid idm);
set zzone;
informat menage f15.0 ;
format menage f15.0 ;
run;
PROC SORT DATA=NAME NODUPKEY;BY REALUKEY;RUN;

proc logistic data=zzone covout outest=esti noprint;
%if &int=no %then %do;
    model yzzz=&x /noint;
%end;
%else %do;
    model yzzz=&x ;
%end;
%if &weight^= %then %do;
    weight &weight;
%end;
%if &corr=ind %then %do;
    output out=resid p=_p_;
%end;
run;

data par(drop=_type_ _name_
%if &sysver^=6.07 %then %do;
    _lnlike_
%end;
  );
    set esti;
    if (_type_ ne 'PARMS') then delete;
run;

%if &corr=ind %then %do;

data c1(drop=_type_ _name_ _link_
%if &sysver^=6.07 %then %do;
    _lnlike_
%end;
  );
    set esti;
    if (_type_  = 'PARMS') then delete;
run;

data resid2;
  set resid;
  _resid_ = yzzz - (1-_p_);
  _z_ = (yzzz - (1-_p_))/sqrt(_p_*(1-_p_) );
  run;

proc sort data=resid2;
  by &id;
run;

data c2dat1;
 set resid2;
 %c2(&x,&p,_resid_);
;
proc means data=c2dat1 noprint;
    by &id;
    var
%if &weight^= %then %do;
    &weight
%end;
%if &int=no %then %do;
     &x;
%end;
%else %do;
     _resid_ &x;
%end;
    output out=c2dat2(drop=_type_ _freq_ &id
%if &weight^= %then %do;
    j0
jj1 - jj&p
%if &int^=no %then %do;
   jj0
%end;

%end;
)
    sum =
%if &weight^= %then %do;
    j0
%end;
%if &int=no %then %do;
    &x
%end;
%else %do;
     &x
%end;
%if &weight^= %then %do;
    mean =
    &weight
%if &int=no %then %do;
    jj1 - jj&p
```

```
%end;
%else %do;
   jj0 jj1 - jj&p
%end;

%end;
 ;
run;

proc corr nocorr sscp out=uusq(type=sscp) noprint;
%if &weight^= %then %do;
    weight &weight;
%end;
 title '                         ';
   ;

data c2(drop=_type_ _name_);
    set uusq;
    if (_type_ ne 'SSCP') then delete;
    if (_name_ = 'INTERCEP') then delete;
    RUN;

proc iml worksize=500;
 reset nolog noprint;

     use par;
     read all into beta;
nbeta = ncol(beta);

     use c1;
     read all into n_1c1_1;

     use c2;
     read all into nc2;

%if &int=no %then %do;
variable = { &x };
%end;
%else %do;
variable = { "INTERCEP" } || { &x };
%end;

variable =   variable`;

     vb = n_1c1_1;   *naive covariance ;

     sebeta=sqrt(vecdiag(vb));      *vector of estimated
                                       standard errors of
                                       beta;

     z=beta`/sebeta;                    *z-statistics;

     zsq=z#z;

     p=1-probchi(zsq,1);               *two-sided p-value;

estimate=beta`;
```

```
se_est=sebeta;

%if &print^=no %then %do;
   print, { 'Correlation Structure: Independence' };
   print, { '                                   ' };
   print, { 'PARAMETER ESTIMATES with naive variance' };
   print, variable estimate[format=&fmt] se_est[format=&fmt]
z[format=&fmt] p[format=&fmt];
%end;

     vb = n_1c1_1*nc2*n_1c1_1;        *estimated covariance ;

     sebeta=sqrt(vecdiag(vb));      *vector of estimated
                                       standard errors of
                                       beta;
     z=beta`/sebeta;                   *z-statistics;

     zsq=z#z;

     p=1-probchi(zsq,1);              *two-sided p-value;

     se_est=sebeta;

%if &print^=no %then %do;
   print, { 'PARAMETER ESTIMATES with robust variance' };
   print, variable estimate[format=&fmt] se_est[format=&fmt]
z[format=&fmt] p[format=&fmt];
%end;

%if &outbeta^= %then %do;

vc= j(1,nbeta,'v');
coln = variable` || ( concat(vc,variable`) );
out = estimate` || (se_est#se_est)` ;
create &outbeta from out [colname=coln];
append from out;
close &outbeta;
%end;

%if &print^=no %then %do;

   contrast= { 0  &c1 };
   %contrast(c=c1);

   contrast= { 0  &c2 };
   %contrast(c=c2);
%end;
quit;
%end;
%else %do;

%if &int=no %then %do;


data x ( keep = &x );
  length &x 8;
set zzone;
```

```
run;

%end;
%else %do;

data x (keep=intercep &x);
 length intercep &x 8;
set zzone;
 run;

%end;

data y ( keep = &y );
set zzone;
run;

data id ( keep = idm );
set zzone;
run;

%if &weight^= %then %do;
data wt ( keep = &weight );
set zzone;
run;
%end;

*******************************************************;
/*creation of the file of the longitudinal weights*/
data W (keep=&weight);
set zzone;
run;
*******************************************************;
WANT TO INDICATE THE NAME OF THE FILE CONTAINING THE WEIGHTS
BOOTSTRAP:
**********************************************************************
;

data boot (keep=bsw1-bsw500);
set in2.boot;
run;

%if &corr=exc or &corr=cs %then %do;

proc iml worksize=500;

 reset nolog noprint;

/*initial marginal parameters */

   USE PAR;
   READ ALL INTO BETA;
beta=beta`;
nbeta = nrow(beta);
   USE Y;
   READ ALL INTO Y;

   USE X;
   READ ALL INTO X;
 nall =nrow(x);           /* number records in dataset, times*ind
*/

   USE ID;
   READ ALL INTO ID;

%if &weight^= %then %do;
   USE WT;
   READ ALL INTO WT;
%end;

 n = max(id);

crit=1;
  theta=.01;


Do it=1 to &maxit while (crit > &crit );

   U= J(Nbeta,1,0);
   dvd= J(Nbeta,nbeta,0);
   usq = dvd;
   u2 = 0;
   ewe = 0;

Do i=1 to n;
   u2_i = 0;
   ewe_i = 0;
    times = loc(id=i);
    T_i = ncol(times);
    Y_i = Y[times,];
    X_i = X[times,];
%if &weight^= %then %do;
   wt_i = wt[times,];
   wt_i = wt_i[1,];
%end;
    p_i = exp(X_i*beta)/(1 + exp(X_i*beta) );
    A_i = Diag( diag(p_i) - p_i*p_i` );
    D_i =  X_i`*A_i;

  V_i = j(T_i,T_i,0);

 if (T_i > 1) then do;
  do s=1 to T_i;
     do t=s+1 to T_i;

 corr_st =   (EXP(theta)-1)/(EXP(theta)+1) ;
   DET = SQRT( p_i[s,]#p_i[t,]#(1-p_i[s,])#(1-p_i[t,]) );
   Pst = p_i[s,]#p_i[t,] + corr_st#det;
   DOR = 2#(EXP(theta))/(EXP(theta)+1)/(EXP(theta)+1)#det;

%if &method=cond %then %do;

   DOR = (Y_i[s,]/p_i[s,])#DOR -
         (1-Y_i[s,])/(1-p_i[s,])#DOR ;
   V_i[s,t] = pst - p_i[s,]#p_i[t,];
   V_i[t,s] = pst - p_i[s,]#p_i[t,];

   nust = (Y_i[s,]/p_i[s,])#pst +
         (1-Y_i[s,])/(1-p_i[s,])#(p_i[t,] - pst) ;

   u2_i = u2_i + Dor#( Y_i[t,] - nust )/(nust#(1-nust));
   ewe_i = ewe_i + Dor#Dor/(nust#(1-nust));
%end;

%if &method=uncond %then %do;

   V_i[s,t] = pst - p_i[s,]#p_i[t,];
   V_i[t,s] = pst - p_i[s,]#p_i[t,];

   u2_i = u2_i + Dor#( (Y_i[s,])#(Y_i[t,]) - pst )/(pst#(1-pst));
   ewe_i = ewe_i + Dor#Dor/(pst#(1-pst));
%end;

     end;
   end;
end;
   V_i = V_i + A_i;

u_i = D_i*inv(V_i)*( Y_i - p_i );
%if &weight^= %then %do;
u = u + wt_i#u_i;
usq = usq + wt_i#u_i*u_i`;
dvd =  dvd + wt_i#D_i*inv(V_i)*D_i`;;

u2 = u2 + wt_i#u2_i;
ewe = ewe + wt_i#ewe_i;
%end;
%else %do;
u = u + u_i;
usq = usq + u_i*u_i`;
dvd =  dvd + D_i*inv(V_i)*D_i`;;

u2 = u2 + u2_i;
ewe = ewe + ewe_i;
%end;

end;

   DELTA1= solve( dvd, U );
   beta = beta+DELTA1;

   DELTA2= solve( ewe, U2 );
   theta = theta + delta2;
   CRIT= MAX( ABS(DELTA1 // delta2));

%if &print^=no %then %do;
   %if &it_his=yes %then %do;
     print, it crit;
   %end;
%end;
```

```
end;

%if &print^=no %then %do;
   print, it crit;
%end;

%if &int=no %then %do;
variable = { &x };
%end;
%else %do;
variable = { "INTERCEP" } || { &x };
%end;

variable =   variable`;

     vb=inv(dvd);       *variance matrix;

     sebeta=sqrt(vecdiag(vb));      *vector of estimated
                                       standard errors of
                                       beta;

     z=beta/sebeta;                   *z-statistics;

     zsq=z#z;

     p=1-probchi(zsq,1);              *two-sided p-value;

estimate=beta;
se_est=sebeta;

%if &print^=no %then %do;
   print, { 'Correlation Structure: Exchangeable' };
   print, { '                                   ' };
   print, { 'PARAMETER ESTIMATES with naive variance' };
   print, variable estimate[format=&fmt] se_est[format=&fmt]
z[format=&fmt] p[format=&fmt];
%end;

     vb=vb*usq*vb;              *robust variance matrix;

     sebeta=sqrt(vecdiag(vb));      *vector of estimated
                                       standard errors of
                                       beta;
     z=beta/sebeta;                   *z-statistics;

     zsq=z#z;

     p=1-probchi(zsq,1);              *two-sided p-value;

     se_est=sebeta;

%if &print^=no %then %do;
   print, { 'PARAMETER ESTIMATES with robust variance' };
   print, variable estimate[format=&fmt] se_est[format=&fmt]
z[format=&fmt] p[format=&fmt];
%end;
```

```
%if &outbeta^= %then %do;

vc= j(1,nbeta,'v');
coln = variable` || ( concat(vc,variable`) );
out = estimate` || (se_est#se_est)` ;
create &outbeta from out [colname=coln];
append from out;
close &outbeta;
%end;

/* Variance of CORR  */

   U= J(Nbeta+1,1,0);
   dvd= J(Nbeta,nbeta,0);
   usq= J(Nbeta+1,nbeta+1,0);
   ewe = 0;
   ewd= J(1,nbeta,0);

Do i=1 to n;
   u2_i = 0;
   ewe_i = 0;
   ewd_i= J(1,nbeta,0);
    times = loc(id=i);
    T_i = ncol(times);
    Y_i = Y[times,];
    X_i =   X[times,];
%if &weight^= %then %do;
   wt_i = wt[times,];
   wt_i = wt_i[1,];
%end;
    p_i = exp(X_i*beta)/(1 + exp(X_i*beta) );
    A_i = Diag( diag(p_i) - p_i*p_i` );
    D_i =  X_i`*A_i;

  V_i = j(T_i,T_i,0);

 if (T_i > 1) then do;
  do s=1 to T_i;
     do t=s+1 to T_i;

 corr_st =  ( (EXP(theta)-1)/(EXP(theta)+1) );
   DET = SQRT( p_i[s,]#p_i[t,]#(1-p_i[s,])#(1-p_i[t,]) );
   Pst = p_i[s,]#p_i[t,] + corr_st#det;
   DOR = 2#(EXP(theta))/(EXP(theta)+1)/(EXP(theta)+1)#det;
   V_i[s,t] = pst - p_i[s,]#p_i[t,];
   V_i[t,s] = pst - p_i[s,]#p_i[t,];


%if &method=cond %then %do;

DPs = p_i[t,] + .5#corr_st#p_i[t,]#(1-p_i[t,])#(1-2#p_i[s,])/DET;
DPt = p_i[s,] + .5#corr_st#p_i[s,]#(1-p_i[s,])#(1-2#p_i[t,])/DET;

   DOR = (Y_i[s,]/p_i[s,])#DOR -
         (1-Y_i[s,])/(1-p_i[s,])#DOR ;

   nust = (Y_i[s,]/p_i[s,])#pst +
         (1-Y_i[s,])/(1-p_i[s,])#(p_i[t,] - pst) ;

   DPs = Y_i[s,]#( DPs/p_i[s,] - pst/( (p_i[s,])##2 ) ) +
(1-Y_i[s,])#( (-1)#DPs/(1-p_i[s,])+(p_i[t,]- pst)/(
(1-p_i[s,])##2 ) );

 DPt = Y_i[s,]#( DPt/p_i[s,]  ) +
(1-Y_i[s,])#( (1-DPt)/(1-p_i[s,]) );

DP = Dps // Dpt;
DB = D_i[,s] || D_i[,t];
DB = DB*DP;

   u2_i = u2_i + Dor#( Y_i[t,] - nust )/(nust#(1-nust));
  ewe_i = ewe_i + Dor#Dor/(nust#(1-nust));
  ewd_i = ewd_i + Dor*( 1/(nust#(1-nust) ) )*db`;
%end;

%if &method=uncond %then %do;

DPs = p_i[t,] + .5#corr_st#p_i[t,]#(1-p_i[t,])#(1-2#p_i[s,])/DET;
DPt = p_i[s,] + .5#corr_st#p_i[s,]#(1-p_i[s,])#(1-2#p_i[t,])/DET;

DP = Dps // Dpt;
DB = D_i[,s] || D_i[,t];
DB = DB*DP;

   u2_i = u2_i + Dor#( Y_i[s,]#Y_i[t,] - pst )/(pst#(1-pst));
  ewe_i = ewe_i + Dor#Dor/(pst#(1-pst));
  ewd_i = ewd_i + Dor*( 1/(pst#(1-pst) ) )*db`;
%end;

     end;
   end;
end;
   V_i = V_i + A_i;

u_i = ( D_i*inv(V_i)*( Y_i - p_i ) ) // u2_i;
%if &weight^= %then %do;
usq = usq + wt_i#u_i*u_i`;
dvd =  dvd + wt_i#D_i*inv(V_i)*D_i`;;

ewe = ewe + wt_i#ewe_i;
ewd = ewd + wt_i#ewd_i;
%end;
%else %do;
usq = usq + u_i*u_i`;
dvd =  dvd + D_i*inv(V_i)*D_i`;;

ewe = ewe + ewe_i;
ewd = ewd + ewd_i;
%end;

end;

EUU = (dvd || j(nbeta,1,0) ) // ( ewd || ewe ) ;
Vb2 = inv(EUU)*usq*inv(EUU`);
```

```
setheta=sqrt(vb2[nbeta+1,nbeta+1]);

    corr =  ( (EXP(theta)-1)/(EXP(theta)+1) ) ;
    secorr =
2#(EXP(theta))/(EXP(theta)+1)/(EXP(theta)+1)#setheta;

%if &print^=no %then %do;

     z=corr/secorr;
     zsq=z#z;
     p=1-probchi(zsq,1);

   print, corr secorr z p;

   contrast= { 0  &c1 };
   %contrast(c=c1);

   contrast= { 0  &c2 };
   %contrast(c=c2);
%end;

/*
%if &outrho^=  %then %do;
   coln = { 'rho' 'vrho' };
   out = corr || (secorr#secorr)` ;
create &outrho from out [colname=coln];
append from out;
close &outrho ;
%end;
*/

   coln = { 'rho' 'vrho' };
   out = corr || (secorr#secorr)` ;
create outrho from out [colname=coln];
append from out;
close outrho ;
quit;
%end;

%if &corr=ar1 %then %do;
  data occas ( keep = &time );
    set zzone;
  run;

proc iml worksize=5000;
 reset nolog noprint;

/*initial marginal parameters */
   USE PAR;
   READ ALL INTO BETA;
beta=beta`;
nbeta = nrow(beta);
   USE Y;
   READ ALL INTO Y;

   USE X;
   READ ALL INTO X;
 nall =nrow(x);           /* number records in dataset, times*ind
*/
   USE ID;
   READ ALL INTO ID;

%if &weight^= %then %do;
   USE W;
   READ ALL INTO W;
%end;
 n = max(id);

   USE occas;
   READ ALL INTO occas;
crit=1;
  theta=.01;

Do it=1 to &maxit while (crit > &crit );

   U= J(Nbeta,1,0);
   dvd= J(Nbeta,nbeta,0);
   usq = dvd;
   u2 = 0;
   ewe = 0;

Do i=1 to n;
   u2_i = 0;
   ewe_i = 0;
    times = loc(id=i);
    T_i = ncol(times);
    Y_i = Y[times,];
    X_i = X[times,];
%if &weight^= %then %do;
   wt_i = wt[times,];
   wt_i = wt_i[1,];
%end;
    occas_i = occas[times,];
    p_i = exp(X_i*beta)/(1 + exp(X_i*beta) );
    A_i = Diag( diag(p_i) - p_i*p_i` );
    D_i =  X_i`*A_i;

  V_i = j(T_i,T_i,0);

 if (T_i > 1) then do;
  do s=1 to T_i;
     do t=s+1 to T_i;


 corr_st =  ( (EXP(theta)-1)/(EXP(theta)+1) )
             ##( (abs( occas[s,] - occas[t,] ))## &power  );
   DET = SQRT( p_i[s,]#p_i[t,]#(1-p_i[s,])#(1-p_i[t,]) );
   Pst = p_i[s,]#p_i[t,] + corr_st#det;
   c_st =  ( (EXP(theta)-1)/(EXP(theta)+1) )
         ##( ( (-1) + (abs( occas[s,] - occas[t,] ))## &power) );
   DOR = 2#(EXP(theta))/(EXP(theta)+1)/(EXP(theta)+1)#
         det#( (abs( occas[s,] - occas[t,] ))## &power  )#c_st;
```

```
%if &method=cond %then %do;

   DOR = (Y_i[s,]/p_i[s,])#DOR -
         (1-Y_i[s,])/(1-p_i[s,])#DOR ;

   V_i[s,t] = pst - p_i[s,]#p_i[t,];
   V_i[t,s] = pst - p_i[s,]#p_i[t,];

   nust = (Y_i[s,]/p_i[s,])#pst +
         (1-Y_i[s,])/(1-p_i[s,])#(p_i[t,] - pst) ;

   u2_i = u2_i + Dor#( Y_i[t,] - nust )/(nust#(1-nust));
  ewe_i = ewe_i + Dor#Dor/(nust#(1-nust));

%end;

%if &method=uncond %then %do;

   V_i[s,t] = pst - p_i[s,]#p_i[t,];
   V_i[t,s] = pst - p_i[s,]#p_i[t,];

   u2_i = u2_i + Dor#( (Y_i[s,])#(Y_i[t,]) - pst )/(pst#(1-pst));
   ewe_i = ewe_i + Dor#Dor/(pst#(1-pst));
%end;

     end;
   end;
end;
   V_i = V_i + A_i;

u_i = D_i*inv(V_i)*( Y_i - p_i );
%if &weight^= %then %do;
u = u + wt_i#u_i;
usq = usq + wt_i#u_i*u_i`;
dvd =  dvd + wt_i#D_i*inv(V_i)*D_i`;;

u2 = u2 + wt_i#u2_i;
ewe = ewe + wt_i#ewe_i;
%end;
%else %do;
u = u + u_i;
usq = usq + u_i*u_i`;
dvd =  dvd + D_i*inv(V_i)*D_i`;;

u2 = u2 + u2_i;
ewe = ewe + ewe_i;
%end;

end;

   DELTA1= solve( dvd, U );
   beta = beta+DELTA1;

   DELTA2= solve( ewe, U2 );
   theta = theta + delta2;
   CRIT= MAX( ABS(DELTA1 // delta2));
```

```
%if &print^=no %then %do;
   %if &it_his=yes %then %do;
     print, it crit;
   %end;
%end;

end;

%if &print^=no %then %do;
   print, it crit;
%end;

%if &int=no %then %do;
variable = { &x };
%end;
%else %do;
variable = { "INTERCEP" } || { &x };
%end;

variable =   variable`;

     vb=inv(dvd);       *variance matrix;

     sebeta=sqrt(vecdiag(vb));      *vector of estimated
                                       standard errors of
                                       beta;

     z=beta/sebeta;                   *z-statistics;

     zsq=z#z;

     p=1-probchi(zsq,1);              *two-sided p-value;

estimate=beta;
se_est=sebeta;

%if &print^=no %then %do;
   print, { 'Correlation Structure: AR1' };
   print, { '                                   ' };
   print, { 'PARAMETER ESTIMATES with naive variance' };
   print, variable estimate[format=&fmt] se_est[format=&fmt]
z[format=&fmt] p[format=&fmt];
%end;

     vb=vb*usq*vb;              *robust variance matrix;

     sebeta=sqrt(vecdiag(vb));      *vector of estimated
                                       standard errors of
                                       beta;

     z=beta/sebeta;                   *z-statistics;

     zsq=z#z;

     p=1-probchi(zsq,1);              *two-sided p-value;
```

```
se_est=sebeta;

%if &print^=no %then %do;
     print, { 'PARAMETER ESTIMATES with robust variance' };
   print, variable estimate[format=&fmt] se_est[format=&fmt]
z[format=&fmt] p[format=&fmt];
%end;

%if &outbeta^= %then %do;
  vc= j(1,nbeta,'v');
  coln = variable` || ( concat(vc,variable`) );
  out = estimate` || (se_est#se_est)` ;
  create &outbeta from out [colname=coln];
  append from out;
  close &outbeta;
%end;

/* Variance of CORR  */
   U= J(Nbeta+1,1,0);
   dvd= J(Nbeta,nbeta,0);
   usq= J(Nbeta+1,nbeta+1,0);
   ewe = 0;
   ewd= J(1,nbeta,0);

Do i=1 to n;
   u2_i = 0;
   ewe_i = 0;
   ewd_i= J(1,nbeta,0);
    times = loc(id=i);
    T_i = ncol(times);
    Y_i = Y[times,];
    X_i =   X[times,];
%if &weight^= %then %do;
   wt_i = wt[times,];
   wt_i = wt_i[1,];
%end;
    occas_i = occas[times,];
    p_i = exp(X_i*beta)/(1 + exp(X_i*beta) );
    A_i = Diag( diag(p_i) - p_i*p_i` );
    D_i =  X_i`*A_i;

  V_i = j(T_i,T_i,0);

 if (T_i > 1) then do;
  do s=1 to T_i;
     do t=s+1 to T_i;

 corr_st =  ( (EXP(theta)-1)/(EXP(theta)+1) )
             ##( (abs( occas[s,] - occas[t,] ))## &power  );
   DET = SQRT( p_i[s,]#p_i[t,]#(1-p_i[s,])#(1-p_i[t,]) );
   Pst = p_i[s,]#p_i[t,] + corr_st#det;
   c_st =  ( (EXP(theta)-1)/(EXP(theta)+1) )
           ##( ( (-1) + (abs( occas[s,] - occas[t,] ))## &power)
);
   DOR = 2#(EXP(theta))/(EXP(theta)+1)/(EXP(theta)+1)#
         det#( (abs( occas[s,] - occas[t,] ))## &power  )#c_st;
```

```
DPs = p_i[t,] + .5#corr_st#p_i[t,]#(1-p_i[t,])#(1-2#p_i[s,])/DET;
DPt = p_i[s,] + .5#corr_st#p_i[s,]#(1-p_i[s,])#(1-2#p_i[t,])/DET;

   V_i[s,t] = pst - p_i[s,]#p_i[t,];
   V_i[t,s] = pst - p_i[s,]#p_i[t,];

%if &method=cond %then %do;

   DOR = (Y_i[s,]/p_i[s,])#DOR -
         (1-Y_i[s,])/(1-p_i[s,])#DOR ;

   nust = (Y_i[s,]/p_i[s,])#pst +
         (1-Y_i[s,])/(1-p_i[s,])#(p_i[t,] - pst) ;

   DPs = Y_i[s,]#( DPs/p_i[s,] - pst/( (p_i[s,])##2 ) ) +
(1-Y_i[s,])#( (-1)#DPs/(1-p_i[s,])+(p_i[t,]- pst)/(
(1-p_i[s,])##2 ) );

 DPt = Y_i[s,]#( DPt/p_i[s,]  ) +
(1-Y_i[s,])#( (1-DPt)/(1-p_i[s,]) );

DP = Dps // Dpt;
DB = D_i[,s] || D_i[,t];
DB = DB*DP;

   u2_i = u2_i + Dor#( Y_i[t,] - nust )/(nust#(1-nust));
  ewe_i = ewe_i + Dor#Dor/(nust#(1-nust));
  ewd_i = ewd_i + Dor*( 1/(nust#(1-nust) ) )*db`;

%end;

%if &method=uncond %then %do;

DPs = p_i[t,] + .5#corr_st#p_i[t,]#(1-p_i[t,])#(1-2#p_i[s,])/DET;
DPt = p_i[s,] + .5#corr_st#p_i[s,]#(1-p_i[s,])#(1-2#p_i[t,])/DET;

DP = Dps // Dpt;
DB = D_i[,s] || D_i[,t];
DB = DB*DP;

   u2_i = u2_i + Dor#( Y_i[s,]#Y_i[t,] - pst )/(pst#(1-pst));
  ewe_i = ewe_i + Dor#Dor/(pst#(1-pst));
  ewd_i = ewd_i + Dor*( 1/(pst#(1-pst) ) )*db`;
%end;
     end;
   end;
end;
   V_i = V_i + A_i;

u_i = ( D_i*inv(V_i)*( Y_i - p_i ) ) // u2_i;
%if &weight^= %then %do;
usq = usq +  wt_i#u_i*u_i`;
dvd =  dvd +  wt_i#D_i*inv(V_i)*D_i`;;

ewe = ewe +  wt_i#ewe_i;
ewd = ewd +  wt_i#ewd_i;
%end;
```

```
%else %do;
usq = usq + u_i*u_i`;
dvd =  dvd + D_i*inv(V_i)*D_i`;;

ewe = ewe + ewe_i;
ewd = ewd + ewd_i;
%end;

end;

EUU = (dvd || j(nbeta,1,0) ) // ( ewd || ewe ) ;

Vb2 = inv(EUU)*usq*inv(EUU`);

     setheta=sqrt(vb2[nbeta+1,nbeta+1]);
    corr =  ( (EXP(theta)-1)/(EXP(theta)+1) ) ;
    secorr =
2#(EXP(theta))/(EXP(theta)+1)/(EXP(theta)+1)#setheta;

%if &print^=no %then %do;
     z=corr/secorr;
     zsq=z#z;
     p=1-probchi(zsq,1);
     print, { "POWER = &power" };
     print, corr secorr z p;

%if &k_j^= %then %do;

    t_s = { &k_j };
    t_s = t_s`;
    its = t_s## &power;
    lnc = its*log(corr);
    vlnc = its*( (secorr/corr)##2 )*its`;
    corr = exp(lnc);
    vcorr = diag(corr)*vlnc*diag(corr);
    secorr =sqrt(vecdiag(vcorr));
    k_j = t_s;
    print k_j corr secorr;

  %end;
%end;

   contrast= { 0  &c1 };
   %contrast(c=c1);

   contrast= { 0  &c2 };
   %contrast(c=c2);

%if &outrho^= %then %do;
   coln = { rho vrho };
   out = corr || (secorr#secorr)` ;
   create &outrho from out [colname=coln];
   append from out;
   close &outrho;
%end;

  quit;
```

```
%end;
%end;
%if &corr = banded or &corr = un %then %do;
proc freq data=zzone;
 tables &time /out=new noprint;
run;

data new (keep=&time ordt);
  set new;
  ordt+1;
run;

data occas ( keep = &time junk);
set zzone;
junk+1;
run;
proc sort data= occas;
  by &time;
run;
data occas(keep=junk ordt);
 merge occas new;
 by &time;
 run;
proc sort data=occas out=occas(drop=junk);
 by junk;
 run;
proc iml worksize=5000;
 reset nolog noprint;
%if &corr = banded %then %do;
  corr = 3;
%end;
%if &corr = un %then %do;
  corr = 4;
%end;

/*initial marginal parameters */
   USE PAR;
   READ ALL INTO BETA;
beta=beta`;
nbeta = nrow(beta);
   USE Y;
   READ ALL INTO Y;
maxy = 2;                 /* # levels of multinomial */
   USE X;
   READ ALL INTO X;
 nall =nrow(x);           /* number records in dataset, times*ind */
   USE ID;
   READ ALL INTO ID;
%if &weight^= %then %do;
   USE W;
   READ ALL INTO W;
%end;
 n = max(id);             /* number of indiv. (clusters) */

 npair =0;                /* number of pairs of times    */
 maxt = 0;                /* maximum # times an indiv was seen */
do i=1 to n;
```

```
  times = loc(id=i);
  times = ncol(times);
   npair =  npair + times#(times-1);
  if times > maxt then maxt=times;
end;
Imaxt = I(maxt);
   USE occas;
   READ ALL INTO occas;
crit=1;
Do it=1 to &maxit while (crit > &crit);
free  lu;
   U= J(Nbeta,1,0);
   dvd= J(Nbeta,nbeta,0);
   usq = dvd;
/* ***************** Correlation matrix ******************** */
  R=j(maxt#(maxy-1),maxt#(maxy-1),0);
  obs=R;
  Do i=1 to n;
    free Y_i X_i p_i A_i Wvar_i W_i weight_i poids_i;;
    times = loc(id=i);
    T_i = ncol(times);
    Y_i = Y[times,];
    X_i = X[times,];
Wvar_i = W[times,];  /* vector to times (T) lines: weights of the ième
cluster*/
    weight_i=Wvar_i[maxy-1]; /*Vector column weights to L-1 elements?
*/
      poids_i=Wvar_i[1]; /* scalaire  poids du ième cluster, scalar
weights*/
%if &time^= %then %do;
    occas_i = occas[times,];
%end;

    A_i = 0;
    W_i=0; /* initialisation of the diagonal matrix of the weights for
the ith cluster dimension */
/* création of diagonal matrix */
    W_it = poids_i @ Imaxy;

    p_i = exp(X_i*beta)/(1 + exp(X_i*beta) );
    A_i = Diag( diag(p_i) - p_i*p_i` );
       W_i = Block(W_i,W_it);

        nrW = nrow(W_i);
      W_i = W_i[2:nrW,2:nrW];
      nrA = nrow(A_i);
      A_i = A_i[2:nrA,2:nrA];
/* inversion de la matrice racine carrée de A_i */
      call eigen(M,ev,A_i);
      e_i = inv(ev*sqrt(DIAG(M))*ev`) * (Y_i - p_i);
%if &time= %then %do;
      e_i = shape(e_i, maxt#(maxy-1), 1, 0);
%end;
%else %do;
      I_i = Imaxt[,occas_i`];
      I_i = I_i @ I(maxy-1);
*******************************************************************;
```

```
/* we introduce the weights for estimation of correlation */
      I_i = (diag(W_i))* I_i;
*****************************************************************;
      e_i = sqrt(I_i) *e_i;
      obs_i = sqrt(I_i[,+]);
      obs = obs + obs_i*obs_i`;
%end;
      R = R + e_i*e_i`;
    end;
end;
if corr = 4 then do;
      R = R/(obs-nbeta);
  ch = 1 - ( (I(maxt)) @ j(maxy-1,maxy-1,1) );
  R = ch#R + I(nrow(R));
end;
if corr = 3 then do;
    free co;
  do ti = 2 to maxt;
      ch = j(maxy-1,maxt#(maxy-1),0);
      ch[, (ti-1)#(maxy-1)+1 : ti#(maxy-1) ] = j(maxy-1,maxy-1,1);
      ch = toeplitz(ch);
      R_st = ch#R;
      obs_st = ch#obs;
      ch = j(maxt,1,1) @ i(maxy-1) ;
      R_st = (ch`*R_st*ch/2)/(ch`*obs_st*ch/2-nbeta);
      co = co || R_st;
  end;
    R = I(maxy-1) || co;
    R = toeplitz(R);
end;
/* **************END Correlation matrix ******************** */
Do i=1 to n;
    free Y_i X_i p_i D_i A_i W_i WW_i Wvar_i weight_i poids_i lu_i;
    times = loc(id=i);
    T_i = ncol(times);
    Y_i = Y[times,];
    X_i = X[times,];
    occas_i = occas[times,];
Wvar_i = W[times,];  /* vecteur poids du ième cluster*/
    weight_i=Wvar_i[maxy-1]; /* vector column weights to L-1 elements
?*/
      poids_i=Wvar_i[1]; /* scalaire  poids du ième cluster*/
%if &time^= %then %do;
    occas_i = occas[times,];
%end;
    A_i = 0;
      W_i=0; WW_i=0;
 W_it = poids_i @ Imaxy;

    p_i = exp(X_i*beta)/(1 + exp(X_i*beta) );
    A_i = Diag( diag(p_i) - p_i*p_i` );
      WW_it = diag(W_it) ;
             W_i = Block(W_i,W_it);
                              WW_i = Block(WW_i,WW_it);
                  D_i = X_i`*A_i;
              * D_i = D_i || D_it;
         end;
 /* one eliminates first line and first column*/
      nrW = nrow(W_i);
      W_i = W_i[2:nrW,2:nrW];
        WW_i = WW_i[2:nrW,2:nrW];
      nrA = nrow(A_i);
      A_i = A_i[2:nrA,2:nrA];
      I_i = Imaxt[occas_i`,];
      A_i1_2 = sqrt(A_i);
if T_i > 1 then do;
         V_i = A_i1_2*I_i*R*I_i`*A_i1_2;
end;
if T_i = 1 then do;
         V_i = A_i ;
end;
u_i = D_i*inv(V_i)*( Y_i - p_i );
%if &weight^= %then %do;
u = u +wvar_i# u_i;
usq = usq + wvar_i#u_i*u_i`;
dvd =  dvd + wvar_i#D_i*inv(V_i)*D_i`;;
%end;
%else %do;
u = u + u_i;
usq = usq + u_i*u_i`;
dvd =  dvd + D_i*inv(V_i)*D_i`;;
%end;

end;
/* CREATE A FILE OF THE TERMS NON BALANCED U_i FOR THE CALCULATION OF
THE VARIANCE BOOTSTRAP LINÉARISÉE*/
   lu = D_i*inv(V_i)*( Y_i - p_i );
   *lu=lu // lu_i`;
end; /* fin de la boucle en i*/
   DELTA= solve( dvd, U );
   beta = beta+DELTA;
   CRIT= MAX( ABS(DELTA));
%if &print^=no %then %do;
   %if &it_his=yes %then %do;
     print, it crit;
   %end;
%end;
end;
/* CREATE A FILE OF THE PARAMETERS WITH THE elements of the sturdy
VARIANCES CALCULATED without THE WEIGHTS
BOOTSTRAP*/
  sandwich= lu;
  CREATE milieu FROM sandwich;
  APPEND FROM sandwich;
  CLOSE milieu;
print, it crit;  print R;
intc = { "int" };
stop=maxy-1;
do j=1 to stop;
 intn = char(j,1);
 int = concat(intc,intn);
 variable = variable || int;
end;
variable = variable || { &x };
variable =   variable`;

     vb=inv(dvd);       *variance matrix;
       izero=vb;         /* matrice de covariance naîve*/
       residw=u`;         /* S(u) avec poids full sample */
       print residw;
     naiv_var=vecdiag(vb); * naive variance;
     sebeta=sqrt(vecdiag(vb));      *vector of estimated
                                       standard errors of
                                       beta;
     z=beta/sebeta;                   *z-statistics;
     zsq=z#z;
     p=1-probchi(zsq,1);              *two-sided p-value;
estimate=beta;
se_est=sebeta;
/* CREATE A FILE OF THE PARAMETERS WITH THE VARIANCES NAIVES
CALCULATED WITH THE WEIGHTS BOOTSTRAP*/
  NAIVE= ESTIMATE||SE_EST||naiv_var||Z||P;
  CREATE PARMNAIV FROM NAIVE;
  APPEND FROM NAIVE;
  CLOSE PARMNAIV;

        if corr = 3 then do;
print, { 'CORRELATION: banded' };
      end;
      if corr = 4 then do;
print, { 'CORRELATION: unstructured' };
      end;

print, { 'PARAMETER ESTIMATES with naive variance' };

     print, variable estimate se_est z p;

     vb=vb*usq*vb;              *robust variance matrix;

     sebeta=sqrt(vecdiag(vb));      *vector of estimated
                                       standard errors of
                                       beta;
     z=beta/sebeta;                   *z-statistics;
     zsq=z#z;
     p=1-probchi(zsq,1);              *two-sided p-value;
se_est=sebeta;
print, { 'PARAMETER ESTIMATES with robust variance' };
     print, variable estimate se_est z p;
/* CREATE A FILE OF THE PARAMETERS WITH THE STURDY VARIANCES*/
  ROBUST= ESTIMATE||SE_EST||Z||P;
  CREATE PARMROB FROM ROBUST;
  APPEND FROM ROBUST;
  CLOSE PARMROB;
  %if &print^=no %then %do;
    create out from R;
    append from R;
    close out;
    print, it crit;
%end;
Imaxb=I(nbeta);
* print Imaxb;
```

```
*--------------------------------------------------------------------;
free lefsb0_d diff_v;
* Calculation of the variance linéarisée by bootstrap;
do B=1 to &&nboot;
   U= J(1,Nbeta,0); /* initialisation to zero of the vector column of
the dimension parameters Nbeta=p*/
Do i=1 to n;
     free  W_i WW_i  poids_i u_i lu_i;
      poids_i=BOOT[i,B]; /* scalaire bème poids bootstrap du ième
cluster*/
/*if i=1 then do;print i B poids_i;end;*/
    lu_i=lu[i,];
/*if i=1 then do;print i B lu_i;end;*/
/* creation of the diagonal matrice of the weights*/
    W_i = poids_i @ Imaxb;
/*if i=1 then do;print W_i;end;*/
       u_i = lu_i*diag(W_i);
      u = u + u_i;
end; /* fin de la boucle en i*/
residb=u;
* print b residb;
lefsb0=residb-residw;
* print b lefsb0;
/* create the file of the gaps */
 diff_v=diff_v ||lefsb0;
* print b diff_v;
 lefsb0_d=lefsb0_d //lefsb0;
*  print b lefsb0_d;
end; /* final bootstrap weights*/
*--------------------------------------------------------------------;
  create residout from lefsb0_d;
  append from lefsb0_d;
  close residout;
use residout;
read all into differ;
nn=nrow(differ);
var_ef=(differ` *differ)/nn;
/* create the file of the covariances of S(u)*/
  CREATE icentral FROM var_ef;
  APPEND FROM var_ef;
  CLOSE icentral;
*--------------------------------------------------------------------;
  * calculation of the variance linéarisée of beta;
     vbeta=izero*var_ef*izero;              *robust variance matrix
linearized;
     sebeta=sqrt(vecdiag(vbeta));      *vector of estimated
                                       standard errors linearized of
                                       beta;
     z=beta/sebeta;                   *z-statistics;
     zsq=z#z;
     p=1-probchi(zsq,1);              *two-sided p-value;
se_est=sebeta;
print, { 'PARAMETER ESTIMATES with robust variance linearized' };
     print, variable estimate se_est z p;
/* CREATE A FILE OF THE PARAMETERS WITH THE STURDY VARIANCES
LINEARISÉES*/
  ROBLIN= ESTIMATE||SE_EST||Z||P;
  CREATE PARMLIN FROM ROBLIN;
  APPEND FROM ROBLIN;
  CLOSE PARMLIN;
*--------------------------------------------------------------------;
%if &outbeta^= %then %do;
  vc= j(1,nbeta,'v');
  coln = variable` || ( concat(vc,variable`) );
  out = estimate` || (se_est#se_est)` ;
  create &outbeta from out [colname=coln];
  append from out;
  close &outbeta;
%end;

%if &print^=no %then %do;
   contrast= { 0  &c1 };
   %contrast(c=c1);
  contrast= { 0  &c2 };
   %contrast(c=c2);
%end;
  quit;

%if &print^=no %then %do;
%if &corr = banded %then %do;
  title 'Banded Correlation Matrix';
%end;
%if &corr = un %then %do;
  title 'Unstructured Correlation Matrix';
%end;
proc print data= outcorr;
  run;
%end;
%end;
title '               ';
%mend gee;
%gee (data= in1.survival1 ,y=asthm, x=fallergy
,time=repeat,id=realukey,corr=ind,nboot=500);
run;
/* fichier des paramètres IEE avec variances naîves  */
data in1.parmnaiv_4RAO;
set parmnaiv;
RENAME COL1=estimate
       COL2=se_est_naiv
       col3=NAIV_VAR
       col4=Z
       col5=P;
run;
/* creation of the file of the parameters GEE with variances robust */
data in1.parmrob_4RAO;
set parmrob;
run;
/* creation of the file of the parameters GEE with variances
linéarisés */
data in1.parmlin_4RAO;
set parmlin;
RENAME COL1=estimate
       COL2=bs_sd_l
       col3=LINEAR_VAR
       col4=Z;
run;
data in1.parmlin_4RAO;
  set in1.parmlin_4RAO;
  cil95=ESTIMATE-1.96*bs_sd_l;
  ciu95=ESTIMATE+1.96*bs_sd_l;
  odds=exp(estimate);
  oddl95=exp(cil95);
  oddu95=exp(ciu95);
run;
proc print data=in1.parmlin_4RAO noobs;
       title "Estimation de la variance à l'aide du bootstrap 500 pour
des";
       title2 "paramètres de la cumlogit POUR LHZ DE Liang-Zeger and
Williamson ";
       title3 "pour des données répétées par GEE AVEC DE LA VARIANCE
LINÉARISÉE";
       title4  "pour une structure de corr=UNSTRUCTURED";
       var   /*VAR1*/ ESTIMATE BS_SD_L cil95 ciu95 odds oddl95 oddu95;
       format  ESTIMATE  BS_SD_L cil95 ciu95 odds oddl95 oddu95 6.4;
run;
```

C.2 SAS macro for Bootstrap analysis

```
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* automatically without notice to you if you fail to comply with any
term of this
* agreement.;

/*******************************************************************/
/* Date: April 2004                                              */
/*******************************************************************/

/*********************************************************************
************/
/***
***/
/***                              MACROE_V30.SAS
***/
```

```
/***                            (Version 3.0.1)
***/
/***
***/
/*** This program calculates variance estimates using the bootstrap
weights    ***/
/*** for different types of estimators.  Using SAS Macros, this
program can    ***/
/*** calculate variance estimates for totals, ratios and differences
between   ***/
/*** ratios.  It can also calculate variance estimates for the
parameters      ***/
/*** of a linear regression or logistic regression. This program can
also be   ***/
/*** customized for other types of analyses.
***/
/***
***/
/*** This program contains the macros that are necessary to use the
             ***/
/*** BOOTVARE_V30.SAS program.
***/
/***
***/
/*** This program is automatically called by BOOTVARE_V30.SAS and NO
MODIFICA- ***/
/*** TIONS SHOULD BE MADE BY THE USER (except for specific cases
mentioned in  ***/
/*** BOOTVARE_V30.SAS)
***/
/***
***/
/**********************************************************************
************/

options ps=64 ls=120 nonotes;


**********************************************************************
***********
*** Section 1: Declaration of the Macro Variables
***
**********************************************************************
***********;

/*  Verification if breakdown variable(s) */

%let by=;
%let cla_tmp="&classes";

data _NULL_;
if substr(&cla_tmp,1,1)='.' then do;
                   call symput ('by' ,'*');
                   call symput ('classes' ,'');
                   call symput ('number',0);
                           end;
run;
```

```
* TO OBTAIN THE MARGINALS IN THE OUTPUT;


&by  %let cla_tmp="&classes"||' #';

&by  data _NULL_;
&by  do i=1 to 10;
&by   call symput ('cla'||left(trim(i)),' ');
&by  end;
&by  init=1; &by  i=1; &by  fin=1; &by  stop=' ';
&by  do until (stop='#');
&by   do until (substr(&cla_tmp,i,1)='');
&by         call symput
('cla'||left(trim(init)),substr(&cla_tmp,fin,i-fin+1));
&by         call symput ('number',init);
&by         i=i+1;
&by   end;
&by   fin=i;
&by   stop=substr(&cla_tmp,i+1,1);
&by   init=init+1;
&by  end;
&by  run;


* VARIABLE SPECIFIC TO EACH VERSION OF SAS ;

data _NULL_;
if &sysver >= 8 then call symput ('inter' ,'intercept');
else call symput ('inter' ,'intercep');
run;

* VARIABLES FOR INDEX(next section):   ;

%let indx=(id=(&ident blank));


**********************************************************************
*****;
*  SECTION 2: READING IN THE MAIN FILE AND MERGING TO THE WEIGHTS
*;
**********************************************************************
*****;

OPTIONS notes;

data Mfile (index=&indx);
   set &Mfile ;
   blank=.;
run;

/* The next step reads the bootstrap weights and standardize the name
of the bootatrap weigths varaibles */
/* FWGT is the same weight as on the analysis file */

OPTIONS nonotes;
```

```
data bsamp (index=&indx);
  set &bsamp;
   blank=.;
         if &bsw.1 ne '' then do;
                           call symput ('bsw_frst' ,'&bsw.1');
                           call symput ('bsw_last' ,'&bsw.&b');
                                    end;

         else if &bsw.001 ne '' then do;
                           call symput ('bsw_frst' ,'&bsw.001');
                           call symput ('bsw_last'
,'&bsw.%sysfunc(putn(&b,z3.))');
                                    end;
         else if &bsw.0001 ne '' then do;
                           call symput ('bsw_frst' ,'&bsw.0001');
                           call symput ('bsw_last'
,'&bsw.%sysfunc(putn(&b,z4.))');
                                    end;
run;

OPTIONS notes;

/* Merging the main file and the bootstrap weights */

     data bs_data ;
       merge Mfile (in=in1) bsamp (keep=&fwgt &ident &bsw_frst-
&bsw_last);
       by &ident;
       if in1;
         drop blank;
       rename &bsw_frst-&bsw_last=bsw1-bsw&b;
     run;


&by  proc sort data=bs_data;
&by     by &classes;
&by  run;


* RESULTS FILES :     ;

data alltots allrats diffrat bs_reg bs_reglg bs_reggen;
      set _NULL_;
run;

%let result= alltots allrats diffrat bs_reg bs_reglg bs_reggen;


/*********************************************************************
************/
/*** Section 3: Declaration of the macros
***/
/*********************************************************************
************/

%let printtot=0;
%let printrat=0;
```

```
%let printdif=0;
%let printreg=0;
%let printlog=0;
%let printgen=0;

%global dep1 dep2;

*************************************;

%macro total(var);

*************************************;

proc means data=bs_data noprint;
  var &fwgt bsw1-bsw&b;
  weight &var;
&by  class &classes;
  output out=ytot
         sum=yhat ybs1-ybs&b;
run;


proc means data=Mfile noprint;
  var &var;
  where &var>0;
&by  class &classes;
  output out=n n=n;
run;

data ytot;
      merge ytot n (drop=_type_ _freq_);
&by by &classes;
run;

     data est;
              set ytot;
              length var $ 8;
              length type $ 8;
              Estimate=yhat;
              bs_var=((&b-1)*(var(of ybs1-ybs&b)))/&b;
              bs_sd=sqrt(bs_var);
              bs_cv=round((bs_sd/yhat)*100,.01);
              cil95=yhat-1.96*bs_sd;
              ciu95=yhat+1.96*bs_sd;
              var="&var";
              type="Total";
              drop ybs1-ybs&b _type_ _freq_;
&by           drop &cla1 &cla2 &cla3 &cla4 &cla5 &cla6 &cla7 &cla8
&cla9 &cla10;

&by               %do k=1 %to &number;
&by               if &&cla&k ne ' ' then cla&k=put(&&cla&k,best8.);
&by               %end;
run;

data alltots;
      set alltots est;
```

```
run;

%let printtot=1;

proc datasets library=work;
      delete ytot est;
run;

%mend total;


*******************************************;

%macro ratio(var1,var2,);

*******************************************;

proc means data=bs_data noprint;
  var &fwgt bsw1-bsw&b;
  weight &var1;
&by  class &classes;
  output out=ytot
         sum=yhat ybs1-ybs&b;
run;

proc means data=bs_data noprint;
  var &fwgt bsw1-bsw&b;
  weight &var2;
  &by  class &classes;
  output out=xtot
  sum=xhat xbs1-xbs&b;
run;

proc means data=Mfile noprint;
  var &var1;
   where &var1>0;
&by  class &classes;
  output out=n n=n1;
run;

data ytot;
      merge ytot n (drop=_type_ _freq_);
&by by  &classes;
run;


data est;
  merge ytot xtot;
  array ybs{&b};
  array xbs{&b};
  array rbs{&b};
  length var1 $ 8;
  length var2 $ 8;
  length type $ 8;
  Estimate=((yhat/xhat));
  do i=1 to &b;
    rbs{i}=((ybs{i}/xbs{i}));
  end;
  bs_var=((&b-1)*(var(of rbs1-rbs&b)))/&b;
  bs_sd=sqrt(bs_var);
  bs_cv=round((bs_sd/Estimate)*100,.01);
  cil95=Estimate-1.96*bs_sd;
  ciu95=Estimate+1.96*bs_sd;
  var1="&var1";
  var2="&var2";
  type="Ratio";
  drop ybs1-ybs&b xbs1-xbs&b rbs1-rbs&b xhat yhat i _type_ _freq_;
&by           drop &cla1 &cla2 &cla3 &cla4 &cla5 &cla6 &cla7 &cla8
&cla9 &cla10;

&by               %do k=1 %to &number;
&by               if &&cla&k ne ' ' then cla&k=put(&&cla&k,best8.);
&by               %end;
run;

data allrats;
      set allrats est;
run;

%let printrat=1;

proc datasets library=work;
    delete ytot xtot est;
run;

%mend ratio;


********************************************************;

%macro diff_rat(var1,var2,var3,var4);

********************************************************;

proc means data=bs_data noprint;
  var &fwgt bsw1-bsw&b;
  weight &var1;
  &by  class &classes;
  output out=ytot
  sum=yhat ybs1-ybs&b;
run;

proc means data=bs_data noprint;
  var &fwgt bsw1-bsw&b;
  weight &var2;
  &by  class &classes;
  output out=xtot
  sum=xhat xbs1-xbs&b;
run;

proc means data=bs_data noprint;
  var &fwgt bsw1-bsw&b;
  weight &var3;
  &by  class &classes;
  output out=yytot
  sum=yyhat yybs1-yybs&b;
run;

proc means data=bs_data noprint;
  var &fwgt bsw1-bsw&b;
  weight &var4;
  &by  class &classes;
  output out=xxtot
  sum=xxhat xxbs1-xxbs&b;
run;

proc means data=Mfile noprint;
  var &var1;
  where &var1>0;
&by  class &classes;
  output out=n1 n=n1;
run;

proc means data=Mfile noprint;
  var &var3;
  where &var3>0;
&by  class &classes;
  output out=n3 n=n3;
run;

data ytot;
      merge ytot n1 (drop=_type_ _freq_) n3 (drop=_type_ _freq_);
&by by &classes;
run;

data est;
  merge ytot xtot yytot xxtot;
  array ybs{&b};
  array xbs{&b};
  array yybs{&b};
  array xxbs{&b};
  array drbs{&b};
  length var1 $ 8;
  length var2 $ 8;
  length var3 $ 8;
  length var4 $ 8;
  length type $ 10;
  Estimate=(((yhat/xhat)-(yyhat/xxhat)));
  do i=1 to &b;
    drbs{i}=(((ybs{i}/xbs{i})-(yybs{i}/xxbs{i})));
  end;
  bs_var=(((&b-1)*(var(of drbs1-drbs&b)))/&b);
  bs_sd=sqrt(bs_var);
  bs_cv=abs(round((bs_sd/Estimate)*100,.01));
  cil95=Estimate-1.96*bs_sd;
  ciu95=Estimate+1.96*bs_sd;
  var1="&var1";
  var2="&var2";
  var3="&var3";
  var4="&var4";
  type="Dif_Rat";
  drop ybs1-ybs&b xbs1-xbs&b yybs1-yybs&b xxbs1-xxbs&b drbs1-drbs&b
       xhat yhat xxhat yyhat i _type_ _freq_;
&by           drop &cla1 &cla2 &cla3 &cla4 &cla5 &cla6 &cla7 &cla8
&cla9 &cla10;

&by               %do k=1 %to &number;
&by               if &&cla&k ne ' ' then cla&k=put(&&cla&k,best8.);
&by               %end;
run;

data diffrat;
      set diffrat est;
run;


%let printdif=1;

proc datasets library=work;
   delete ytot xtot yytot xxtot est;
run;

%mend diff_rat;


*********************************************;

%macro regress(yvar,xvar);

*********************************************;

proc reg data=bs_data outest=orig(keep=&classes &inter &xvar) noprint;
  model &yvar=&xvar;
  weight &fwgt;
&by  by &classes;
run;

proc transpose data=orig out=origest(drop=_label_) prefix=beta
name=param;
  var &inter &xvar;
&by  by &classes;
run;

data _NULL_;
    L=int((&b/10)+0.999);
    call symput ('L' , trim(left(L)));
run;

OPTIONS nonotes;

%let j_dep=1;

%do k=1 %to 10;
  %let j=%eval(1+((&k-1)*&L));
  %let kL=%eval(&k*&L);

data _NULL_;
if (&b - &kL) >0  then do;
```

```
                          k=&k;
                          j=1+((&k-1)*&L);
                          kL=&k*&L;
                       end;
                  else do;
                          k=10;
                          j=&j_dep;
                          kL=&b;
                       end;

call symput ('k' , trim(left(k)));
call symput ('j' , trim(left(j)));
call symput ('kL' , trim(left(kL)));
run;

data poids (keep = bsw&j-bsw&kL &yvar &xvar &classes);
  set bs_data;
run;

  %do i=&j %to &kL;

     %put Regression &i completed;

   %let j_dep=%eval(&kl+1);

   proc reg data=poids outest=betas(keep=&classes &inter &xvar)
noprint;
     model &yvar=&xvar;
     weight bsw&i;
&by  by &classes;
   run;

   proc transpose data=betas out=betat prefix=best name=param;
     var &inter &xvar;
&by  by &classes;
   run;

   data betat;
     set betat;
     drop _label_;
     rename best1=best&i;
      if &i=1 then test=1;
      else test=test+1;
   run;

   %if (&i =1) %then %do;

     data bsbeta;
       set betat;
     run;

   %end;
   %else %do;

     data bsbeta;
       merge bsbeta betat;
&by    by &classes;
```

```
     run;

   %end;
  %end;
%end;

OPTIONS notes;

data est;
  merge origest bsbeta;
  rename beta1=beta;
  bs_var=((&b-1)*(var(of best1-best&b)))/&b;
  bs_sd=sqrt(bs_var);
  bs_cv=abs(round((bs_sd/beta1)*100,.01));
  cil95=beta1-1.96*bs_sd;
  ciu95=beta1+1.96*bs_sd;
  ydep="&yvar";
  drop best1-best&b;
run;

data bs_reg;
    set bs_reg est;
run;

%let printreg=1;
%let dep1=&yvar;

proc datasets library=work;
    delete betas betat bsbeta origest;
run;


%mend regress;

*********************************************;

%macro logreg(yvar,xvar);

*********************************************;

proc logistic data=bs_data outest=orig(keep=&classes &inter &xvar)
descending noprint;
  model &yvar=&xvar;
  &by by &classes;
  weight &fwgt;
run;

proc transpose data=orig out=origest prefix=beta name=param;
  var &inter &xvar;
  &by by &classes;
run;


data _NULL_;
    L=int((&b/10)+0.999);
    call symput ('L' , trim(left(L)));
run;
```

```
OPTIONS nonotes;

%let j_dep=1;

%do k=1 %to 10;
  %let j=%eval(1+((&k-1)*&L));
  %let kL=%eval(&k*&L);

data _NULL_;
if (&b - &kL) >0  then do;
                          k=&k;
                          j=1+((&k-1)*&L);
                          kL=&k*&L;
                       end;
                  else do;
                          k=10;
                          j=&j_dep;
                          kL=&b;
                       end;

call symput ('k' , trim(left(k)));
call symput ('j' , trim(left(j)));
call symput ('kL' , trim(left(kL)));
run;


data poids (keep = bsw&j-bsw&kL &yvar &xvar &classes);
  set bs_data;
run;

  %do i=&j %to &kL;

     %put Logistic regression &i completed;

     %let j_dep=%eval(&kl+1);

    proc logistic data=poids outest=betas (keep=&classes &inter &xvar)
noprint descending;
      model &yvar=&xvar;
      &by by &classes;
      weight bsw&i;
    run;



    proc transpose data=betas out=betat prefix=best name=param;
      var &inter &xvar;
      &by by &classes;
    run;

    data betat;
      set betat;
      rename best1=best&i;
    run;

    %if (&i =1) %then %do;
```

```
      data bsbeta;
        set betat;
      run;

    %end;
    %else %do;

      data bsbeta;
        merge bsbeta betat;
        &by by &classes;
      run;

    %end;
  %end;
%end;

OPTIONS notes;


data est;
  merge origest bsbeta;
  rename beta1=beta;
  bs_var=((&b-1)*(var(of best1-best&b)))/&b;
  bs_sd=sqrt(bs_var);
  bs_cv=abs(round((bs_sd/beta1)*100,.01));
  wald=(beta1/bs_sd)*(beta1/bs_sd);
  pvalue=1-probchi(wald,1);
  lo95=beta1-1.96*bs_sd;
  hi95=beta1+1.96*bs_sd;
  odds=exp(beta1);
  cil95=exp(lo95);
  ciu95=exp(hi95);
  ydep="&yvar";
  drop best1-best&b;
run;

data bs_reglg;
    set bs_reglg est;
run;

%let printlog=1;
%let dep2=&yvar;

proc datasets library=work;
    delete betas betat bsbeta origest;
run;


%mend logreg;

*********************************************;

%macro genreg(yvar,xvar);

*********************************************;
```

```
ods output GEEEmpPEst=orig;
proc genmod data=bs_data descending;
  &by by &classes;
  class realukey time;
  model &yvar=&xvar / dist=binomial;
  repeated subject=realukey / within=time type=ar(1);
  weight fwgt;
run;

data origest; set orig;
beta=parm; bhat1=estimate;
run;

data _NULL_;
    L=int((&b/10)+0.999);
    call symput ('L' , trim(left(L)));
run;

OPTIONS nonotes;

%let j_dep=1;

%do k=1 %to 10;
  %let j=%eval(1+((&k-1)*&L));
  %let kL=%eval(&k*&L);

data _NULL_;
if (&b - &kL) >0  then do;
                          k=&k;
                          j=1+((&k-1)*&L);
                          kL=&k*&L;
                       end;
                  else do;
                          k=10;
                          j=&j_dep;
                          kL=&b;
                       end;

call symput ('k' , trim(left(k)));
call symput ('j' , trim(left(j)));
call symput ('kL' , trim(left(kL)));
run;


data poids (keep = bsw&j-bsw&kL &yvar &xvar &classes realukey time);
  set bs_data;
run;

  %do i=&j %to &kL;

     %put Genmod Logistic regression &i completed;

     %let j_dep=%eval(&kl+1);
    ods select none;
    ods output GEEEmpPEst=betas;
    proc genmod data=poids descending;
      &by by &classes;
      class realukey time;
      model &yvar=&xvar / dist=binomial;
      repeated subject=realukey / within=time type=exch;
      weight bsw&i;
    run;
    ods select all;


    data betat; set betas;
    beta=parm; best1=estimate;
    run;

    data betat;
      set betat;
      rename best1=best&i;
    run;

    %if (&i =1) %then %do;

      data bsbeta;
        set betat;
      run;

    %end;
    %else %do;

      data bsbeta;
        merge bsbeta betat;
        &by by &classes;
      run;

    %end;
  %end;
%end;

OPTIONS notes;

data est;
  merge origest bsbeta;
  rename bhat1=bhat;
  bs_var=((&b-1)*(var(of best1-best&b)))/&b;
  bs_sd=sqrt(bs_var);
  bs_cv=abs(round((bs_sd/bhat1)*100,.01));
  wald=(bhat1/bs_sd)*(bhat1/bs_sd);
  pvalue=1-probchi(wald,1);
  lo95=bhat1-1.96*bs_sd;
  hi95=bhat1+1.96*bs_sd;
  odds=exp(bhat1);
  cil95=exp(lo95);
  ciu95=exp(hi95);
  ydep="&yvar";
  drop best1-best&b;
run;

data bs_reggen;
    set bs_reggen est;
run;
```

```
%let printgen=1;
%let dep2=&yvar;

proc datasets library=work;
    delete betas betat bsbeta origest;
run;


%mend genreg;

****************;

%macro prntgen;

****************;
%if &printgen=1 %then %do;

/********************************************/
/*Prints the results of the genreg macro    */
/********************************************/

   proc print data=bs_reggen;
     title "Variance estimation using &B bootstraps for ";
     title2 "Genmod Logistic regressions";
     title3 "Dependent variable: &dep2";
     var  &classes beta bhat odds wald pvalue bs_var bs_sd bs_cv cil95
ciu95;
       run;
%end;


/**********************************************************************
*****/
        /***  Where:
***/
        /***   beta       : parameter to estimate
***/
        /***   bhat       : parameter estimate
***/
        /***   odds       : odds ratio
***/
        /***   wald       : Wald's statistic
***/
        /***   pvalue     : p-value of Wald's statistic
***/
        /***   bsvar      : variance of the parameter estimate
***/
        /***   bs_sd      : standard deviation of the parameter
estimate        ***/
        /***   bs_cv      : coefficient of variation for the parameter
estimate ***/
        /***   cil95      : lower bound of the 95% confidence interval
***/
        /***   ciu95      : upper bound of the 95% confidence interval
***/
```

```
/*********************************************************************
*****/


%mend prntgen;
****************;

%macro prnttot;
****************;
%if &printtot=1 %then %do;

&by  data alltots;
&by   set alltots;
&by     ind1=3; &by  ind2=3; &by  ind3=3; &by  ind4=3;&by   ind5=3;
&by  ind6=3; &by  ind7=3;&by   ind8=3;&by   ind9=3;&by   ind10=3;
&by      %do i=1 %to &number;
&by        &&cla&i=cla&i;
&by        if &&cla&i=" " then &&cla&i="     All";
&by        if &&cla&i="     All" then ind&i=1;  &by  else ind&i=2;
&by   %end;
&by   run;

&by   proc sort data=alltots;
&by     by ind1 ind2 ind3 ind4 ind5 ind6 ind7 ind8 ind9 ind10
&classes;
&by   run;
/*******************************************/
/* Prints the results of the total macro   */
/*******************************************/
proc print data=alltots;
       title "Variance Estimation for Totals";
       title2 "using &B bootstrap replicates";
           title3 ;
       var &classes type var n Estimate bs_sd bs_cv cil95 ciu95;
       format Estimate bs_sd cil95 ciu95 11.2;
run;
%end;

/*****************************************************************/
        /*** Where:
***/
        /*** type         : estimate type (total )
***/
        /*** var          : variable used to calculate the estimate
***/
        /*** n            : sample size for the estimate
***/
        /*** Estimate     : parameter estimate
***/
        /*** bs_sd        : standard deviation
***/
        /*** bs_cv        : coefficient of variation
***/
        /*** cil95        : lower bound of the 95% confidence interval
***/
```

```
        /*** ciu95        : upper bound of the 95% confidence interval
***/
/*****************************************************************/
%mend prnttot;
****************;
%macro prntrat;
****************;
%if &printrat=1 %then %do;
&by  data allrats;
&by   set allrats;
&by     ind1=3; &by  ind2=3; &by  ind3=3; &by  ind4=3;&by   ind5=3;
&by  ind6=3; &by  ind7=3;&by   ind8=3;&by   ind9=3;&by   ind10=3;
&by      %do i=1 %to &number;
&by        &&cla&i=cla&i;
&by        if &&cla&i=" " then &&cla&i="     All";
&by        if &&cla&i="     All" then ind&i=1;  &by  else ind&i=2;
&by   %end;
&by   run;

&by   proc sort data=allrats;
&by     by ind1 ind2 ind3 ind4 ind5 ind6 ind7 ind8 ind9 ind10
&classes;
&by   run;
/*******************************************/
/* Prints the results of the ratio macro   */
/*******************************************/
proc print data=allrats;
       title "Variance Estimation for Ratios";
       title2 "using &B bootstrap replicates ";
           title3 ;
       var &classes type var1 var2 n1 Estimate bs_sd bs_cv cil95
ciu95;
     format  bs_sd cil95 ciu95 Estimate 11.4;
run;
%end;
/*****************************************************************/
        /*** Where:
***/
        /*** type         : estimate type (ratio)
***/
        /*** var1 et var2 : variables used to calculate the estimates.
***/
        /*** n1           : sample size for the numerator (var1)
***/
        /*** Estimate     : parameter estimate
***/
        /*** bs_sd        : standard deviation
***/
        /*** bs_cv        : coefficient of variation
***/
        /*** cil95        : lower bound of the 95% confidence interval
***/
        /*** ciu95        : upper bound of the 95% confidence interval
***/

/*****************************************************************/
%mend prntrat;
```

```
****************;
%macro prntdiff;
****************;
%if &printdif=1 %then %do;

&by  data diffrat;
&by   set diffrat;
&by     ind1=3; &by  ind2=3; &by  ind3=3; &by  ind4=3;&by   ind5=3;
&by  ind6=3; &by  ind7=3;&by   ind8=3;&by   ind9=3;&by   ind10=3;
&by      %do i=1 %to &number;
&by        &&cla&i=cla&i;
&by        if &&cla&i=" " then &&cla&i="    Tous";
&by        if &&cla&i="    Tous" then ind&i=1;  &by  else ind&i=2;
&by   %end;
&by   run;

&by   proc sort data=diffrat;
&by     by ind1 ind2 ind3 ind4 ind5 ind6 ind7 ind8 ind9 ind10
&classes;
&by   run;
/**********************************************/
/* Prints the results of the diff_rat macro   */
/**********************************************/
proc print data=diffrat;
       title "Variance Estimation for Differences between Ratios";
       title2 "using &B bootstrap replicates ";
       title3 ;
     var &classes type var1 var2 var3 var4 n1 n3 Estimate bs_sd bs_cv
cil95 ciu95;
     format  bs_sd cil95 ciu95 Estimate 11.4;
   run;
%end;


/*****************************************************************/
        /*** Where:
***/
        /*** type         : estimate type (ratio difference)
***/
        /*** var1, var2,
***/
        /*** var3 and var4: variables used to calculate the estimates.
***/
        /*** n1           : sample size for the first numerator (var1)
***/
        /*** n3           : sample size for the second numerator
(var2)***/
        /*** Estimate     : estimate
***/
        /*** bs_sd        : standard deviation
***/
        /*** bs_cv        : coefficient of variation
***/
        /*** cil95        : lower bound of the 95% confidence interval
***/
        /*** ciu95        : upper bound of the 95% confidence interval
***/
```

```
/****************************************************************/
%mend prntdiff;
****************;
%macro prntlog;
****************;
%if &printlog=1 %then %do;
/********************************************/
/*Prints the results of the logreg macro    */
/********************************************/

   proc print data=bs_reglg;
     title "Variance Estimation for a Regression ";
     title2 "Dependent variable: &dep2";
     title3 "using &B bootstrap replicates ";
     var  &classes param beta odds wald pvalue bs_var bs_sd bs_cv
cil95 ciu95;
       run;
%end;
**********************************************************************
****/
        /***  Where:
***/
        /***   param      : parameter to estimate
***/
        /***   beta       : parameter estimate
***/
        /***   odds       : odds ratio
***/
        /***   wald       : Wald's statistic
***/
        /***   pvalue     : p-value of Wald's statistic
***/
        /***   bsvar      : variance of the parameter estimate
***/
        /***   bs_sd      : standard deviation of the parameter
estimate        ***/
        /***   bs_cv      : coefficient of variation for the parameter
estimate ***/
        /***   cil95      : lower bound of the 95% confidence interval
***/
        /***   ciu95      : upper bound of the 95% confidence interval
***/

/*********************************************************************
/
%mend prntlog;
****************;
/*%macro output;
****************;
      %prnttot;
      %prntrat;
      %prntdiff;
      %prntreg;
      %prntlog;
      proc datasets library=work;
            delete Mfile bsamp version tmp;
      run;
      quit;
%mend output;*/
****************;
%macro output;
****************;
      %prnttot;
      %prntdiff;
      %prntreg;
      %prntlog;
      %prntgen;   /* add in to print the results of Genmod Logistic
Regression */
      data time;
       set time;
        format stop datetime16.;
       stop=datetime();
        output;
      run;
      proc print data=time;
            title ' Length of time required to run the program ';
      run;

%mend output;
/* End of MACROE_V30.SAS SAS program */
```

C.3 SAS macro for WGEE analysis

```
/*Macros "DROPOUT" and "DROPWGT" to create dataset for WGEE analysis
*/
%macro dropout(data=,id=,time=,response=,out=);
%if %bquote(&data)= %then %let data=&syslast;
proc freq data=&data noprint;
tables &id /out=freqid;
tables &time / out=freqtime;
run;
proc iml;
reset noprint;
use freqid;
read all var {&id};
nsub = nrow(&id);
use freqtime;
read all var {&time};
ntime = nrow(&time);
time = &time;
use &data;
read all var {&id &time &response};
n = nrow(&response);
dropout = j(n,1,0);
ind = 1;
do while (ind <= nsub);
  j=1;
  if (&response[(ind-1)*ntime+j]=.) then print "First Measurement is
Missing";
  if (&response[(ind-1)*ntime+j]^=.) then
    do;
```

```
      j = ntime;
      do until (j=1);
        if (&response[(ind-1)*ntime+j]=.) then
          do;
            dropout[(ind-1)*ntime+j]=1;
                  j = j-1;
              end;
          else j = 1;
      end;
      end;
  ind = ind+1;
end;
prev = j(n,1,1);
prev[2:n] = &response[1:n-1];
i=1;
do while (i<=n);
  if &time[i]=time[1] then prev[i]=.;
  i = i+1;
end;
create help var {&id &time &response dropout prev};
append;
quit;
data &out;
merge &data help;
run;
%mend;

%macro dropwgt(data=,id=,time=,pred=,dropout=,out=);
%if %bquote(&data)= %then %let data=&syslast;
proc freq data=&data noprint;
tables &id /out=freqid;
tables &time / out=freqtime;
run;
proc iml;
reset noprint;
use freqid;
read all var {&id};
nsub = nrow(&id);
use freqtime;
read all var {&time};
ntime = nrow(&time);
time = &time;
use &data;
read all var {&id &time &pred &dropout};
n = nrow(&pred);
wi = j(n,1,1);
ind = 1;
do while (ind <= nsub);
      wihlp=1;
      stay=1;
      /* first measurement */
      if (&dropout[(ind-1)*ntime+2]=1)
        then do;
            wihlp = pred[(ind-1)*ntime+1];
            stay=0;
        end;
      else if (&dropout[(ind-1)*ntime+2]=0)
```

```
        then wihlp = 1-pred[(ind-1)*ntime+2];
      /* second to penultimate measurement */
      j=2;
      do while ((j <= ntime-1) & stay);
        if (&dropout[(ind-1)*ntime+j+1]=1)
          then do;
              wihlp = wihlp*pred[(ind-1)*ntime+j+1];
              stay=0;
            end;
        else if (&dropout[(ind-1)*ntime+j+1]=0)
          then wihlp = wihlp*(1-pred[(ind-1)*ntime+j+1]);
        j = j+1;
      end;
      j=1;
      do while (j <= ntime);
        wi[(ind-1)*ntime+j] = wihlp;
        j = j+1;
      end;
      ind = ind+1;
end;
create help var {&id &time &pred &dropout wi};
append;
quit;
data &out;
merge &data help;
data &out;
set &out;
wi = 1/wi;
run;
%mend;

/* using both macros, the following code can be used to prepare for a
WGEE analysis */
%dropout(data=in1.dummy, id=realukey, time=repeat, response=asthm,
out=test);
proc genmod data=test descending;
class prev fallergy oallergy ulcer1 bronch agr4 incom imm time
new_prov ethnic bmi smk_sts
smk_hh locate;
model dropout = prev fallergy oallergy ulcer1 bronch agr4 incom imm
time new_prov ethnic bmi smk_sts
smk_hh locate locate*smk_sts locate*incom
ethnic*incom smk_hh*time smk_sts*agr4 agr4*incom/ pred dist=binomial;
/* we use trt and time as covariates for dropout model */
ods output obstats=pred;
run;
data pred;
set pred;
keep observation pred;
run;
data test;
merge pred test;
run;

%dropwgt(data=test,id=realukey,time=repeat,pred=pred,dropout=dropout,o
ut=wgee);run;
```

```
/* After this preparatory work, we include the weights by means of the
WEIGHT*/
/* (or, equivalently, SCWGT) statement within the GENMOD procedure*/

data in1.missing;
set wgee;
wtmiss=wi*wt64ls;
run;

ODS TRACE ON/LISTING;
/*Keeping drop, main effect * drop interaction amd drop*interaction*/
PROC GENMOD DATA=in1.missing;
CLASS REPEAT REALUKEY fallergy oallergy ulcer1 bronch agr4 incom imm
time new_prov ethnic bmi smk_sts
smk_hh locate;
MODEL ASTHM=fallergy oallergy ulcer1 bronch agr4 incom imm time
new_prov ethnic bmi smk_sts
smk_hh locate locate*smk_sts locate*incom
ethnic*incom smk_hh*time smk_sts*agr4 agr4*incom/DIST=BIN LINK=LOGIT;
                  repeated subject=realukey / corrw within=repeat
type=exch;
                  weight wtmiss;
                  ODS OUTPUT GEEEmpPEst=myests1;
RUN;
data myests1;
set myests1;
or=exp(estimate);
low_or=exp(estimate-1.96*stderr);
hi_or=exp(estimate+1.96*stderr);
run;
proc print DATA=myests1;
var parm estimate stderr or low_or hi_or;
RUN;

proc printto;
run;
```

APPENDIX D

D. 1 Remote access to National Population Health Survey data

APPENDIX E

E. 1 Exemption from ethics approval letter

UNIVERSITY OF SASKATCHEWAN

Ethics Office

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Behavioural Research Ethics Board
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MEMORANDUM

To: Dr. Punam Pahwa – Institute of Agricultural, Rural, and Environmental Health
Sunita Ghosh – Institute of Agricultural, Rural, and Environmental Health

Date: April 13, 2006

Re: Statistical Modeling of Longitudinal Complex Survey Data with Binary Outcome

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The study entitled, "Statistical Modeling of Longitudinal Complex Survey Data with Binary Outcome" is exempt from the Research Ethics Board review process. This decision is based on the information provided in your ethics application on March 29, 2006.

Article 3.3 of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (1998) specifies that REB review and approval is not required to conduct a secondary analysis of data that cannot be linked to individuals, and for which there is no possibility that individuals can be identified in any published reports.

It should be noted that though your project is exempt of ethics review, your project should be conducted in an ethical manner (i.e. in accordance with the information that you submitted). It should also be noted that any deviation from the original methodology and/or research question should be brought to the attention of the Behavioural Research Ethics Board for further review.

Sincerely,

Thompson

Dr. Valerie Thompson, Chair
Behavioural Research Ethics Board
University of Saskatchewan

To whom it may concern

This is to verify that Sunita Ghosh has had remote access privileges with us in the Data Access Unit since 2004/09/30 and her current application has a proposed end date of 2007/12/31 with access to NPHS cycles 1-5.

Regards,

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