

PASSIVE SMOKING AND MORTALITY:

**Exposure to second-hand smoke in the home and
mortality amongst 45-77 year old never-smokers
in the New Zealand Census-Mortality Study**

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Abstract

Objectives

1. To measure the association between household exposure to second-hand smoke (SHS) and all-cause mortality in 45-77 year old never-smokers.
2. To measure the association between household SHS exposure and disease-specific mortality in 45-77 year old never-smokers.

Methods

Study data were drawn from two cohorts of linked census and mortality records. The two cohorts comprised New Zealand never-smokers aged 45-74 years at the time of the 1981 and 1996 censuses, and followed for mortality over the subsequent three years. Domestic exposure to SHS was inferred from the smoking behaviour of other household members aged 15 years and over: never-smokers living in households with one or more current smokers were defined as exposed to SHS in the home, while those living in households with no current smokers were defined as unexposed to domestic SHS.

Age- and ethnicity-standardised mortality rates were calculated according to domestic SHS exposure. All-cause and disease-specific mortality rates amongst never-smokers with domestic SHS exposure were compared with those of never-smokers without SHS exposure in the home. Relative risk estimates were controlled for age, ethnicity, marital status and socio-economic position using Poisson regression.

Sensitivity analyses were undertaken to explore the likely impact of misclassification on relative risk estimates. Analyses attempted to correct for any misclassification that may have occurred due to misreported personal smoking status and varying sensitivity and specificity of the SHS exposure measure used in this study.

Results

Full data for standardised analyses were available for 87.0% of never-smoking census respondents in the 1981 census and 85.3% in the 1996 census. Never-smoking census respondents contributed 0.8 million person-years and 10,188 deaths in 1981-84, and 1.1 million person-years and 9,153 deaths in 1996-99.

In never-smokers with household SHS exposure, the age- and ethnicity-standardised rate ratio (95% confidence interval) for all-cause mortality was 1.10 (0.99-1.22) in men and 1.04 (0.96-1.13) in women for 1981-84, and 1.17 (1.05-1.31) in men and 1.27 (1.15-1.41) in women for 1996-99. Adjustment for marital status and socio-economic position had little impact on relative risk estimates; adjusted relative risk estimates (95% confidence interval) were 1.17 (1.05-1.30) in 1981 men, 1.06 (0.97-1.16) in 1981 women, 1.16 (1.04-1.30) in 1996 men and 1.28 (1.16-1.42) in 1996 women.

Correction for possible misclassification did not significantly change the relative risk of mortality in those with SHS exposure. Using crude data from 1996 men, the unadjusted RR was 1.14; after correction for likely misclassification the adjusted RR was thought to lie between 1.09 and 1.18.

Conclusions

This study found an association between SHS exposure in the home and all-cause mortality, with around 15% excess mortality amongst exposed never-smokers. The association does not appear to be due to confounding, misclassification of personal smoking status or random error. Excess mortality in never-smokers living with smokers resulted from an increased risk of conditions known to be related to tobacco use, chiefly cardiovascular diseases.

This study is the largest of its kind to date, and its findings add to the weight of evidence for a causal association between SHS and mortality. Such an association highlights the need for governments, employers, families and individuals to protect the public from the health effects of second-hand smoke.

Statistics New Zealand Security Statement

The New Zealand Census-Mortality Study was initiated by Dr Tony Blakely and his co-researchers from the Wellington School of Medicine & Health Sciences, University of Otago. It was approved by the Government Statistician as a Data Laboratory project under the Microdata Access Protocols.

Requirements of the Statistics Act

Under the Statistics Act 1975 the Government Statistician has legal authority to collect and hold information about people, households and businesses, as well as the responsibility of protecting individual information and limits to the use to which such information can be put. The obligations of the Statistics Act 1975 on data collected under the Act are summarised below.

1. Information collected under the Statistics Act 1975 can be used only for statistical purposes.
2. No information contained in any individual schedule is to be separately published or disclosed to any person who is not an employee of Statistics New Zealand, except as permitted by sections 21(3B), 37A, 37B and 37C of the Act.
3. This project was carried out under section 21(3B). Under Section 21(3B) the Government Statistician requires an independent contractor under contract to Statistics New Zealand, and any employee of the contractor, to make a statutory declaration of secrecy similar to that required of Statistics New Zealand employees where they will have access to information collected under the Act. For the purposes of implementing the confidentiality provisions of the Act, such contractors are deemed to be employees of Statistics New Zealand.
4. Statistical information published by Statistics New Zealand, and its contracted researchers, shall be arranged in such a manner as to prevent any individual information from being identifiable by any person (other than the person who supplied the information), unless the person owning the information has consented to the publication in such manner, or the publication of information in that manner could not reasonably have been foreseen.
5. The Government Statistician is to make office rules to prevent the unauthorised disclosure of individual information in published statistics.
6. Information provided under the Act is privileged. Except for a prosecution under the Act, no information that is provided under the Act can be disclosed or used in any proceedings. Furthermore no person who has completed a statutory declaration of secrecy under section 21 can be compelled in any proceedings to give oral testimony regarding individual information or produce a document with respect to any information obtained in the course of administering the Act, except as provided for in the Act.

Census data

The Population Census is the most important stocktake of the population that is carried out. The statistics that are produced provide a regular picture of society. Results are used widely in making decisions affecting every neighbourhood. They are used in planning essential local services, and they also help to monitor social programmes ranging from housing to health.

Traditionally census data is published by Statistics New Zealand in aggregated tables and graphs for use throughout schools, business and homes. Recently Statistics New Zealand has sought to increase the benefits that can be obtained from its data by providing access to approved researchers to carry out research projects. Microdata access is provided, at the discretion of the Government Statistician, to allow authoritative statistical research of benefit to the public of New Zealand.

This project used anonymous census data and mortality data which were integrated using a probabilistic linking methodology to create a single dataset that allows the researchers to undertake a statistical study of the association of mortality and socio-economic factors. This is the first time that the census has been linked to an administrative dataset for purposes apart from improving the quality of Statistics New Zealand surveys. The project has been closely monitored to ensure it complies with Statistics New Zealand's strict confidentiality requirements.

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Chapter 1: Introduction

In 1954, Doll and Hill reported the first prospective evidence of increased mortality in active smokers.¹ Smoking is now widely recognised as a major risk factor for lung cancer, cardiovascular disease, respiratory disease and many other conditions causing premature morbidity and death.² By the year 2020, tobacco is estimated to become the single greatest contributor to the global burden of disease.³

An association between passive smoking and mortality was first reported by Hirayama, whose 1981 paper described increased lung cancer mortality in non-smoking women married to smoking men.⁴ Since then, a number of researchers have sought to clarify the relationship between passive smoking and tobacco-related disease. Meta-analyses suggest that non-smokers exposed to second-hand smoke (SHS) have around 30% increased risk for developing lung cancer and ischaemic heart disease.⁵⁻⁷ Yet some authors continue to doubt these findings, pointing to misclassification bias and confounding as possible sources of a non-causal association between passive smoking and mortality.⁸⁻¹⁰

Few studies have examined the relationship between second-hand smoke exposure and mortality. Many of these studies have been hamstrung by limited statistical power, particularly in studying mortality from specific diseases.¹¹⁻¹³ Other limitations are the potential for confounding due to socio-economic and lifestyle differences in exposure groups, and possible misclassification bias arising from current- and ex-smokers who misreport themselves as never-smokers.¹⁴ These three issues present a challenge to any researcher investigating the health effects of passive smoking.

This thesis describes a large prospective study of mortality amongst 45-77 year old never-smokers according to second-hand smoke exposure occurring in the home. The study uses data from two population cohorts followed for three-year mortality. In undertaking this thesis, I have sought to answer two questions:

1. What is the association between domestic exposure to second-hand smoke and all-cause mortality?
2. What is the association between domestic exposure to second-hand smoke and disease-specific mortality?

In answering these two questions I have also sought to address the issues described above – ie problems with inadequate study power, potential confounding of the passive smoking-mortality relationship, and the effects of misclassification. These three issues are exacerbated by the likely small magnitude of any association between second-hand smoke exposure and mortality. In this respect, the health effects of passive smoking are much more difficult to measure than those arising from active tobacco smoking.

I am fortunate to have access to a large dataset that includes two population cohorts with information on smoking at both a personal and a household level. This has provided me with substantial statistical power and the ability to make relatively precise estimates. I have also been able to control for a broad range of socio-economic factors and (by proxy) for many aspects of individual lifestyle, thus minimising the potential for uncontrolled confounding. The impact of misclassification bias has been addressed in data analysis, through sensitivity analyses correcting for different (assumed) levels of misclassification.

The following chapters present the results of my research in the traditional thesis framework. Thus I have started by reviewing the published literature on passive smoking and mortality, including previous research in this area, issues surrounding assessment of the passive smoking-mortality association, and biological and experimental evidence for the health effects of SHS exposure. Chapter 3 describes the data and epidemiological methods used in my own study of passive smoking and mortality. Chapter 4 presents the results of data analysis, and Chapter 5 discusses these results in the context of existing evidence for a causal association between passive smoking and mortality. My final summary and conclusions are presented in Chapter 6.

As with any new study, it is important to interpret the results of this research in the context of existing evidence on passive smoking and mortality. This study is larger than any previously published report, and as such makes a substantial contribution to what is known about second-hand smoke exposure and mortality. The findings of this thesis are particularly relevant at a time when many governments (including that in New Zealand) are contemplating measures to further restrict smoking in workplaces and public areas. I hope that the results of this thesis will make a useful contribution to public debate around the issue of passive smoking.

Chapter 2: Literature Review & Background

Chapter Outline

There is now a substantial base of published research examining the association between passive smoking and the incidence of various diseases such as lung cancer and ischaemic heart disease. The relationship between passive smoking and *mortality* is less well established, and is thus a matter of ongoing controversy.

Since 1981, 14 published studies have examined the association between second-hand smoke (SHS) exposure and mortality. These studies have produced mixed results. Many have reported a small positive association between passive smoking and mortality, but issues around precision, systematic error and publication bias make it difficult to interpret these results in the absence of a formal meta-analysis.

Existing epidemiological evidence suggests that exposure to second-hand smoke is unlikely to increase all-cause mortality by more than 20%. While such an effect is important at a population level, it is very difficult to demonstrate with certainty on the basis of observational data. Small effects are particularly susceptible to study error, including both lack of precision and systematic error from confounding and misclassification. These issues present a challenge to any researcher investigating the relationship between passive smoking and mortality.

The first part of this chapter reviews published studies of second-hand smoke exposure and mortality, including 12 cohort studies and two case-control studies. This is followed by a brief summary of the evidence linking passive smoking and the incidence of tobacco-related diseases.

The second part of the chapter addresses issues involved in interpreting the above evidence. These include questions of internal validity arising from misclassification of exposure status and the potential for confounding. The chapter finishes with a brief review of biological mechanisms by which second-hand smoke exposure may cause disease.

2.1. Existing evidence on passive smoking and mortality

The published (English language) scientific literature was reviewed with respect to SHS exposure and mortality. A Medline search was conducted using the MESH subject heading “tobacco smoke pollution” and the keywords “environmental tobacco smoke”, “passive smoking”, “second-hand smoke”, and “involuntary smoking”. Bibliographies of major review articles were also searched for relevant references.

The review was limited to material on SHS exposure and mortality in adults. With the exception of major review articles and research specific to New Zealand, data on passive smoking and morbidity were not included in this literature review. Also excluded from this review were the significant number of published studies examining the association between maternal smoking and infant mortality from Sudden Infant Death Syndrome (SIDS).

Publications were also sought with respect to measurement of passive smoking exposure and the potential for misclassification; potential confounding factors such as diet and socio-economic position; and causal mechanisms by which passive smoking has an effect on health. These are discussed in the second part of this chapter.

2.1.1 Passive smoking and mortality: cohort studies

Twelve published cohort studies have attempted to measure the association between passive smoking and mortality. These are outlined in Table 1.

Figure 1 presents the results of these studies in graphical form. Relative risk estimates are given for mortality from ischaemic heart disease (IHD), lung cancer (lung ca) and all causes combined. RRs are plotted on a log scale so that the horizontal distance from the null value (RR=1) indicates the direction and magnitude of the reported association.

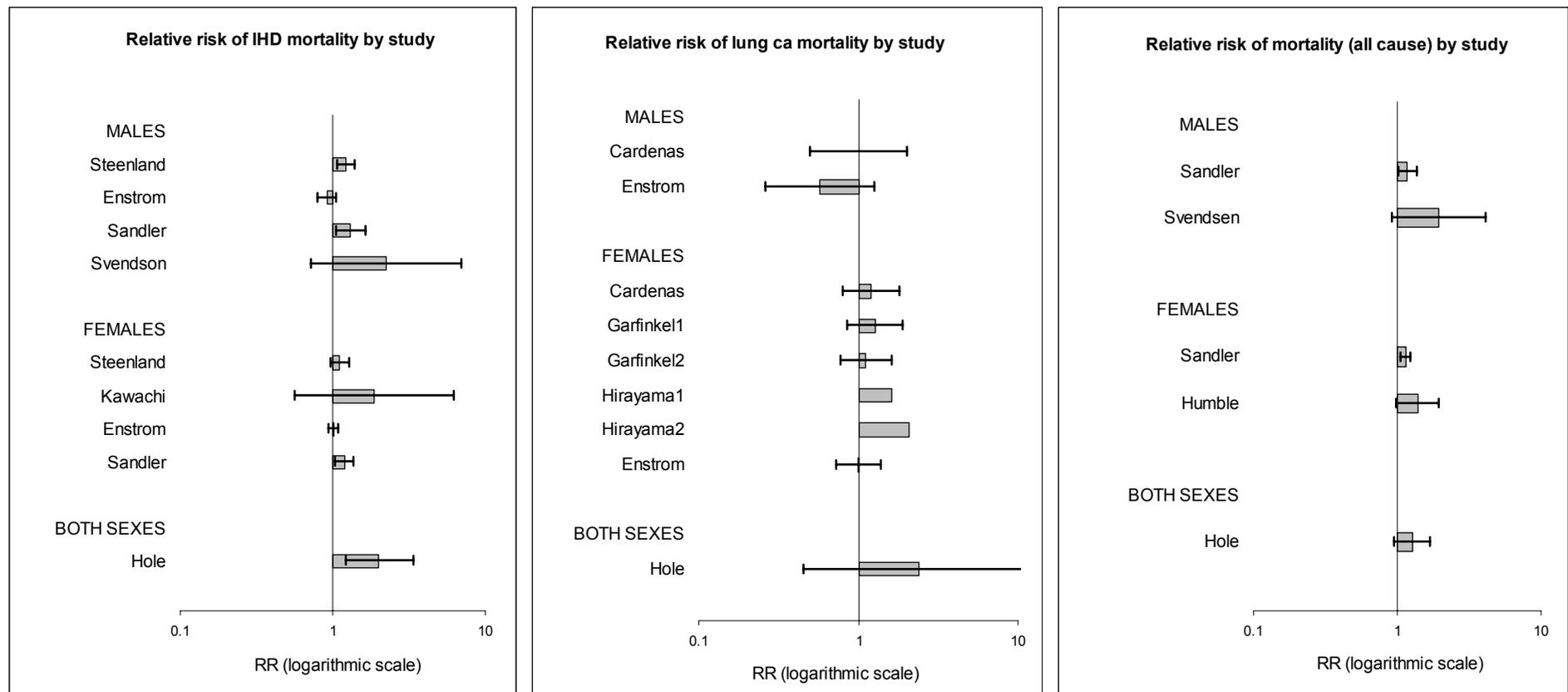
Table 1: Published cohort studies of SHS exposure and mortality

1 st Author	Published	Country	Number* in cohort	Source of exposure	Follow-up	Cause of death	Deaths	Relative risk of mortality in those with SHS exposure** (95% CI)			
								Men	Women		
Cardenas ¹⁵ (CPS-II)	1997	USA	288,776	Home (spouse)	7 years	Lung cancer	185	1.0	(0.5-2.0)	1.2	(0.8-1.8)
Steenland ¹⁶ (CPS-II)	1996	USA	232,200	Home (spouse)	7 years	IHD	3,145	1.22	(1.07-1.40)	1.10	(0.96-1.27)
Garfinkel ¹⁷ (CPS-I)	1981	USA	176,739	Home (spouse)	12 years	Lung cancer	153		<i>moderate exposure:</i>	1.27	(0.85-1.89)
									<i>heavy exposure:</i>	1.10	(0.77-1.61)
Hirayama ^{4 18 19}	1981	Japan	91,540	Home (spouse)	14 years	Lung cancer	346		<i>moderate exposure:</i>	1.61	Test for trend
									<i>heavy exposure:</i>	2.08	p=0.001
Kawachi ¹³ (NHS)	1997	USA	32,046	Home and work (self-reported)	10 years	IHD	25			1.87	(0.56-6.20)
Enstrom ¹⁰ (CPS-I)	2003	USA	28,079	Home (spouse)	39 years	IHD	4,747	0.92	(0.80-1.05)	1.01	(0.94-1.08)
						Lung cancer	200	0.57	(0.26-1.26)	0.99	(0.72-1.37)
						COPD	209	1.28	0.72-2.27)	1.13	(0.80-1.58)
Sandler & Helsing ^{20 21}	1989	USA	19,035	Home (co-habitants)	12 years	All cause	3,623	1.17	(1.01-1.36)	1.15	(1.06-1.24)
						IHD	1,358	1.31	(1.05-1.64)	1.19	(1.04-1.36)
						Cerebrovascular	655	0.97	(0.65-1.46)	1.24	(1.03-1.49)
						Respiratory	193	1.44	(0.75-2.75)	1.21	(0.87-1.69)
Hole & Gillis ^{12 22}	1989	Scotland, UK	2,455	Home (spouse / co-habitant)	11 years	All cause	263		Both sexes:	1.27	(0.95-1.70)
						IHD	84			2.01	(1.21-3.35)
						Lung cancer	9			2.41	(0.45-12.83)
Svensden ¹¹	1987	USA	1,245	Home (spouse)	7 years	All cause	30	1.94	(0.91-4.09)		
						IHD	13	2.23	(0.72-6.92)		
Vandenbroucke ²³	1984	Netherlands	803	Home (spouse)	25 years	All cause	not specified		not specified		not specified
Humble ²⁴	1990	USA	513	Home (spouse)	20 years	All cause	147			1.39	(0.99-1.94)
						CVD	76			1.59	(0.99-2.57)
Garland ²⁵	1985	USA	300	Home (spouse)	10 years	IHD	4				not specified

* Numbers in each study cohort refer to non-smokers with current or no SHS exposure at baseline (ie excludes those with previous but not current SHS exposure). The only exception to this is Hirayama's study, where wives of moderate smokers and wives of ex-smokers were grouped together and could not be distinguished in the published report.

** Relative risk estimates are for mortality amongst non-smokers with SHS exposure compared to non-smokers without SHS exposure. RR estimates are adjusted for potential study-specific confounders using multivariable regression techniques, except RR estimates for studies by Garfinkel and Hirayama which refer to standardised mortality ratios (standardised by age and age plus husband's occupation respectively).

Figure 1: Relative risk estimates for mortality (IHD, lung cancer and all cause) in non-smokers with SHS exposure, from published cohort studies (listed in Table 1)



The null value (no association) is indicated by a vertical line at RR = 1.

Error bars indicate 95% confidence intervals around the RR estimate. The upper confidence interval for the RR of lung cancer mortality in Hole's study was 12.8 (ie just beyond the upper limit of the y axis in middle figure).

Studies by Garfinkel and Hirayama (SHS exposure and lung cancer mortality) reported RR estimates separately for subjects with moderate and heavy SHS exposure; these estimates are presented separately (1 = moderate exposure, 2 = heavy exposure). No confidence intervals are given in Hirayama's study (test for trend $p=0.001$).

Interestingly, no formal meta-analysis of passive smoking and mortality has yet been published. In reviewing Table 1 and Figure 1, however, it can be seen that most published studies report a small positive association between SHS exposure and mortality, with relative risk estimates in the order of 1 to 2. The precision of these RR estimates is variable; in many cases 95% confidence limits are wide relative to the magnitude of the effect measure estimate.

This apparent association between SHS exposure and mortality may reflect a real effect; it may be due to chance; or it may arise from systematic bias. In studies of passive smoking and mortality the most important sources of error are likely to be misclassification of exposure status and confounding. The possibility of publication bias should also be taken into account when reviewing the results of published studies (this issue is discussed later in the chapter).

The studies described in Table 1 indicate that if there is an association between passive smoking and mortality, this is likely to be of small magnitude. Those studies with the largest RR estimates also tend to have the widest confidence intervals (see estimates from studies by Svendsen, Kawachi and Hole). The most powerful studies tend to produce RR estimates of modest size (see those reported by Steenland, Enstrom and Sandler). The largest study of all-cause mortality in passive smokers is that published by Sandler, who reports relative risks of 1.17 (95% CI 1.01-1.36) in men and 1.15 (1.06-1.24) in women.²¹

The most recently published analysis is that by Enstrom and Kabat, who re-examined a subset of data from the American Cancer Society's first Cancer Prevention Study.¹⁰ The authors failed to find any association between domestic exposure to SHS and mortality from ischaemic heart disease or lung cancer, although they did report a small (non-significant) increase in mortality from chronic obstructive respiratory disease. Their's is the only sizeable published study to have found no increase in IHD mortality amongst passive smokers.

All twelve cohort studies have used a study population of never-smoking adults. Eleven of the twelve are based on domestic exposure to SHS, with exposure status imputed from the smoking behaviour of subjects' spouses or other cohabitants. The Nurses' Health Study (published by Kawachi et al)¹³ is the only exception to this pattern; this study uses both workplace and home exposure to define exposure categories.

Individual studies are discussed in more detail below, starting with the earliest and finishing with those most recently published.

2.1.1.1 Hirayama: Japan (1966-79)

The first study to link passive smoking and lung cancer was that published by Takeshi Hirayama in 1981.⁴ Hirayama examined data from a cohort of 91,540 married women, all of whom were lifetime non-smokers. The women were followed for 14 years (from 1966 to 1979), and lung cancer mortality rates calculated according their husbands' smoking behaviour at baseline. Hirayama reported that women married to heavy smokers had higher lung cancer mortality than those married to either moderate smokers or non-smokers, with rate ratios of 2.08, 1.61 and 1.00 respectively (test for trend $p=0.001$).

Hirayama's study has some potential for confounding due to differences between the exposure groups in terms of diet or other sources of air pollution; however it seems unlikely that such confounding would fully explain the observed association between passive smoking and lung cancer mortality. Mortality rate ratios were standardised by the age and occupation of the subject's husband, but were not controlled for other potential confounders.⁴ In standardising for the husband's occupation, Hirayama sought to exclude possible confounding from urban air pollution. When the study cohort was divided into agricultural and non-agricultural groups (according to the husband's occupation), lung cancer mortality was found to be higher amongst passive smoking women from agricultural families. Hirayama suggests that rural couples

spent more time together than those in urban areas where husbands were more likely to work outside the home.

The absence of substantial confounding is supported by the lack of any association between passive smoking and mortality from stomach cancer (RR=1.02 for women with moderate exposure, 0.99 for those with heavy exposure).⁴ Stomach cancer is one of the more common forms of cancer in Japan, and its aetiology is known to be diet-related.²⁶ (Active smoking is also a risk factor for stomach cancer, but the association is relatively weak.²⁷) Similar stomach cancer mortality rates in women with smoking and non-smoking husbands suggest the two groups did not differ significantly in terms of their diet.

In a later paper (based on the same cohort), Hirayama reports increased rate ratios for IHD mortality amongst non-smoking wives whose husbands smoke.¹⁹ In women married to moderate smokers, the RR of IHD was around 1.15; in those married to heavy smokers the RR was around 1.40. Unfortunately no confidence intervals or p values are reported for these estimates.

2.1.1.2 Garfinkel: CPS-I, USA (1960-1972)

Results from another major study were published around the same time as Hirayama's report. Lawrence Garfinkel examined the association between passive smoking and lung cancer mortality using data from the American Cancer Society's first cancer prevention study (CPS-I).¹⁷ A cohort of 176,739 non-smoking married women were enrolled in the study in 1959 and followed over the next 12 years. As with Hirayama's study, participants' SHS exposure was classified according to their husbands' smoking status at baseline.

Results from this study suggested an increased risk of death from lung cancer amongst wives whose husbands smoked, but 95% confidence intervals included the null value. Mortality rate ratios (standardised by age) were 1.27 (95% CI 0.85-1.89) amongst women whose husbands smoked less than 20 cigarettes per day, and 1.10 (95% CI 0.77-1.61) amongst those whose husbands smoked 20 or more cigarettes per day.

This study was limited by a relatively small number of outcomes. The CPS-I cohort had fewer lung cancer deaths than Hirayama's cohort - 153 among a population of 176,739, compared with 174 lung cancer deaths in Hirayama's much smaller cohort of 91,540. (Duration of follow-up was similar for the two studies.) Mortality rates from the CPS-I cohort were not adjusted for potential confounders other than age. Garfinkel comments on the difficulty involved in classifying SHS exposure, and notes the potential for exposure misclassification bias in this study.

2.1.1.3 Sandler, Helsing et al, USA (1963-1975)

Sandler et al report results from 19,035 white non-smoking adults followed over 12 years for death from all causes.^{20 21} Unlike most other cohort studies (which use spousal smoking to define participants' passive smoking status), Sandler categorises participant's exposure according to the smoking habits of other household members. His study is based on a population census conducted in Washington County, Maryland in 1963. Census records were linked with death certificates in the same region over the following 12 years. Non-smoking census respondents were classified according to the smoking habits of their fellow household members, and mortality rates calculated for non-smokers (with no domestic SHS exposure), passive smokers and active smokers.

The authors report a significant association between passive smoking and all-cause mortality. Compared with participants living in non-smoking households, the mortality rate ratio for those living in smoking households was 1.17 (95% CI 1.01-1.36) in men and 1.15 (1.06-1.24) in women. The authors also report a significant association between passive smoking and mortality from ischaemic heart disease, with RR estimates of 1.31 (95% CI 1.05-1.64) in men and 1.19 (1.04-1.36) in women. Women from smoking households also had significantly greater mortality from cerebrovascular disease, with a rate ratio of 1.24 (1.03-1.49).

One major advantage of Sandler's study is that rate ratios were adjusted for several potential sources of confounding - i.e. age, marital status, education (years of schooling) and housing quality (based on running water, number of bathrooms, type of heating system, cooking fuel, and availability of a telephone).²¹ Education and

housing quality are two markers of socio-economic position, which is a potential confounder in the relationship between passive smoking and mortality. Both smoking and other health-related behaviours (such as diet and exercise) tend to be patterned by socio-economic position; those individuals exposed to second-hand smoke are more likely to have poor diet and inadequate exercise, and may therefore have increased mortality independent of their passive smoking exposure.^{28 29} (The interaction between socio-economic position and lifestyle and their role as potential confounders is discussed in more detail later in this chapter – see section 2.2.3.)

Adjustment for the above covariates was achieved by Poisson regression.²¹ Socio-economic status was therefore largely controlled for, although there is still some potential for confounding from lifestyle factors (such as alcohol intake and diet).

2.1.1.4 Steenland et al: CPS-II, USA (1982-1989)

Data from the second American Cancer Society cancer prevention study (CPS-II) was used by Steenland et al to examine the association between passive smoking and death from ischaemic heart disease.¹⁶ The authors analysed a cohort of 232,200 non-smokers enrolled in 1982 and followed for IHD mortality over the next seven years. Relative risk estimates are controlled for a variety of potential confounders (including history of hypertension or diabetes, body-mass index, exercise and employment status) using Cox regression analyses.

Participants' SHS exposure was defined on the basis of spousal smoking status at baseline. Information was also collected on participants' self-reported SHS exposure, although these data were incomplete for a large proportion of the cohort. The authors did make use of these data by carrying out a sub-analysis on those participants whose self-reported SHS exposure concurred with their spouse's smoking status (ie those with smoking spouses who reported regular SHS exposure at home, or those with non-smoking spouses who reported no domestic exposure to SHS). They reasoned that this sub-analysis would involve less misclassification of SHS exposure, since it excluded those individuals whose self-reported exposure did not align with their spouse's smoking status. This improvement in exposure classification may have been

at the expense of increased selection bias, as only 50% of the total study cohort were included in the restricted analysis.

Interestingly, analyses based on spousal smoking status and those based on the highly selected cohort (with concordant self-report and spousal smoking) offer similar estimates of the relative risk associated with SHS exposure. For men whose wives smoked the RR of IHD mortality was 1.22 (95% CI 1.07-1.40), while for women whose husbands smoked the RR was 1.10 (0.96-1.27). In the subgroup with concordant self-reported and spousal smoking exposure, the RR was 1.23 (1.03-1.47) in men and 1.19 (0.97-1.45) in women.

The strengths of this study are the large number of participants and endpoints, and the ability to control for multiple potential confounders (including both lifestyle and socio-economic factors). The use of two measures of SHS exposure allowed the authors to explore the potential for misclassification of exposure status.

It should be noted that Steenland et al failed to find any dose-response relationship in the relative risk of IHD mortality, neither in the cohort defined by spousal smoking nor in the subgroup with concordant self-reported and spousal SHS exposure. The lack of any dose-response trend somewhat attenuates the otherwise compelling findings of this study (although it is consistent with a threshold effect for smoke exposure and IHD – see section 2.2.4.2 later in this chapter).

2.1.1.5 Cardenas et al: CPS-II, USA (1982-1989)

Cardenas et al also analysed data from the second cancer prevention study, looking at mortality from lung cancer.¹⁵ The cohort they used was slightly smaller than that analysed by Steenland et al, and the number of outcomes was considerably smaller (reflecting the much lower incidence of lung cancer relative to ischaemic heart disease). Exposure to SHS was derived both from data on spousal smoking status and from self-report, but the latter was less informative (as data was missing for many individuals). Relative risk estimates are therefore presented only for the analysis based on spousal smoking status.

As with Steenland's analysis, the authors used Cox proportional hazards regression to control RR estimates for a variety of potential confounders, including age, ethnicity, education, occupation, dietary factors, and past history of lung disease. Relative risk estimates for lung cancer mortality were increased in women with smoking husbands (RR 1.2, 95% CI 0.8-1.8), but not in men with smoking wives (RR 1.0, 95% CI 0.5-2.0). Confidence intervals include the null in both instances.

2.1.1.6 Kawachi et al: Nurses' Health Study, USA (1982-1992)

Kawachi et al used data from the US Nurses' Health Study to measure the relative risk of ischaemic heart disease (both incident and fatal) amongst non-smokers exposed to SHS.¹³ This study used both workplace and domestic exposure to determine participants' SHS exposure status, in contrast to every other published cohort study which has relied solely on domestic exposure. SHS exposure (both at home and at work) was ascertained by self-report.

A particular strength of this study was the collection of data on a wide range of potential confounding factors. This information allowed the authors to adjust relative risk estimates for known cardiovascular risk factors (hypertension, diabetes, hypercholesterolaemia), dietary and alcohol intake, and socio-economic background (as indicated by father's occupation when the subject was 16 years old).

Unfortunately, multivariable analysis could not be undertaken for IHD mortality due to the small number of IHD deaths (25) that occurred during the 10 years of follow-up. Proportional hazards regression analysis was used to adjust the relative risk estimate for all IHD (both incident and fatal) amongst those with SHS exposure. Adjustment for the above factors produced some attenuation of the age-adjusted RR, from 1.97 (95% CI 1.20-3.24) to 1.71 (1.03-2.84). This reduction reflects the slightly higher prevalence of these factors in women with self-reported SHS exposure, pointing to the potential for confounding of the association between SHS exposure and IHD mortality.

The small number of IHD fatalities in this cohort is reflected by wide confidence intervals around the rate ratio estimate. Amongst those with SHS exposure the age-adjusted RR of IHD mortality was 1.87 (95% CI 0.56-6.21).

2.1.1.7 Enstrom & Kabat: CPS-I (Californian subgroup), USA (1960-1998)

The most recent report of passive smoking and mortality appeared in the *British Medical Journal* in May 2003. Enstrom and Kabat examined data from a subgroup of the first American Cancer Society cancer prevention study (CPS I).¹⁰ This is the same study group from which Garfinkel's earlier report was drawn,¹⁷ but Enstrom and Kabat have restricted their analysis to those participants living in California, and extended the follow-up period to 39 years. The authors analyse data from 35,561 never-smokers who were married at the time of enrolment and followed for mortality until 1998. SHS exposure is based on the spouse's smoking status at baseline. Follow up was completed for over 90% of this cohort.

The authors used Cox proportional hazards regression analysis to estimate the relative risk of death from ischaemic heart disease, lung cancer and chronic obstructive pulmonary disease amongst never-smokers who were married to smokers in 1959. Results were adjusted for age and for several potential confounders including ethnicity, education, body-mass index and fruit intake at baseline. No significant associations were found for SHS exposure and any of the three causes of death. The authors conclude that these results "do not support a causal relation between environmental tobacco smoke and tobacco related mortality, although they do not rule out a small effect."

The publication of this analysis in the *British Medical Journal* caused some controversy, not least because the authors had received tobacco industry funding to undertake their analyses. Nevertheless, the study does highlight the ongoing uncertainty surrounding the health effects of SHS exposure.

The most important limitation of Enstrom and Kabat's analysis is the significant potential for misclassification of SHS exposure.^{30 31} Where exposure is dichotomised, the presence of nondifferential misclassification will bias any association measure towards the null. In this analysis, exposure status was determined at the beginning of a very long follow-up period. Actual exposure to SHS may well have varied during the follow-up period, with changes in living and working conditions, changes in

spousal smoking behaviour, and changes in participants' own smoking status. The ubiquitous nature of smoking in 1960s US society meant that virtually no one was truly non-exposed with respect to SHS, and spousal smoking status may be a poor guide to SHS exposure in this cohort. The authors' own follow-up assessment shows a relatively poor correlation between spousal smoking status at baseline and participants' self-reported SHS exposure in 1959: almost a quarter of those whose spouses were recorded as current smokers stated that they had no regular exposure to cigarette smoke.

2.1.1.8 Other cohort studies

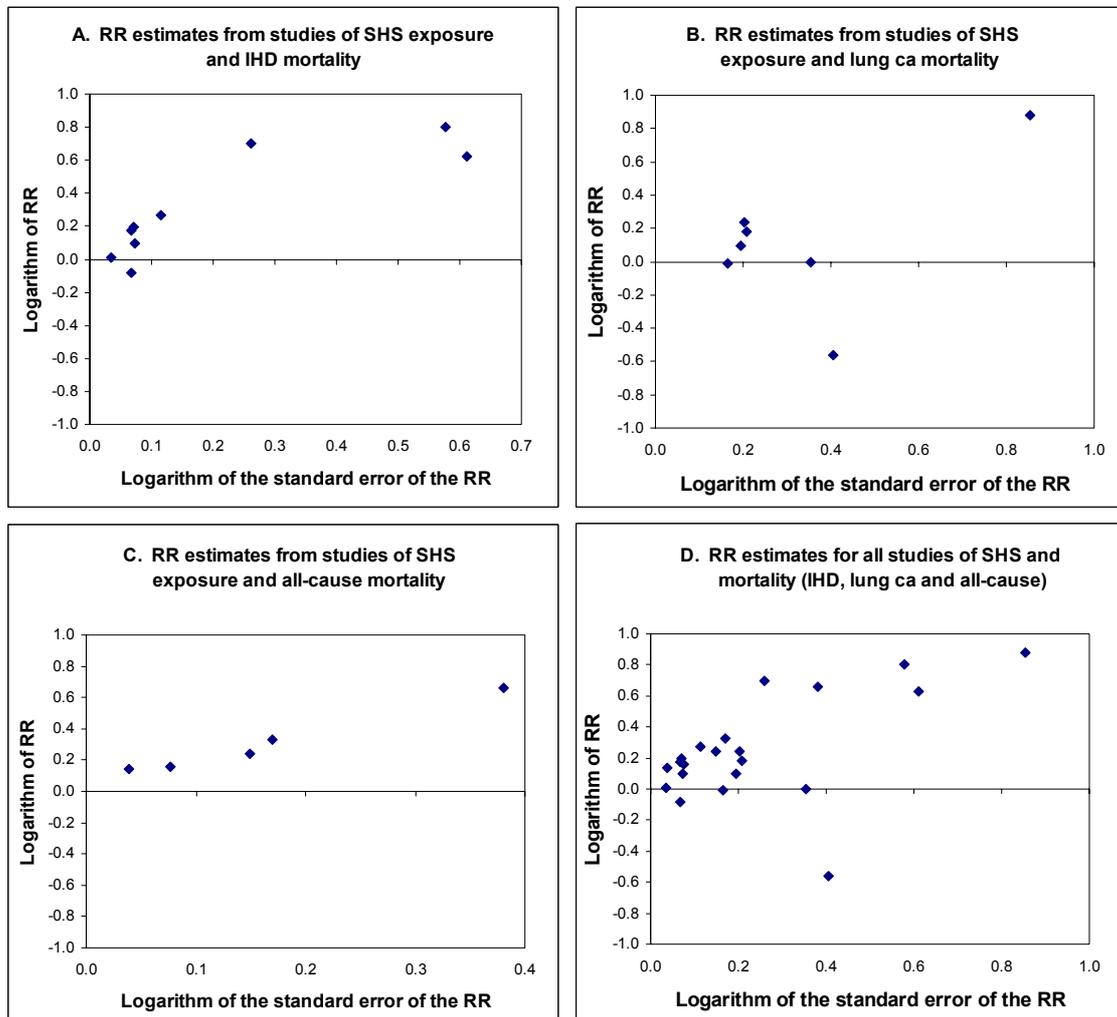
Smaller cohort studies examining passive smoking and mortality are reported by Hole and Gillis,^{12 22} Svendsen,¹¹ Vandenbroucke,²³ Garland²⁵ and Humble.²⁴ All these studies are small (less than 3,000 participants), being subsets of larger cohort studies designed to address research issues other than passive smoking. Despite its small cohort size, the study by Hole and Gillis found a significantly increased risk of IHD mortality amongst non-smoking individuals exposed to SHS from a spouse or partner (RR 2.01, 95% CI 1.21-3.35).¹² The authors themselves seem surprised at this finding, commenting that this risk seems disproportionately large compared with the risk of IHD mortality in active smokers.¹²

2.1.1.9 Publication bias

In evaluating the published literature on passive smoking and mortality, it is worth considering whether there may be a bias toward publishing studies that report a positive association. Other authors have considered the possibility of publication bias in studies of passive smoking and the incidence of ischaemic heart disease and lung cancer; most have concluded that such bias is unlikely.^{32 33}

The possibility of publication bias was explored by constructing funnel plots of published cohort studies. These are presented in Figure 2:

Figure 2: Funnel plots of RR vs standard error from cohort studies of SHS exposure and mortality



Funnel plots present study findings in terms of precision vs magnitude of effect. In Figure 2, the standard error of the RR estimate (‘precision’) is plotted on the x axis, while the RR estimate (‘magnitude of effect’) is plotted on the y axis. Both axes use a logarithmic scale; thus the null effect (RR=1.0) is represented by the horizontal line $y=0$ (ie the logarithm of 1). Studies that find a positive association (RR>1) are represented by points above the line $y=0$, while negative associations (RR<1) appear below this line.

In the absence of publication bias, the funnel plot should appear roughly symmetrical. As studies increase in precision (and the log of the standard error approaches 0), their RR estimates should converge towards the ‘true’ association between the exposure

and outcome of interest (ie the apex of the funnel). Studies of lesser precision will show greater variation in their RR estimates (the base of the funnel). On the basis of random error, we would expect there to be equal variation in either direction; in other words, the funnel should be roughly symmetrical around the true RR value ($y=RR_T$). The presence of publication bias should be suspected when there are far more studies on one side of the line $y=RR_T$ than on the other.

The funnel plots shown in Figure 2 are strongly suggestive of publication bias in studies of passive smoking and mortality. Graphs A, B and C show funnel plots for SHS exposure and mortality from ischaemic heart disease, lung cancer and all causes respectively. The funnel plot for lung cancer mortality (Graph B) is roughly symmetrical, but those for IHD (A) and all causes (C) are both skewed in an upward direction. This suggests that studies are more likely to be published if they find a positive association between passive smoking and mortality than a negative or no association. Graph D shows the funnel plots of A, B and C combined. (This approach is not strictly correct since different causes of disease may show associations of different magnitude; however the RRs for mortality from IHD, lung cancer and all causes are sufficiently similar for us to consider them together in this instance.) This graph demonstrates a clear weighting towards cohort studies reporting positive associations between passive smoking and mortality.

The apparent publication bias demonstrated in Figure 2 is largely confined to small studies with limited power. In all four graphs, the more powerful studies (at the apex of the funnel) are roughly symmetrical in distribution, and clustered above the line $y=0$. Asymmetry is seen only in less powerful studies with large standard error (at the base of the funnel). These studies are skewed in an upward direction, creating an asymmetrical funnel plot.

This pattern suggests that larger studies of passive smoking and mortality are likely to be published, regardless of whether they produce positive or negative results. It is the small studies of limited power that are more likely to be submitted and published if they show a positive association. Many of these smaller studies are subsets of larger studies that were undertaken to address exposures other than passive smoking (for example, the study by Svendsen et al was based on data collected serendipitously in

the Multiple Risk Factor Intervention Trial¹¹). Such small studies are more likely to be identified, written up and published where the data suggests a positive association, especially if such an association has been newly discovered or suspected (as was the case for passive smoking and mortality in the 1980s). It is not difficult to imagine an equal quantity of incidental cohort data that failed to show any passive smoking-mortality association and therefore remained in the investigators' filing cabinets.

The funnel plots in Figure 2 all tend to converge at the apex of the funnel. In each case the point of convergence is above the line $y=0$, suggesting a positive association between SHS exposure and mortality. The symmetrical distribution of studies at the apex of each funnel indicates the absence of publication bias for these more powerful studies and thus strengthens the evidence for a true passive smoking-mortality association.

2.1.2 Passive smoking and mortality: case-control studies

Only two published studies have used a case-control methodology to explore the association between passive smoking and mortality. Both of these illustrate some of the pitfalls associated with a case-control approach to this issue. Other studies have included fatal cases in counts of total ischaemic heart disease events;^{34 35} these studies generate odds ratios for *total* ischaemic heart disease, but not IHD *mortality*.

2.1.2.1 Miller, USA (1975-1980)

Miller reports an association between passive smoking exposure and death from all forms of cancer.³⁶ This association is based on a retrospective study of 906 non-smoking married women who died in Erie County, Pennsylvania between 1975 and 1980. On the basis of interviews with relatives, subjects were divided into three exposure categories: (a) non-employed women with a history of exposure to SHS (from other family members); (b) employed women (all of whom were assumed to be exposed to SHS in the workplace); and (c) a non-employed unexposed reference group. Reported odds ratios for death from all forms of cancer are 10.2 for group (a) and 22.8 for group (b) (no confidence intervals are given).

This study is limited by several major flaws. The most important of these is the significant potential for selection bias in obtaining study subjects. During the four years in which data were gathered, a total of 4,653 women residents of Erie County died; yet information was collected for only 1,498 of these due to “logistical problems” in interviews for the remaining two thirds of cases.³⁶ There is also significant potential for information bias given that both interviewers and relatives were aware of subjects’ cause of death, and were making a retrospective assessment of exposure to SHS. The potential for bias is of particular concern given the extraordinarily low proportion of cancer deaths reported in the unexposed reference group (ie 2.2% of deaths). In view of these problems it is not possible to apply any meaningful interpretation to the results of Miller’s study.

2.1.2.2 Laynard, USA (1986)

Laynard reported no association between spousal smoking and mortality from ischaemic heart disease in his analysis of 4,317 never-smoking decedents.³⁷ These 1,389 cases and 2,928 controls comprised a subset of subjects from the National Mortality Followback Survey, conducted by the US National Center for Health Statistics in 1986. Laynard examined the association between spousal smoking and ischaemic heart disease and reported odds ratios of 0.97 (95% CI 0.73-1.28) in men and 0.99 (0.84-1.16) in women exposed to spousal smoking.

Weaknesses in this study include limited study power and the potential for selection and misclassification bias. Never-smoking decedents were excluded from analysis if their marital status was unknown or unmarried, or if their spousal smoking status was unknown; over 20% of subjects were excluded on this basis. There was significant potential for misclassification of decedents' exposure to spousal smoking: subjects' personal smoking status and their SHS exposure status were based on information obtained from their next-of-kin. Furthermore, the investigators did not distinguish between current or previous smoking on the part of the spouse, or whether exposure was from a current or former marriage. Misclassification of spousal smoking status is likely to be non-differential and would therefore tend to bias results towards the null.

2.1.3 Passive smoking and morbidity

Many studies have now examined the association between passive smoking and the incidence of tobacco-related disease. On the basis of meta-analyses, reasonably robust estimates have been obtained for the relative risk of lung cancer and ischaemic heart disease in those with SHS exposure. The association between passive smoking and cerebrovascular disease has only recently been explored. Using estimates of incident disease, several authors have calculated mortality attributable to passive smoking for specific countries.

2.1.3.1 Incident disease

This section provides a very brief summary of the evidence linking passive smoking with specific tobacco-related diseases.

2.1.3.1.1 Lung cancer

The relative risk of lung cancer amongst passive smokers is estimated to be around 1.3.^{5 38 39} The most comprehensive review of the evidence linking passive smoking and lung cancer is that conducted by Hackshaw et al, published in the *British Medical Journal* in 1997.⁵ Hackshaw and colleagues reviewed data from 37 published studies of non-smokers with and without exposure to SHS (based on the smoking status of spouses/cohabitantes). Their pooled RR estimate is 1.24 (95% CI 1.13-1.36). The authors also conducted sensitivity analyses to explore the likely effects of exposure misclassification and dietary confounding. After adjusting for these potential sources of bias, the RR estimate increased slightly to 1.26 (1.07-1.47).

2.1.3.1.2 Ischaemic heart disease

Several authors have conducted meta-analyses of the risk of ischaemic heart disease with passive smoking.^{6 7 32 40-42} Relative risk estimates converge around 1.3, suggesting a similar effect to that observed for lung cancer. In their review of 19 published studies, Law et al explore the possible effects of dietary confounding on the

association between passive smoking and ischaemic heart disease.⁶ Based on the degree of dietary confounding seen in active smokers, they postulate that correction for confounding would reduce the RR estimate for passive smoking from 1.30 to 1.23. In one of the largest single studies of passive smoking and ischaemic heart disease, Kawachi et al collected data on a broad range of lifestyle factors. Adjustment for these potential confounders produced only a small reduction in the relative risk estimate for IHD mortality (see section 2.2.3.1 later in this chapter).

No meta-analyses of passive smoking and ischaemic heart disease have included an attempt to model the likely effects of exposure misclassification. Several authors have discussed this issue and conclude it is unlikely to account for the observed association between passive smoking and ischaemic heart disease.^{7 40} Reasons given for this conclusion include low reported rates of misclassified personal smoking status and the weak association between active smoking and IHD (relative to that for active smoking and lung cancer).

2.1.3.1.3 Cerebrovascular disease

While active smoking is recognised as a risk factor for stroke, a connection between passive smoking and cerebrovascular disease has been made only recently. In the past few years a handful of studies have reported a positive association between SHS exposure and incident stroke, with RR estimates in the order of 1.8.

Bonita et al conducted a case-control study involving 521 individuals with first-ever stroke and 1,851 community controls in Auckland, New Zealand.⁴³ They found that SHS exposure at home or at work was associated with an increased risk of stroke, with an overall odds ratio of 1.82 (95% CI 1.34-2.49) after adjusting for age, sex and cardiovascular risk factors. Although exposure data was obtained retrospectively, the authors comment that differential recall amongst cases and controls is very unlikely given low public awareness of the potential connection between SHS and stroke.

Around the same time, You et al published results of another case-control study conducted in Victoria, Australia.⁴⁴ (An earlier analysis of the same study had been published in 1989.⁴⁵) The authors calculated odds ratios for ischaemic stroke among

452 hospital cases and 452 age- and sex-matched community controls. Amongst subjects whose spouses smoked, the OR for stroke was 2.03 (95% 1.3-3.1). This estimate was slightly lower when the analysis was restricted to subjects who were lifetime never-smokers; in this group the OR was 1.70 (0.98-2.92). The authors note that their study may have been affected by selection bias, given that cases were hospital-based whereas controls were community-based.

2.1.3.2 Attributable Mortality

Using disease-specific relative risks, several authors have modelled mortality attributable to passive smoking in particular countries.⁴⁶⁻⁵⁰ This modelling is based on population-specific prevalence rates for SHS exposure and the number of deaths per year amongst non-smokers from each tobacco-related disease.

Woodward and Laugesen have estimated the number of deaths attributable to second-hand smoke in New Zealand each year.⁴⁸ This estimate takes account of deaths due to lung cancer, ischaemic heart disease, stroke, and sudden infant death syndrome (SIDS). Based on current SHS exposure levels, passive smoking could be expected to account for a future 325 deaths per year, including seven from lung cancer, 186 from ischaemic heart disease, 82 from stroke, and 50 from SIDS.

Table 2: Yearly deaths attributable to second-hand smoke, New Zealand*

Cause of Death	Number
Lung cancer	7
Ischaemic heart disease	186
Stroke	82
Sudden infant death syndrome	50
Total deaths	325

* Data from Woodward A, Laugesen M, How many deaths are caused by second-hand cigarette smoke? *Tobacco Control* 2001;10:383-388

2.1.4 Existing evidence on passive smoking and mortality: Summary & conclusions

A number of published studies have explored the relationship between passive smoking and mortality in adults. The majority of these report a small positive association between SHS exposure and mortality, although there is evidence of publication bias for studies of IHD and all-cause mortality.

Early studies of passive smoking and mortality had limited ability to control for potential confounders other than age. Later studies have benefitted from the development of statistical techniques that make it possible to control simultaneously for multiple factors. These developments have allowed researchers to take account of potential differences in diet, socio-economic position and other cardiovascular risk factors when comparing individuals with and without SHS exposure.

Exposure misclassification is an ongoing issue in studies of SHS exposure and its health effects. Exposure categorisation is usually based on the smoking habits of the spouse or other adults with whom a study subject lives. This approach is relatively easy to apply in large population studies, but does not take account of SHS exposure occurring outside the home. Data is usually analysed according to baseline SHS exposure, although most cohort studies follow subjects for several years (typically seven or more). Changes in SHS exposure during study follow-up introduce another source of exposure misclassification.

Any association between passive smoking and mortality is likely to be small in epidemiological terms. Many published studies have had insufficient power to demonstrate a small effect with adequate precision. This problem highlights the need for large studies with significant numbers of outcomes. Associations of small magnitude are particularly prone to distortion through misclassification and confounding.

Apart from studies that directly examine SHS exposure and mortality, indirect evidence may be drawn from research linking passive smoking with an increased incidence of tobacco-related diseases. Data from many individual studies have been drawn together in meta-analyses. These indicate SHS-associated relative risks around 1.3 for both lung cancer and ischaemic heart disease. Evidence on passive smoking and stroke has emerged only recently, with two published studies producing RR estimates around 1.8. On the basis of these morbidity data, passive smoking in New Zealand is estimated to account for around 325 deaths per year.

It is important to interpret new results in the context of existing evidence (both positive and negative) for an association between passive smoking and mortality. Associations of small magnitude are easily created or masked by errors in study design and analysis, making it unwise to place too much credence on the findings of an isolated study. Interpretation should also take account of potential bias from misclassification and confounding.

2.2. Interpreting the evidence on passive smoking and mortality

There are particular issues involved in demonstrating and interpreting an exposure-outcome association of small magnitude. The largest published study of all-cause mortality amongst passive smokers found a rate ratio in the order of 1.15²¹ – hardly a strong association by anyone’s reckoning. Studies producing such modest association measures require particularly careful evaluation of the potential roles of bias and confounding. Small increases in mortality may be explained by differential misclassification of exposure or confounding from other factors associated with ill-health. On the other hand, even a modest degree of non-differential misclassification may mask a small but true causal association between passive smoking and mortality.

This section reviews the different ways of measuring exposure to second-hand smoke, evaluates the potential for misclassification of exposure status and discusses ways in which this misclassification can be corrected for in data analysis. It then explores potential sources of confounding in the relationship between SHS exposure and mortality. Finally, biological mechanisms by which passive smoking may increase mortality are reviewed.

2.2.1 Measurement of SHS exposure

There are three ways in which exposure to second-hand smoke can be measured: questionnaires or self-reported exposure, biological markers, and environmental measurement of SHS levels.⁵¹ In practice, self-reported or imputed exposure is the only feasible means of exposure assessment in a large-scale population study.

2.2.1.1.1 Biological markers

Metabolites of nicotine and tobacco may be detected in body fluids, providing markers of recent tobacco smoke exposure.⁵² Biological markers such as cotinine have a short half-life in serum, urine and saliva, and thus reflect SHS exposure only in the past 24 hours or so. This is not particularly useful in investigating the association between SHS exposure and mortality, where we are primarily interested in prolonged exposure occurring in the months or years prior to death. Biomarkers may be used to validate recent self-reported exposure,⁵¹ but again this may not give a good indication of how accurately self-report represents long-term SHS exposure.

More recently, nicotine levels in hair or nail clippings have been used as a marker of more prolonged tobacco smoke exposure.⁵³ Nicotine in hair comes mainly from nicotine in blood, and thus reflects cumulative systemic absorption of tobacco smoke.⁵¹ Hair nicotine levels in children show a close correlation with parental smoking over the preceding six months.⁵⁴ Nicotine levels in hair and nail clippings may thus provide a means of assessing more long-term SHS exposure in future studies.

2.2.1.1.2 Environmental measurement

Several components of tobacco smoke may be measured in the environment, including nicotine, particulates and a number of gases.⁵¹ Personal environmental monitors may be used to measure SHS levels over a short time period, but are not practical for large-scale surveys or studies of long duration.

2.2.1.1.3 Self-reported exposure

Self-reported or imputed SHS exposure is the most practical means of exposure assessment in large-scale studies. ('Imputed exposure' is where a subject's SHS exposure is imputed from the smoking habits of those with whom they live or work.) As with most forms of exposure classification, self-reported SHS exposure has some inherent limitations. SHS exposure is difficult to quantify on the basis of self-reporting. Unlike active smoking, exposure is not simply determined by the number of cigarettes smoked by others. The intensity of SHS exposure is related to many other factors, including the inhalation pattern of the smoker, the size of the space in

which smoking occurs, the amount and quality of ventilation, the proximity of the respondent to the tobacco source, and the time spent in that place.^{51 55 56} Furthermore, many individuals have biological evidence of SHS exposure even though they are unaware of having been exposed.^{57 58}

2.2.2 Misclassification

Misclassification may arise from inaccuracies in the measurement of both exposure and outcome. Misclassified exposure status is likely to be the most important source of misclassification when studying the relationship between passive smoking and mortality. There is some potential for misclassification of outcome, but this is likely to be small in studies where the outcome of interest is vital status or all-cause mortality.

Kawachi identifies two major sources of SHS exposure misclassification:³²

- i) Misclassification of personal smoking status.
- ii) Misclassification of SHS exposure.

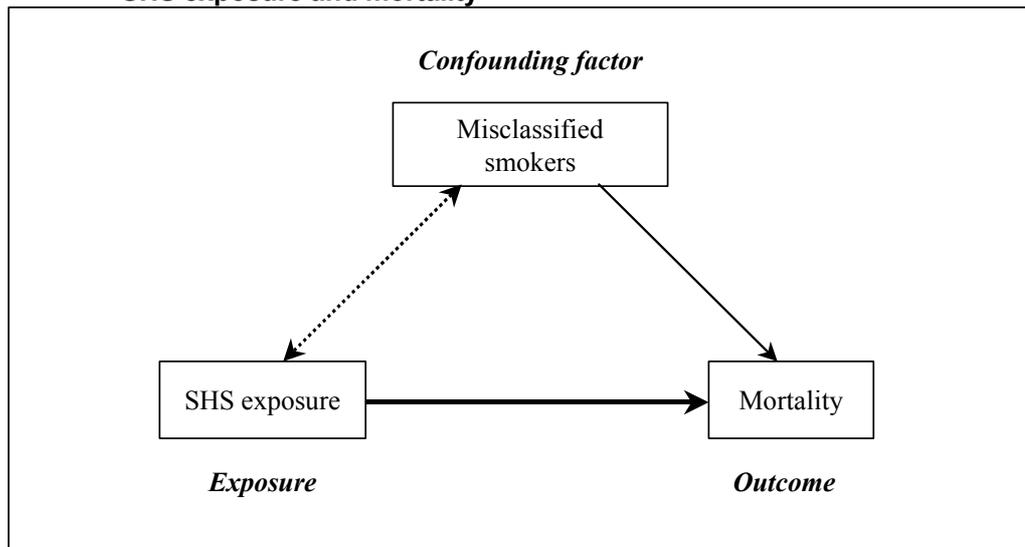
2.2.2.1 Misclassification of personal smoking status

Several authors have suggested that the apparent association between SHS exposure and mortality may be largely due to misclassification of personal smoking status.^{8 9} Some people who claim to be never-smokers may actually be current or ex-smokers. Given the strong association between active smoking and mortality, these misclassified smokers will artificially inflate the observed mortality rate in a supposedly non-smoking group or cohort. If the proportion of misclassified smokers is greater in the cohort with SHS exposure compared with the non-exposed cohort, the apparent association between SHS exposure and mortality will be positively biased.

In this instance, such differential misclassification bias may also be regarded as a form of confounding. Active smoking is known to be strongly associated with

increased mortality. If it also has an independent association with SHS exposure (in other words, if the proportion of misclassified smokers in the SHS-exposed group is greater than the proportion in the non-exposed group), the relationship between SHS exposure and mortality will be confounded. This confounding will result in a falsely elevated risk estimate amongst those with SHS exposure.

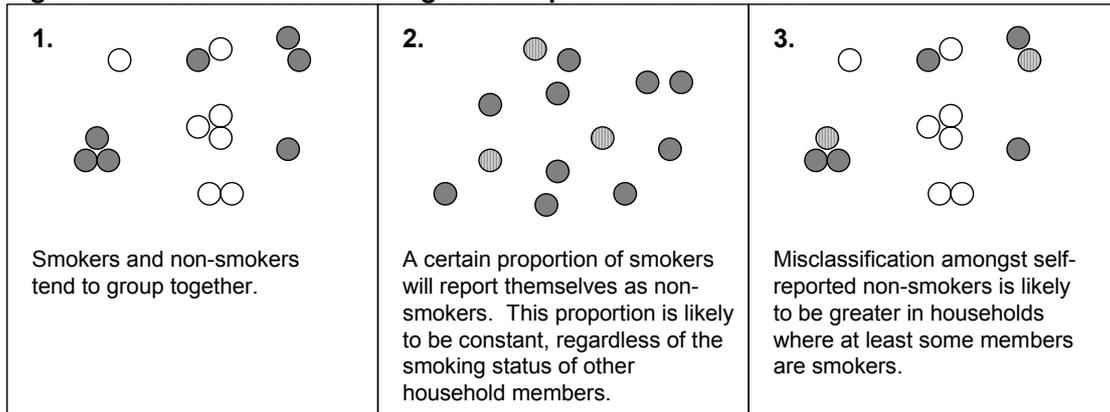
Figure 3: Misclassified smokers as a confounding factor in the relationship between SHS exposure and mortality



Misclassified smokers are likely to be found more frequently amongst those self-reported non-smokers with SHS exposure. This premise may be reasoned as follows:

1. Partners and associates of smokers have a greater than average probability of being smokers themselves^{8 59} – in other words, smokers tend to live with other smokers;
2. The proportion of actual smokers who report themselves as non-smokers is likely to be constant, regardless of the smoking status of other household members; therefore
3. Actual smokers who report themselves as non-smokers are more likely to be found in households with other smokers than in households where all other adults are non-smokers (see Figure 4 below):

Figure 4: Misclassification amongst self-reported non-smokers



Several studies have estimated the overall misclassification rate amongst self-reported non-smokers (ie the proportion of self-reported non-smokers who are actually misclassified smokers). Unfortunately, there are no estimates of how this rate may vary by SHS exposure status. Nevertheless, it seems reasonable to assume that misclassification amongst those with SHS exposure will be higher than the misclassification rate seen in those without SHS exposure (as reasoned above).

2.2.2.2 Misclassification of SHS exposure

Kawachi identifies two important sources of error in assessing SHS exposure: background exposure to SHS (or SHS exposure occurring outside the setting of interest), and changes in exposure status over time.^{14 32}

2.2.2.2.1 Exposure to SHS in other settings

Failure to correct for background SHS exposure will result in misclassification of exposure status, thus biasing study results towards the null.³² Exposure to tobacco smoke is virtually ubiquitous, with detectable markers of tobacco smoke present even in those unaware of having been exposed.^{57 58} Biomarker studies indicate that workplace and home exposure deliver similar levels of SHS, and so may be expected to exert health effects of similar magnitude^{60 61} (although the balance of these effects will probably vary over time depending on factors such as the existence of workplace smoking restrictions). Where studies measure SHS exposure in only one setting (such as the home), individuals with unmeasured exposure may be misclassified as

unexposed. This misclassification will diminish any true association between SHS exposure and mortality.¹⁴

2.2.2.2.2 *Changes in exposure status over time*

Changes in SHS exposure over time will also introduce misclassification error. Cohort studies examining the health effects of SHS usually measure exposure only at baseline,³² although the outcome of interest may not occur until some time later. Depending on the outcome under study, the time from exposure to onset of disease may vary from days (in the case of acute respiratory illness) to decades (in the case of lung cancer). Changing SHS exposure will introduce significant non-differential misclassification, especially in studies of long duration. The potential for exposure misclassification was a major criticism of Enstrom & Kabat's re-analysis of data from the American Cancer Society's CPS-I study; in this version of the study, mortality data was collected over 39 years following baseline determination of SHS exposure.¹⁰

31 62

The sensitivity and specificity of self-reported SHS exposure have been estimated through validation studies comparing self-reported exposure against biochemical markers of tobacco smoke exposure. Patrick et al reviewed 26 validation studies, and found a mean sensitivity of 87.5% and specificity of 89.2%.⁶³ In reviewing the literature on SHS exposure measurement, Woodward and Al-Delaimy conclude that a simple bimodal classification (exposed/unexposed) is more reproducible than attempts to quantify exposure in terms of duration or intensity.⁵¹ No studies were found that reported the accuracy of imputed SHS exposure status.

2.2.2.3 Correcting for misclassification: sensitivity analyses

The effect of misclassified exposure status may be explored by undertaking sensitivity analyses on observed study results. The published literature provides several examples of analyses that explore the effect of misclassified personal smoking status on the association between SHS exposure and health outcomes. No published sensitivity analyses were found for the effect of misclassified SHS exposure.

There are several different approaches to this kind of analysis, each of which has its own strengths and limitations.^{5 9 64} It is useful to bear in mind that all sensitivity analyses are based on a number of assumptions, and that the primary aim of such an analysis is to test the robustness of an observed association (rather than to provide a perfect measure of the true association).

2.2.2.3.1 Correcting for misclassified personal smoking status

Hackshaw et al explored the effect of misclassified smoking status on the observed association between passive smoking and lung cancer.⁵ Adjustment for misclassification bias reduced the risk estimate for lung cancer amongst passive smokers from 1.24 to 1.18. Since active smoking confers a smaller relative risk for other smoking-related illnesses (such as cardiovascular disease), it seems unlikely that misclassification would account for more than a fraction of the observed association of these conditions with passive smoking.

Sensitivity analyses require some estimate of the likely misclassification rate in the study cohort. Misclassification estimates are generally based on validation studies, which use biomarkers (such as cotinine) to determine the proportion of self-reported non-smokers who are actually smokers. Most validation studies estimate around 5% of self-identified non-smokers are actually smokers.^{53 59 65} Some authors report much lower rates of misclassification (around 2.5%),^{5 66} while one author estimates that as many as 12% of non-smoking claimants are actually clandestine smokers.⁸ It is important to note that the extent of under-reporting depends strongly on the context in which people are asked about their smoking habits. Population surveys of smoking prevalence generally report much lower rates of misclassification than smoking cessation trials or clinical studies.

Misclassified smokers

Wells et al argue that misclassification among self-reported never-smokers is more accurately calculated from estimates of the misclassification rate amongst smokers (ie

the proportion of smokers who report themselves as never-smokers) and the smoking prevalence in the study population.⁶⁷ In epidemiological terms, misclassification amongst self-reported never-smokers is driven by the negative predictive value of the self-reported smoking ‘test’; thus it depends not only on the sensitivity and specificity of this ‘test’, but also on the smoking prevalence in the study population.

This point can be illustrated as follows. If we regard self-reported smoking as our ‘test’ and actual smoking as our ‘disease’, classification of smokers and non-smokers may be presented in the familiar 2x2 table:

		‘Disease’: Actual smoking	
		Positive	Negative
‘Test’: Self-reported smoking	Positive	a true smokers	b misclassified non-smokers
	Negative	c misclassified smokers	d true non-smokers

(For reasons of clarity, smoking is treated as a bimodal behaviour- ie people are categorised only as smokers or non-smokers. In reality there is of course a third category, namely ex-smokers.)

The performance of our self-reported smoking test may then be quantified in familiar terms:

$$\begin{aligned} \text{Sensitivity} &= a / (a + c) & \text{Positive predictive value (PPV)} &= a / (a + b) \\ \text{Specificity} &= d / (b + d) & \text{Negative predictive value (NPV)} &= d / (c + d) \end{aligned}$$

The misclassification rate amongst self-reported non-smokers refers to misclassified smokers as a proportion of all those who report themselves as non-smokers. Referring to the 2x2 table, misclassification amongst self-reported non-smokers is equal to $c / (c + d)$. (This is the same as $1 - \text{NPV}$.) This proportion will depend not only on the sensitivity and specificity of our self-reported smoking ‘test’, but also the prevalence of smoking within the study population. Thus the misclassification rate amongst self-reported non-smokers in one population will apply to another population only if the prevalence of smoking is the same for both populations.

A more transferable measure of the accuracy of self-reported smoking is provided by the sensitivity of the smoking 'test'. This sensitivity refers to the proportion of all actual smokers who self-report as smokers – ie $a / (a + c)$. The misclassification rate for smokers is then given by $(1 - \text{sensitivity})$, which is not affected by changes in the prevalence of smoking.

Having established the misclassification rate amongst smokers, this rate can now be applied to populations of differing smoking prevalence to calculate the number of self-reported non-smokers who are actually smokers. This is achieved by applying the smoker misclassification rate to the cohort of smokers, and so calculating the number of misclassified smokers (ie actual smokers who self-report as non-smokers) for that cohort.

Estimates of misclassification amongst current smokers range from 0.5% to 2.0%.^{38 67-}

⁶⁹ Wells et al reviewed raw data from 10 validation studies and report pooled misclassification rates by sex and ethnicity⁶⁷. The resultant rates for smokers misclassified as never-smokers are 1.6% in majority women, 4.9% in minority women, 2.0% in majority men and 5.7% in minority men. (While their review includes data from several different countries, the data on ethnic minorities is limited to US Hispanics.) The overall misclassification rate for majority smokers was 1.7%.

Misclassified ex-smokers

Ex-smokers reporting themselves as never-smokers pose a problem in any attempt to correct for misclassification among self-reported never-smokers. Biomarker validation studies cannot detect ex-smokers who claim to be never-smokers, unless relatively little time has elapsed since quitting. This makes it difficult to estimate the likely misclassification rate amongst ex-smokers (or the proportion of self-reported never-smokers who are actually ex-smokers). Some indication of ex-smoker misclassification is provided by studies that assess self-reported smoking status in the same cohort at two different points in time, and calculate the proportion of current and

ex-smokers who later claim to be never-smokers. Such studies yield misclassification rates ranging from 4.8 to 8.2% of ever-smokers,⁶⁹⁻⁷¹ with the larger studies producing lower misclassification rates.

2.2.2.3.2 *Correcting for misclassified SHS exposure status*

I could find no specific examples of sensitivity analyses undertaken to explore the effect of SHS exposure misclassification on the relationship between passive smoking and mortality. However, Kawachi points out that such misclassification is likely to be non-differential, and will therefore bias study results towards the null.³² A general method of correcting for misclassified exposure status is described by Greenland.^{64 72} This is based on the estimated sensitivity and specificity of the exposure measure.

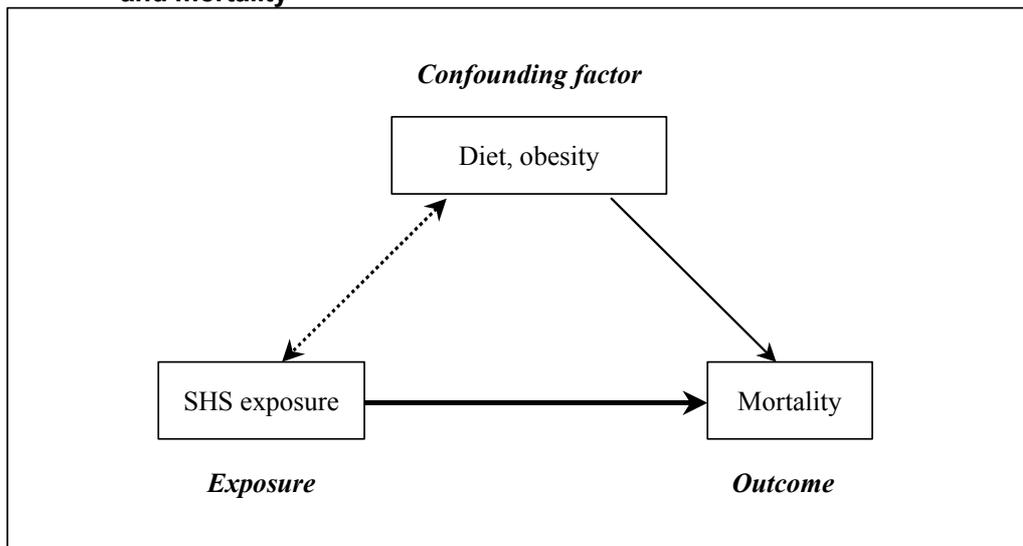
2.2.3 Confounding

The relationship between passive smoking and mortality may be confounded by other health risk factors with the same pattern of distribution as SHS exposure. Such factors may include poor diet, lack of exercise, and socio-economic position.

2.2.3.1 Confounding by diet and other lifestyle factors

Several studies have examined the health characteristics of those with and without self-reported SHS exposure.¹⁴ Overall, individuals with SHS exposure tend to have less healthy lifestyles, as indicated by higher consumption of saturated fats,^{28 29 73 74} lower consumption of fruit, vegetables, fibre and vitamins;^{28 29 73-76} higher alcohol consumption,^{28 29 74 75 77} and higher average body mass index.^{73 75 77} Many of these factors are known or suspected to increase the risk of cancer and cardiovascular disease; thus they are potential confounders in the relationship between SHS exposure and mortality.

Figure 5: Lifestyle factors as confounders in the relationship between SHS exposure and mortality



Studies examining the health effects of passive smoking should ideally control for factors such as diet, alcohol intake and exercise. In practice, such adjustment is often difficult to achieve since it requires fairly detailed data on these covariates.

In their commentary on studies of passive smoking, Kawachi and Colditz suggest that lifestyle factors are likely to produce only a modest degree of confounding in the relationship between SHS exposure and lung cancer.¹⁴ A more serious possibility is the potential for confounding in the relationship between passive smoking and ischaemic heart disease. The aetiology of ischaemic heart disease is multifactorial, and dietary and other lifestyle factors play a much greater role than in the development of lung cancer.

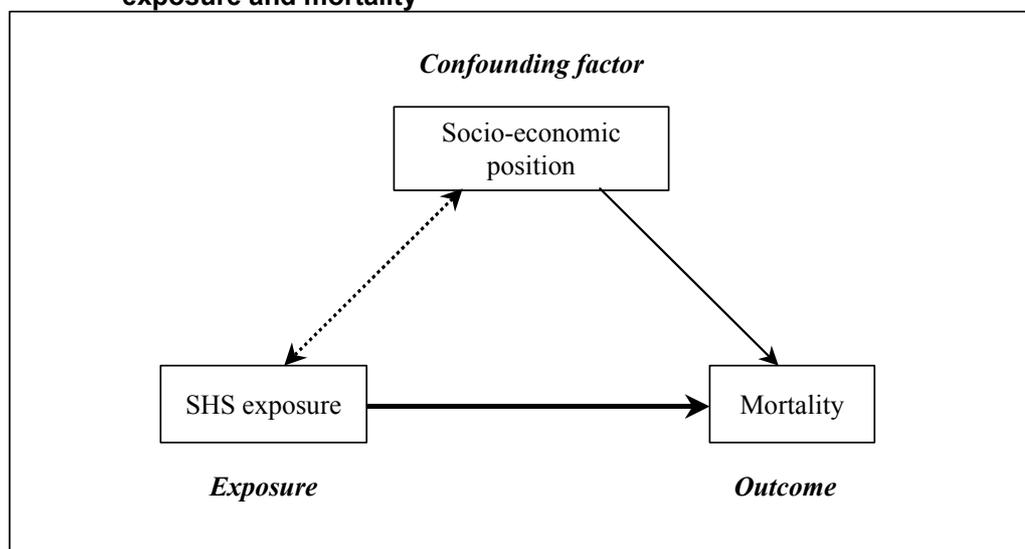
In the Nurses' Health Study, the relative risk for ischaemic heart disease amongst passive smokers was adjusted for a broad range of lifestyle factors.¹³ The authors undertook multivariate analysis to control for intake of saturated fat, alcohol and vitamin E, exercise, body mass index and a number of other cardiovascular risk factors. Adjustment for these factors produced some attenuation in the relative risk for ischaemic heart disease, which fell from 1.97 (95% CI 1.20-3.24) to 1.71 (1.03-2.84). This suggests that confounding from lifestyle factors may modestly inflate the association between passive smoking and ischaemic heart disease, but that an association persists even after adjusting for this effect.

2.2.3.2 Confounding by socio-economic position

Several studies have found that exposure to second-hand smoke is associated with lower socio-economic position. Whitlock et al looked at self-reported SHS in a sample of 7,725 New Zealanders, and found that passive smoking was associated with lower socio-economic position (as indicated by educational level, occupational status and median neighbourhood household income).⁷⁸ Studies from other countries report that non-smokers who live with smokers tend to have lower education^{28 73 74 76 77} and lower occupational class^{29 79} compared to those who live with other non-smokers.

There is a well-established association between socio-economic position and mortality in New Zealand and other countries.⁸⁰⁻⁸³ Since low socio-economic position is also associated with passive smoking, it fulfils the role of a potential confounder in the relationship between SHS exposure and mortality.

Figure 6: Socio-economic position as a confounder in the relationship between SHS exposure and mortality



As with lifestyle factors, it is desirable to control for socio-economic position when assessing the association between passive smoking and health-related outcomes.

2.2.3.3 Correlation of lifestyle factors and socio-economic position

Lifestyle factors such as diet and exercise tend to be patterned by socio-economic position.⁸⁴⁻⁸⁸ Thus those individuals with less healthy diets and other behaviours tend to be the same individuals who have poor socio-economic profiles. This correlation is supported by studies that found passive smokers were more likely to have both unhealthy lifestyles and low education and occupational class.^{28 73 74 76 77}

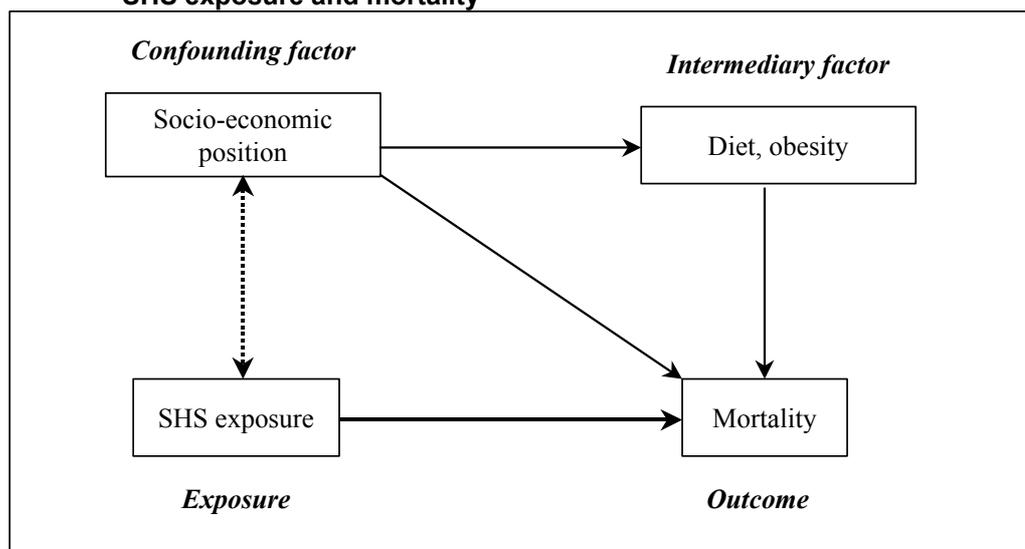
A cross-sectional study in Italy looked at both socio-economic and lifestyle characteristics in 1,938 never-smoking women who were currently or previously married.⁸⁹ Women with smoking and non-smoking husbands were compared in terms of education, household crowding, diet, alcohol intake, physical activity, body mass index, and a number of clinical and laboratory characteristics. After adjusting for educational level, there were found to be no significant differences between the two groups apart from a lower intake of vegetables and higher usage of vitamin supplements amongst women whose husbands smoked. The authors conclude that “once socioeconomic differences are considered, the possibility of confounding in studies on the health effects of [SHS] is minimal.”

This conclusion is supported by two US studies comparing cardiovascular risk factors in those with and without SHS exposure after adjusting for educational level. Steenland et al examined data from 3,338 never-smoking adults, comparing those with and without SHS exposure in terms of lifestyle and physical characteristics associated with vascular disease.⁹⁰ After controlling for age, sex, race and education, the only significant difference in those with and without SHS exposure was in dietary carotene intake (which was higher in the non-exposed group). There were no significant differences in other cardiovascular risk factors including dietary fat intake, alcohol intake, diabetes, blood pressure, body mass index and low physical activity.

Matanoski et al studied the lifestyle characteristics of 3,896 non-smoking women according to the smoking status of their husbands.²⁸ Women married to smoking men were significantly more likely to eat fatty meats, consume over four alcoholic drinks per day, and not take vitamin supplements. After controlling for subjects' education

level these apparent associations disappeared (apart from a weak association between SHS exposure and consumption of non-lean beef). The authors postulate that poor diet is an intermediary factor in the causal chain between poverty and disease; controlling for socio-economic position therefore eliminates most of the effect of dietary confounding.

Figure 7: Socio-economic position and lifestyle factors in the relationship between SHS exposure and mortality



2.2.4 Biological mechanisms

Several studies have explored the biological mechanisms by which tobacco smoke exposure induces cardiovascular and other diseases. Mechanisms are likely to involve a mixture of acute and chronic processes, including platelet activation, endothelial dysfunction and exposure to carcinogens. The existence of an apparently non-linear relationship between smoke exposure and cardiovascular disease risk raises questions about possible low-dose effects from tobacco smoke.

2.2.4.1 Disease processes

2.2.4.1.1 Vascular disease

Mechanisms by which smoke exposure is thought to induce cardiovascular disease include increased platelet activity, impaired endothelial function, impaired oxygen

delivery, impaired oxygen usage by cardiac muscle, and generation of oxygen free radicals.^{91 92} Components of SHS that are implicated in these processes include carbon monoxide, nicotine, polycyclic aromatic hydrocarbons and other elements.⁹²

Most of the above processes have been demonstrated in humans exposed to SHS in controlled, experimental settings.^{56 92 93} Non-smokers with passive smoking exposure have also been found to have lower levels of ‘protective’ (high-density lipoprotein) cholesterol.^{92 94} SHS exposure is associated with increased thickness of the carotid arterial wall,^{95 96} indicating accelerated atherosclerosis in passive smokers. (Atherosclerosis refers to plaque built-up and subsequent narrowing of arterial blood vessels, increasing the risk of vessel blockage and downstream tissue injury.)

Many of these pathophysiological mechanisms will be activated by relatively short-term exposure to second-hand smoke.⁴² While atherosclerosis develops over several years, processes such as platelet activation, impaired endothelial function and impaired oxygen delivery have been shown to occur after as little as 20 minutes of SHS exposure.⁴¹ Thus it seems plausible that cardiovascular risk will be elevated even in those with SHS exposure of relatively short duration.

2.2.4.1.2 *Malignant disease*

Tobacco smoke is known to contain an array of carcinogenic substances, several of which have been demonstrated in the body fluids of non-smokers exposed to second-hand smoke.⁹⁷⁻¹⁰⁰ In 1992 the US Environmental Protection Agency classified environmental tobacco smoke as a Class A carcinogen.¹⁰¹ Their report reviews the evidence linking environmental tobacco smoke and lung cancer, and concludes that “comparison of the chemical composition of the mainstream smoke inhaled by smokers with that of sidestream smoke in ETS inhaled by nonsmokers strongly suggested that the toxic and carcinogenic effects would be qualitatively similar. Further, there is no known threshold for the carcinogenic effect in general, and the data on active smokers and lung cancer suggests a sizable [sic] effect from even low-level exposure to the carcinogens present in ETS.”¹⁰¹

These findings suggest that second-hand smoke exerts the same carcinogenic effect as directly inhaled smoke, albeit at a lower dose. Epidemiological evidence supports a linear dose-response relationship between smoke exposure and cancer risk.¹⁰²

Hackshaw et al reviewed data from 37 published studies, and found an excess lung cancer risk of 24% (95% CI 13% to 36%) in passive smokers. This equates to approximately 1% of the excess risk seen in active smokers (in whom the relative risk of lung cancer is around 19).⁵

2.2.4.2 Non-linear risk patterns and threshold effects

Several authors have commented on the apparently non-linear relationship between tobacco smoke exposure and cardiovascular disease risk.^{6 76} Biomarker studies indicate that passive smokers have around 1% of the nicotine exposure of active smokers.^{5 103 104} Yet the excess risk of ischaemic heart disease in passive smokers is almost half that seen in smokers of 20 cigarettes per day.⁶

This non-linear relationship between tobacco smoke exposure and disease risk may reflect a threshold effect for some pathological processes induced by smoke exposure. Possible candidates for such an effect are platelet aggregation and endothelial dysfunction – both of which play a role in the development of cardiovascular disease.

2.2.4.2.1 *Platelet aggregation*

Law et al conducted meta-analyses of ischaemic heart disease risk in passive and active smokers.⁶ In passive smokers the overall relative risk for ischaemic heart disease was 1.30 (95% CI 1.22-1.38). This compared with relative risks of 1.78 (1.31-2.44) in smokers of 20 cigarettes per day, and 1.39 (1.18-1.64) in smokers of one cigarette per day. The authors undertook modelling (based on experimental studies) to explore the dose-response relationship between tobacco smoke exposure and platelet aggregation. They conclude that tobacco smoke exposure exerts a threshold effect on platelet aggregation, so that much of the excess risk of ischaemic heart disease occurs at very low exposure levels. This finding has been supported by other reviewers.⁹² Such a phenomenon would explain the relatively high risk of ischaemic heart disease seen in both passive smokers and light active smokers.

2.2.4.2.2 *Endothelial dysfunction*

Another biological process that may exert a threshold effect is endothelial dysfunction. Celemajer et al conducted an experimental study of arterial dilatation in young non-smokers, passive smokers and active smokers.⁵⁶ The authors used ultrasonography to measure brachial artery dilatation in response to increased blood flow (a process mediated by vascular endothelium). Relative to dilatation in non-smokers, arterial dilatation was impaired by a similar magnitude in passive and active smokers.

2.2.4.3 Disease Latency

As with most exposure-disease relationships, there is likely to be an incubation period between exposure to SHS and subsequent development of disease. The length of this latency period will vary for different types of disease with differing pathophysiology. An understanding of disease latency is important in studying the health effects of passive smoking.

Since most evidence on passive smoking and incident disease comes from case-control studies, there is no direct data on the latency period between SHS exposure and subsequent disease development. Indirect evidence, however, may be drawn from epidemiological and toxicological studies of active smoking. This evidence points to a relatively long period between tobacco exposure and the development of cancer,¹⁰⁵ but somewhat shorter latency in the development of vascular disease.

Active smoking has both short-term and long-term effects on vascular function: processes such as platelet aggregation and serum coagulability show changes after hours or days of active smoking, while atherosclerotic narrowing of coronary and other arteries follows smoke exposure over several years.¹⁰⁶⁻¹⁰⁸ Long-term smoke exposure is also required for malignant transformation and the development of cancer.¹⁰⁹ Ecological data suggests a delay of 20 or more years between peak population smoking rates and associated peaks in tobacco-related disease.¹¹⁰ Similar latency periods are likely to apply to the effects of passive smoking.

2.2.5 Interpreting the evidence: Summary and conclusions

When interpreting studies of passive smoking and mortality it is important to consider potential systematic bias arising from misclassification and confounding. Such bias may result in both positive and negative distortion of an observed association, with both effects often occurring in the same study.

There is no ‘gold standard’ measure of long-term second-hand smoke exposure. The most practicable means of assessing exposure is by self-report, or imputation from the smoking habits of those with whom the study subject lives. This form of assessment will inevitably entail a degree of measurement error. Misreporting of personal smoking status will very likely upwardly bias study results, as misclassified smokers (with higher mortality than non-smokers) will tend to be found more commonly in households with SHS exposure. Unmeasured SHS exposure in other settings and changes in exposure status over time will produce a downward bias in study results, since both sources of error will result in non-differential misclassification of exposure status.

Lifestyle and socio-economic factors are potential confounders in the relationship between passive smoking and mortality. Less healthy behaviours such as poor diet are found more commonly amongst those with SHS exposure, who also represent a more socio-economically disadvantaged group. Since these factors are independently associated with increased mortality, they will tend to inflate the observed association between passive smoking and mortality.

Misclassification and confounding are ideally addressed in both study design and analysis. Information on potential confounders should be collected at the same time as SHS exposure status, allowing mortality data to be controlled for these factors. The literature suggests that socio-economic position may be used as a proxy measure of diet and other lifestyle characteristics in this setting. The effect of exposure misclassification may be explored through sensitivity analyses. Sensitivity analyses

provide an indication of the robustness or fragility of an observed association between passive smoking and mortality.

Several biological mechanisms provide a plausible account of how passive smoking may contribute to disease development and subsequent mortality. Passive smoking appears to exert a threshold effect on some processes associated with cardiovascular disease - most notably platelet aggregation. This effect may explain the apparently non-linear relationship between tobacco smoke exposure and mortality from ischaemic heart disease. Lung cancer incidence and mortality shows a more linear relationship with smoke exposure, suggesting a dose-response effect from contact with carcinogens in tobacco smoke.

Chapter 3: Data & Methods

Chapter Outline

The primary aim of this study is to measure the association between domestic exposure to second-hand smoke (SHS) and all-cause mortality. A secondary aim is to measure the association between SHS exposure in the home and disease-specific mortality for tobacco-related diseases.

The study uses data from two population cohorts, each followed for mortality over a period of three years. These data come from the New Zealand Census-Mortality Study (NZCMS), a dataset made up of linked census and mortality records.

Data analysis includes calculation of crude and standardised mortality rates. Multivariable (Poisson) regression was then undertaken to provide relative risk estimates adjusted for a number of potential confounders. Sensitivity analyses have been conducted to explore the effect of misclassification bias on the observed results.

This chapter describes the advantages and limitations of a cohort study approach in assessing the association between domestic SHS exposure and mortality; the data source for this study (the NZCMS); measures of exposure, covariates and outcome in the study population; the statistical methods employed in analysing study data; and the methods used for sensitivity analyses.

3.1. Cohort study design: advantages and limitations

The majority of published studies examining passive smoking and mortality have been based on cohort data (see Chapter 2: 2.1). In researching the health effects of a particular exposure or risk factor, cohort studies offer the advantages of minimal recall bias and a clear temporal relationship between the exposure and outcome of interest. Cohort studies also have some important limitations: these include the potential for unmeasured changes in exposure status over time, and the risk of underestimating a true exposure-outcome association where disease latency exceeds the period of follow-up.¹¹¹

An important advantage of cohort studies is the avoidance of recall bias, whereby individuals who have developed the outcome of interest (or – in the case of death – the family member from whom a history is obtained) may be more likely to recall past exposure to the factor under suspicion. Such bias would be particularly problematic in assessing previous exposure to SHS, since nearly everyone has some passive smoke exposure and categorisation of individuals as ‘exposed’ or ‘unexposed’ is more a question of degree than a precise distinction. In a cohort study, participants’ exposure status is determined at the beginning of the study period and thus cannot be retrospectively influenced by their eventual outcome.

Another advantage of a cohort approach in studying the health effects of passive smoking is the clear precedence of exposure to disease. Since exposure status is determined some time before death has occurred, reverse causality is less likely than in a case-control study (where information on the outcome and exposure are usually collected concurrently). In the case of SHS exposure, the development of severe disease and disability in the study member might prompt other household members to take up or resume smoking in response to stressful domestic circumstances, thus creating a non-causal association between death and domestic exposure to SHS. Data from a cohort study is less likely to be complicated by reverse causality.

One of the disadvantages of a cohort study is that exposure to the factor of interest may change over time. Where participants' exposure status is determined only at baseline, changes in exposure during the study period may lead to misclassification with respect to exposure. (This type of misclassification is discussed in Chapter 2: 2.2.2.) Changing exposure status is certainly a possibility in the present study. Exposure is based on the smoking behaviour of other household members at the time of the census, while data on mortality is accumulated from the following three years. Any change in household composition or in the smoking behaviour of existing household members may thus lead to a change in actual SHS exposure. Such misclassification is likely to be non-differential, and will therefore attenuate any real association between domestic SHS exposure and mortality.

This study has a relatively short follow-up period (three years) compared with other cohort studies of mortality and SHS exposure (typically 7-12 years in duration). While there is some potential for misclassification due to changing SHS exposure, this is likely to be less than in cohort studies of longer duration. A limitation created by the shorter follow-up period is that diseases with a long latency period (such as lung cancer) will almost certainly correlate more closely with SHS exposure many years previously than with exposure during the preceding three years. This study may therefore underestimate the association between SHS exposure and mortality from slow-developing conditions (if such an association exists).

Unlike randomised intervention studies, cohort studies do not generally control for confounding factors in the study design. Potential confounders must therefore be addressed in the data analysis. An important advantage of this study is the ability to control for socio-economic status through a variety of measures included in the census. This is discussed in more detail in the next section.

3.2. Data source: the New Zealand Census-Mortality Study

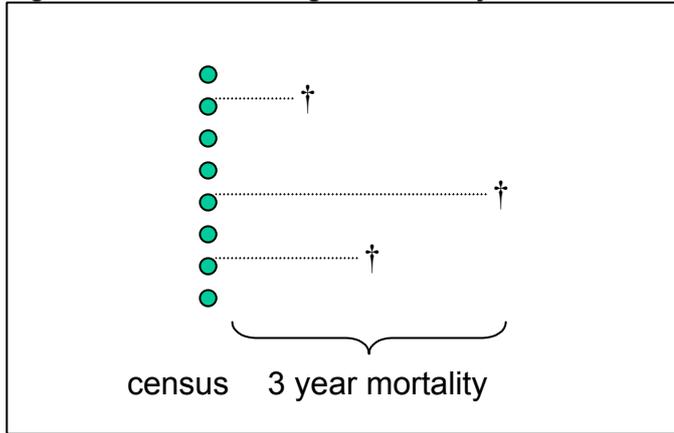
Data used in this study is a subset of a larger cohort dataset called the New Zealand Census-Mortality Study (NZCMS). The methodology and structure of the NZCMS is described in detail elsewhere.^{112 113} A brief overview is provided here as background to the current study.

The NZCMS is essentially a large cohort dataset, comprising four discrete cohorts from 1981, 1986, 1991 and 1996. Each cohort consists of the New Zealand census population at that point in time, and each has been followed-up for deaths occurring in the three years following the census.

The NZCMS was compiled by linking mortality records back to their census records. New Zealand census data does not include respondents' names or text addresses. Linkage of census and mortality records was therefore undertaken using other information contained in both types of records, a process known as *probabilistic record linkage*.^{114 115} Using specialised software, individual census and mortality records were compared in terms of sex, date of birth, ethnicity, country of birth, and area of residence. 'Matching' record pairs were assumed to belong to the same person.¹¹²

This linkage process produced four population cohorts, each followed-up for three year mortality. Where a mortality record was linked back to its census record, that census respondent was known to have died during the follow-up period. Census respondents whose records remained unlinked were assumed to be alive at the end of follow-up (see Figure 8).

Figure 8: NZCMS - linkage of mortality and census records



Overall, around three-quarters of all eligible mortality records were linked back to their corresponding census record. Estimates of linkage accuracy indicate a high degree of precision in this process, with a positive predictive value of around 97%.¹¹²

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Table 3: Linkage rates and accuracy for the 1981 and 1996 NZCMS cohorts

Census Cohort	Proportion of mortality records linked back to census records	Estimated accuracy of linkage process
1981	71.0%	96.9%
1996	78.2%	97.4%

Since some mortality records remained unlinked, there will be some census respondents in the NZCMS misclassified as alive when they had in fact died during the three-year follow-up period. This incomplete linkage introduces the potential for bias in calculating mortality rates for particular exposure groups. This issue is addressed in the following section (3.2.1).

The NZCMS census population was restricted to 0-74 year olds. Since the follow-up period was three years for each census, mortality rates can be calculated for individuals aged up to 77 years. This is the upper age limit for all mortality data calculated in this study.

3.2.1 Linkage bias and correction weights

Incomplete linkage of mortality records introduces the potential for misclassification of subject outcome. The architects of the NZCMS have estimated the extent of this outcome misclassification or ‘linkage bias’, and devised a method of correcting for it at the unit record level. (This method is described in detail elsewhere.¹¹⁷)

As discussed above, around one-quarter of all eligible mortality records were not linked back to their corresponding census record. If the proportion of unlinked to linked deaths is similar for all strata of the population, mortality rates will be underestimated but the mortality rate ratio for different exposure groups will remain the same.^{118 119} If linkage rates are differential, however, this undercounting of deaths introduces a potential bias in comparing mortality rates and estimating rate ratios for different exposure groups.

The architects of the NZCMS have calculated weighting factors to correct for linkage bias.¹¹⁷ The estimation and application of these linkage weights is illustrated by the following example. Assume that there were 200 deaths amongst Māori men aged 45-64 years during a three-year follow-up period. If 126 of these deaths were linked back to the relevant census records, the linkage rate for this group is 126/200 or 63%. The linked deaths in the NZCMS may be weighted up to the actual number of deaths by applying a weight of $200/126 = 1.587$. This linkage weight is therefore applied to all linked deaths amongst Māori men in the 45-64 year age group – ie $126 \times 1.587 = 200$.

Linkage bias and linkage weights have been calculated by strata of age, sex, ethnicity, small area deprivation, rurality and cause of death.¹¹⁷ Linkage weights therefore correct for bias where linkage rates differ by any of the above characteristics. There is still some potential for bias where linkage rates differ by some other exposure *within* strata of age, sex, ethnicity, small area deprivation, rurality and cause of death; however the potential for such bias is very small.

3.3. Data used in this study: exposure, covariates and outcome

The NZCMS cohorts used in this study were those from 1981 and 1996 – the two censuses that included questions on smoking status. Analyses were limited to a subset of each cohort, comprising never-smoking adults aged 45-74 years at the time of the census, and for whom data was available on the smoking status of all other adult household members. Each cohort included mortality data for the three years following the census, so that mortality rates are reported for ages up to 77 years (ie 74 + 3).ⁱ

All exposure and covariate data in this study are derived from census questionnaires. The New Zealand census is conducted every five years by Statistics New Zealand, and includes both individual and household questionnaires. Since information is collected at both an individual and a household level, it is possible to classify individuals according to household-level characteristics.

3.3.1 Exposure

Census respondents in the 1981 and the 1996 census were asked to answer a question on their smoking behaviour. This question was limited to those individuals aged 15 years or over.

In the 1981 census, the smoking question was presented as follows:

<p>Cigarette smoking. Tick the box which best describes your current cigarette smoking:</p> <p><input type="checkbox"/> Never smoked cigarettes at all, or never smoked them regularly</p> <p><input type="checkbox"/> Do not smoke cigarettes now, but used to smoke them regularly (1 or more per day)</p> <p><input type="checkbox"/> Currently smoke cigarettes regularly (1 or more per day) Specify number smoked yesterday:</p>

ⁱ Mortality data is reported for 45-77 year olds who were aged 45-74 years on census night. This does *not* include those individuals who were less than 45 years old on census night but who turned 45 during the three-year follow-up period; nor does it include anyone aged 75 or more on census night.

In the 1996 census, the question was presented as follows:

Do you smoke cigarettes regularly (that is, one or more per day)?

Count only tobacco cigarettes. Don't count pipes, cigars or cigarillos.

YES / NO

If NO -

Have you ever been a regular smoker of one or more cigarettes per day?

YES / NO

On the basis of these questions, census respondents were categorised as current smokers, ex-smokers or never-smokers.

New Zealand census data is recorded at both an individual and a household level. Thus it is possible to determine not only the smoking status of individual respondents, but also the smoking status of other household members. This provided the opportunity to examine mortality amongst never-smokers according to the 'smoking status' of the household in which they lived.

Household smoking status was imputed from the smoking status of adult household members. Where all adults living in a particular household were self-reported never-smokers or ex-smokers, that household was deemed to be a 'non-smoking household'. If one or more adults reported themselves to be current smokers, the household was considered a 'smoking household'. Household smoking status thus provided a dichotomous variable by which exposed and unexposed cohorts were categorised and analysed.

In order to determine a household's smoking status, it was necessary to know the smoking status of every adult normally resident in that household. This required those adults to have been present at their usual residence on census night, and to have completed the smoking question in their individual census questionnaire. (Adults who were away from their usual residence on census night would still have completed an individual census questionnaire, but this was not linked back to their usual household.) It was therefore necessary to exclude respondents belonging to households for which this information was not available. The study cohort also excluded those never-smokers whose normal residence was not a private dwelling (eg those living in boarding houses, hospitals or prisons).

3.3.2 Covariates

As well as providing information on personal and household smoking status, census records include data on a wealth of demographic and socio-economic factors. This allowed mortality rates and rate ratios to be adjusted for a number of potential confounders.

3.3.2.1 Sex

All analyses were conducted separately for men and women.

3.3.2.2 Age

All standardised and regression analyses were controlled for age by five-year age bands (according to person-time of follow-up).

In order to control for age (in both standardised and regression analyses), respondents were divided into five-year age bands (eg 45-49, 50-54, 55-59 years etc). Some census respondents crossed from one age band to the next during the three years of follow-up; in this case, total person-years of observation contributed by that person were divided accordingly between the two relevant age bands, while their death event (where relevant) was assigned to the second age band. Mortality data were standardised or controlled according to these five-year age bands.

3.3.2.3 Ethnicity

Standardised and regression analyses controlled for ethnicity using three mutually exclusive ethnic groups: Māori, Pacific and non-Māori non-Pacific.

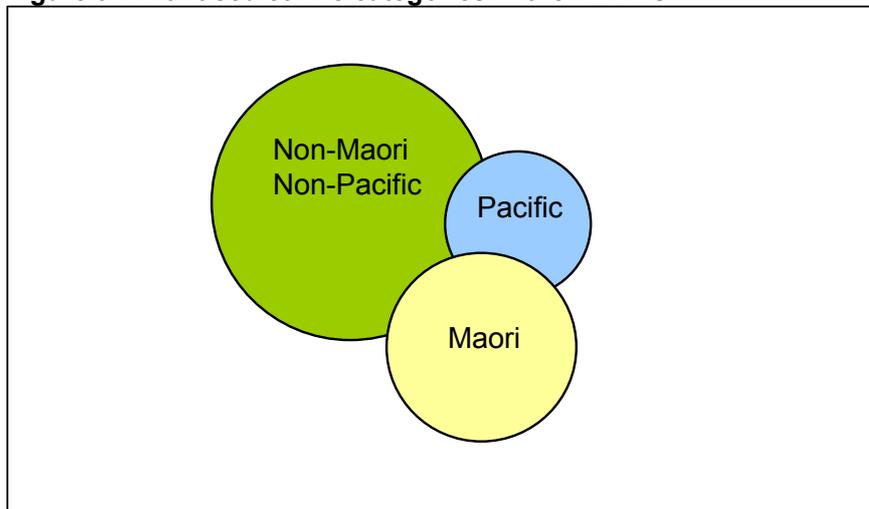
Ethnicity has been ascertained in slightly different ways in each of the four census questionnaires from 1981 to 1996. All four census questionnaires allowed respondents to identify with more than one ethnic group. The architects of the NZCMS have developed a system for classifying ethnicity that is comparable over all four census cohorts. This system classifies respondents into three mutually exclusive ethnic categories, based on a prioritised ordering of ethnicity.

Using this system, ‘Māori’ refers to anyone who identifies in whole or in part with Māori ethnicity. Thus for the 1996 census ‘Māori’ refers to anyone who identified NZ Māori as one of the ethnic groups to which they belong, and for 1981 census data refers to anyone who identified themselves as of Māori ethnic origin (partial or full).

‘Pacific’ refers to anyone who identifies in whole or in part with Pacific but not Māori ethnicity. For 1996 census data, ‘Pacific’ refers to anyone who identified a Pacific group (but *not* NZ Māori) as one of the ethnic groups to which they belong, and in the 1981 census refers to those who identified their ethnic origin (partial or full) as Pacific but *not* Māori.

‘Non-Māori non-Pacific’ refers to anyone whose ethnic identity does not include Māori or Pacific ethnicity. Thus for both censuses, ‘non-Māori non-Pacific’ refers to all those not included in the above two groups. The majority of these respondents are Pakeha/New Zealand European.

Figure 9: Prioritised ethnic categories in the NZCMS



Census respondents are able to identify with more than one ethnic group, so that census ethnic categories are overlapping. The prioritised ethnic classification used in the NZCMS creates three mutually exclusive ethnic categories, based on a prioritised ordering of Māori, Pacific and other census ethnic categories. Based on this classification, the 1981 census population comprised 12% Māori, 3% Pacific and 85% non-Māori non-Pacific. The 1996 census population was 14% Māori, 5% Pacific and 81% non-Māori non-Pacific.

3.3.2.4 Marital status

Regression analyses controlled for marital status as a three-level variable: currently married, previously married and never married.

Respondents in the 1981 census cohort were categorised on the basis of their legal marital status. The 1996 census included a question on de facto living arrangements; respondents were categorised on the basis of their social marital status (ie respondents living in de facto relationships were considered to be married).

3.3.2.5 Education

Regression analyses controlled for education, based on respondents' highest level qualification. Highest level qualification was categorised as post-school, school or none.

Data on highest level qualification was missing for a significant proportion of the 1981 adult census population (around 10%, compared with around 5% of adults in the 1996 census population). For some members of the 1981 cohort, highest level qualification could be imputed from their highest level of educational attendance (which was asked as a separate question on the census questionnaire). For example, if an individual had attended university, teachers' college or a polytechnic, it could be inferred that they had attained some form of school qualification. Where possible, imputed values were used for those 1981 cohort members with missing census data on highest level qualification.

3.3.2.6 Income

Regression analyses controlled for income, using total household income equivalised for the number of household members.

Equivalised household income was categorised into quintiles, based on its distribution over the whole census population. Thus equivalised household income was treated as a five-level variable.

Total household income was calculated by adding the individual incomes of all household members (from their individual census questionnaires). The architects of the NZCMS undertook equivalisation using the Luxembourg method (ie total household income divided by the square root of the number of household members).¹²⁰ Having determined the distribution of equivalised household income within each census population, they then determined the income cut-off values that would divide this distribution into equal fifths, and assigned each census respondent a value for the income quintile to which their household belonged.

3.3.2.7 Car access

Multivariable analyses controlled for car access, using a three-level variable – ie none, one, and two or more.

Car access refers to the number of motor vehicles to which a household has access (excluding motorbikes and motorscooters). This information is collected in the household census form.

3.3.2.8 Small area deprivation (NZ Deprivation Index)

Regression analyses controlled for small area socio-economic deprivation, as measured by the New Zealand Deprivation Index (NZDep). The NZDep96 index (based on 1996 census data) was used for both the 1981 and the 1996 cohort. Index scales were aggregated into a five-level variable (ie deciles 1&2, 3&4, 5&6, 7&8, and 9&10).

The NZDep is similar to indices developed by Townsend¹²¹ and Carstairs¹²², which use UK census data to construct area-based measures of material deprivation. The NZDep index is scaled from 1 (least deprived) to 10 (most deprived), with the census population distributed evenly across this 10-step scale. The scale is based on 10 variables taken from individual census questionnaires, including income, employment, receipt of a benefit, living space, home ownership, and support.¹²³ While these variables are derived from individual-level data, the NZDep is applied at a small area level and thus reflects average deprivation within a small geographically-

defined population. Individuals are assigned an NZDep score according to their address of usual residence.

As a covariate in this study, NZDep probably captures both individual- and area-level characteristics of socio-economic position. The multivariable regression model includes direct measures of individual-level socio-economic position (such as income and education); as an additional covariate, NZDep may act more as a marker of area-level socio-economic deprivation.

3.3.2.9 Housing tenure

Housing tenure was included in multivariable analyses as a two-level variable – ie ‘owned’ and ‘rented or other’.

Housing tenure was assessed in the household census questionnaire. Answers were aggregated into a two-level variable – those who owned the house in which they lived (with or without a mortgage) and those who did not own the house in which they lived. Housing tenure was applied at a household level – in other words, where a house was owned by one of its inhabitants, *all* members of that household shared ownership status for the purpose of this variable.

3.3.2.10 Labour force status

Multivariable analyses controlled for labour force status as a three-level variable.

Labour force status was assessed in the individual census questionnaires. Answers were aggregated into a three-level variable – ie ‘employed’, ‘unemployed’ and ‘not in labour force’. The last category comprises those not seeking or not available for work (including the retired, homemakers, students, and sickness beneficiaries).

3.3.3 Outcome

The primary outcome of interest in this study is all-cause mortality. A secondary outcome is disease-specific mortality from tobacco-related diseases (ie cardiovascular disease, ischaemic heart disease, cerebrovascular disease, lung cancer and respiratory disease). Mortality from non-lung cancer was also examined.

Mortality data in the NZCMS is derived from mortality records provided by New Zealand Health Information Services.¹¹² Cause of death is recorded on each mortality record according to the International Cause of Death (ICD) classification (9th revision). Cause-specific deaths were grouped as shown in Table 4.

Table 4: ICD codes for grouping of cause-specific mortality

Cause of Death	ICD codes
Cardiovascular disease	393-459
Ischaemic heart disease (IHD)	410-414
Cerebrovascular disease	430-438
Lung Cancer	162
Respiratory disease	470-478, 490-519
Non-lung cancer	140-161, 163-209

3.4. Analysis

Analysis of cohort data took place in three stages: calculation of crude mortality rates, calculation of standardised mortality rates and rate ratios, and calculation of multivariable adjusted rate ratios using Poisson regression analysis. All aspects of analysis were undertaken using SAS® version 8.0.

Data were analysed separately by census cohort and by sex. At all levels of analysis, exposure status was classified as a dichotomous variable (ie those in smoking households and those in non-smoking households).

3.4.1 Crude mortality rates

3.4.1.1 Numerator and Denominator

In calculating mortality rates, the numerator comprised the number of deaths that had occurred in the relevant cohort during the three-year follow-up period. The denominator was the total person-time of observation that had accumulated within the three years of follow-up. Resultant mortality rates are expressed as deaths per 100,000 persons per year.

$$\text{Mortality} = \frac{\text{Number of deaths}}{\text{Person-years of observation}}$$

Person-years of observation were calculated on the basis of age at census and age at the end of follow-up. For those census respondents who died during the three-year follow-up period, person-time of observation was equal to age at death minus age at census. For those respondents who were alive at the end of follow-up, person-time of observation was equal to three years (or 36 months).

3.4.1.2 Weighting

As discussed in Section 3.2, around 75% of all deaths in each three-year follow-up period were linked back to a census record. While this linkage rate is high, there is still significant potential for bias in the linkage process. Linkage weights were therefore applied to correct for potential bias due to misclassification of outcome.

Linkage weights are applied at the individual unit level during data analysis. Thus for each sub-group there is both an unweighted and a weighted value for deaths, person-years of observation and mortality. Weighting effectively increases the number of deaths (to account for unlinked death records) and decreases the person-years of observation (to account for unlinked census respondents who actually died during follow-up and therefore did not contribute a full three years of observed person-time). The weighted mortality rates are therefore higher than the unweighted rates.

Linkage weights adjust for linkage bias by age, sex, ethnicity, small area deprivation, rurality and cause of death.¹¹⁷

3.4.2 Standardised mortality rates and rate ratios

3.4.2.1 Standardised mortality rates

Mortality data were standardised by age and ethnicity, using direct standardisation (as described in Rothman & Greenland, 1998⁷²). The 1996 census population was used as the standard population. Standardisation by age was undertaken using five-year age bands (see 3.3.2.2). Standardisation by ethnicity was performed using the three prioritised ethnic groups (see 3.3.2.3).

3.4.2.2 Rate Ratios

Rate ratios were calculated by dividing the mortality rate for those in smoking households by the mortality rate amongst those from non-smoking households (the reference group). Thus a RR greater than one indicates higher mortality in those with household SHS exposure, while a RR less than one indicates lower mortality in those with domestic SHS exposure.

3.4.2.3 Confidence intervals

Confidence intervals around mortality rates and rate ratios were calculated according to the method given by Rothman & Greenland.⁷² In calculating confidence intervals, linkage weights were applied (to take account of data weighting to adjust for potential linkage bias).

3.4.3 Adjusted relative risks

Adjustment for multiple covariates was undertaken using Poisson regression analysis. Poisson regression is appropriate for data with a person-time denominator, a categorical measure of exposure (eg exposed/not exposed), and a relatively rare outcome. A Poisson regression model assumes a log-linear relationship between the exposure and outcome variables, and that covariate variables have a multiplicative effect when combined in a regression model.

3.5. Sensitivity Analyses

The final aspect of data analysis was to conduct sensitivity analyses on the observed results. The purpose of these analyses was to explore the effect of bias potentially arising from misclassification of census respondents with respect to both personal smoking status and SHS exposure status. Sensitivity analyses allow us to test the robustness or susceptibility of our risk estimates to various sources of measurement error.

Sensitivity analyses were carried out on a subset of the total study population – ie males from the 1996 cohort. This group was chosen because crude and adjusted analyses produced very similar estimates for the relative risk of all-cause mortality for exposed vs unexposed cohorts (the crude RR was 1.14, compared with a multivariable-adjusted RR of 1.17). Analyses were limited to crude data, as the methods used to correct for misclassification require person-time and death counts as well as mortality rates. The effect of misclassification on adjusted relative risks is likely to be of similar magnitude to that seen with crude rate ratios.

As discussed in section 2.2.2, this study has two potential sources of error with respect to exposure measurement: misclassification of census respondents' personal smoking status, and misclassification of their SHS exposure status. Each of these sources is addressed in turn.

3.5.1 Correcting for misclassification of personal smoking status

Two slightly different methods were employed to correct for misclassified personal smoking status (see below). The two methods use the same basic assumptions about the proportion of self-reported never-smokers who are actually misclassified current or ex-smokers. The methods differ in the way they calculate deaths amongst misclassified current and ex-smokers. Method A assumes constant mortality rates amongst current and ex-smokers, regardless of their SHS exposure. Method B

assumes a constant relative risk of mortality from SHS exposure, regardless of personal smoking status.

3.5.1.1 Misclassification rates

Correcting for misclassification of personal smoking status requires an estimate of the misclassification rate amongst different parts of the study population. The different types of misclassification and the groups to which they apply are illustrated in the table below:

		Actual smoking status		
		Current	Ex	Never
Self-reported smoking status	Current	true smokers	misclassified ex-smokers	misclassified never-smokers
	Ex	misclassified smokers	true ex-smokers	misclassified never-smokers
	Never	misclassified smokers	misclassified ex-smokers	true never-smokers

Most misclassification of personal smoking status is thought to arise from smokers and ex-smokers who self-report as never-smokers, probably in response to changing social norms and the perceived expectations of health researchers. For the age group under study (45-77 year olds), misclassification of actual never-smokers as current or ex-smokers and misclassification of actual ex-smokers as current smokers is likely to be very small. The above table may therefore be simplified as follows:

		Actual smoking status		
		Current	Ex	Never
Self-reported smoking status	Current	A true smokers		
	Ex	B misclassified smokers	C true ex-smokers	
	Never	D misclassified smokers	E misclassified ex-smokers	F true never-smokers

Since our study is restricted to self-reported never-smokers, the types of misclassification we are primarily interested in are current and ex-smokers misclassified as never-smokers (ie D and E). (Misclassification of current smokers as ex-smokers is also relevant in determining household smoking status, but this source of misclassification is not addressed in sensitivity analyses.) Thus there are three misclassification ‘rates’ of relevance to our analysis:

Misclassification amongst actual current smokers (M_C) = $[D + B] / [A + B + D]$

Misclassification amongst actual ex-smokers (M_E) = $E / [C + E]$

Misclassification amongst self-reported never-smokers (M_N) = $[D + E] / [D + E + F]$

Note that misclassification amongst self-reported never-smokers (M_N) is the sum of

- misclassification due to current smokers ($M_{NC} = D / [D + E + F]$); and
- misclassification due to ex-smokers ($M_{NE} = E / [D + E + F]$).

Estimates of misclassification amongst current smokers generally come from biomarker validation studies. Biomarker levels are used to detect self-reported never-smokers who are actually current smokers. These misclassified smokers are then reported as the misclassification rate amongst actual current smokers.⁶⁷ In other words, misclassification amongst actual current smokers is simplified as $M_C = D / [A + D]$.

3.5.1.1.1 *Sensitivity analyses: correction for misclassified personal smoking status*

Sensitivity analyses used the following additional pieces of information (specific to 45-77 year old males from the 1996 census cohort):

- a. The sub-population (ie 45-77 year old males from the 1996 cohort) comprised 20.2% current smokers, 39.1% ex-smokers and 40.7% never-smokers.
- b. Crude all-cause mortality rates (per 100,000 per year) were 1,645 amongst smokers, 1,397 amongst ex-smokers and 788 amongst never-smokers. Thus the rate ratio for all-cause mortality was 2.09 amongst smokers and 1.77 amongst ex-smokers (using never-smokers as the reference group).¹²⁴

These figures were based on self-reported smoking status and did not take account of misclassification bias.

Sensitivity analyses were based on the following assumptions:

- i. Misclassification amongst actual ex-smokers (M_E) was taken to be four times the rate of misclassification amongst actual current smokers (M_C).
- ii. Misclassification amongst self-reported never-smokers (M_N) was taken to be three times as common in those with SHS exposure compared to those without exposure.

The first assumption was based on 5.4% of actual ever-smokers self-reporting as never-smokers, and 1.7% of actual current smokers self-reporting as never- or ex-smokers. (The first figure is the weighted average of rates reported by Nyberg, Heller and Machlin;⁶⁹⁻⁷¹ the second figure comes from Wells' pooled analysis.⁶⁷)

Multiplying these misclassification rates by the prevalence of current and ex-smokers in our study cohort yields a misclassification rate of 7.3% amongst ex-smokers – approximately four times the misclassification rate for current smokers.

The second assumption was taken from Hackshaw's review of the association between passive smoking and lung cancer.⁵ Hackshaw's sensitivity analysis used an 'aggregation ratio' of 3:1, based on studies of married women who smoke and the extent to which they are more likely to have a husband who smokes. Since our study used a more general population (including men and unmarried women), this ratio may overestimate the extent to which smokers co-habitate with other smokers and so overestimate the misclassification rate for our cohort with domestic SHS exposure.

Correction for misclassified personal smoking was undertaken as follows (a worked example is also given in the Appendix: 7.1.1):

1. The misclassification rate amongst actual current smokers in the study population (M_C) was set.
2. Numbers of misclassified current and ex-smokers in the observed cohort were calculated, based on the number of self-reported never-smokers, the prevalence of never, current and ex-smoking in the study population (a), and the misclassification ratio for actual ex-smokers vs actual current-smokers (ii).
3. Rates of misclassified current and ex-smokers were calculated for each exposure group in the observed cohort. This was undertaken using basic algebra, based on the (known) total numbers in each exposure group, misclassification rates within the self-reported non-smoking cohort for current (M_{NC}) and ex-smokers (M_{NE}) (from Step 2), and the ratio of misclassification in exposed vs unexposed participants (assumption ii).
4. Numbers of misclassified current and ex-smokers and true never-smokers were calculated for each exposure group in the observed cohort, based on the misclassification rates calculated in Step 3.

Steps 5 and 6 differ, depending on which method is used.

Method A (assumes that mortality amongst current and ex-smokers is constant regardless of SHS exposure):

5. The numbers of deaths amongst misclassified current and ex-smokers were calculated, based on the numbers in each group and the (known) mortality rates for current and ex-smokers within the same study population (b).
6. Finally, the numbers of deaths amongst true never-smokers (with and without SHS exposure) were calculated, followed by the mortality rate for each exposure group and the true relative risk for those with SHS exposure.

Method B (assumes that the relative risk of mortality from SHS exposure is constant regardless of personal smoking status):

5. The numbers of deaths amongst misclassified current and ex-smokers were calculated, based on the numbers in each group, the number of observed deaths in

each exposure group and the (known) mortality rate ratios for current and ex-smokers within the same study population (b).

6. Finally, the numbers of deaths amongst true never-smokers (with and without SHS exposure) were calculated, followed by the mortality rate for each exposure group and the true relative risk for those with SHS exposure.

A limitation of Method A is that mortality amongst current and ex-smokers is assumed to be constant, regardless of SHS exposure. This may not be the case. If SHS exposure is associated with increased mortality risk regardless of active smoking status, mortality amongst current or ex-smokers with SHS exposure will be higher than in those without this exposure. Such an effect is likely to be small, however, given the small magnitude of any association between passive smoking and mortality relative to the much stronger association between active smoking and mortality.

A limitation of Method B is that it assumes that SHS exposure has the same relative effect (in terms of mortality risk) regardless of personal smoking behaviour. In other words, SHS exposure is assumed to increase mortality by the same relative amount, regardless of whether the person being exposed is a current, ex- or never-smoker. In practice this is probably not the case. There is evidence that tobacco smoke exposure may have a threshold effect on processes such as platelet aggregation,⁶ so that the impact of SHS exposure on mortality risk in current smokers is likely to be less than its impact in never-smokers. Thus Method B will tend to overestimate the effect of misclassified personal smoking status.

A consideration of both methods is that they assume the same mortality rate or risk amongst misclassified current and ex-smokers as amongst self-reported current and ex-smokers. In practice, misclassified smokers tend to have lighter tobacco consumption and will therefore have a mortality rate lower than smokers in general.⁶⁹ Thus the approach adopted here is likely to exaggerate the importance of misclassified personal smoking status.

Sensitivity analyses were carried out using a range of misclassification rates. No data could be found on misclassification rates amongst the New Zealand population during the relevant time periods. Sensitivity analyses were therefore based on

misclassification rates reported in overseas studies (see Chapter 2: 2.2.2). The most likely level of misclassification was taken from a review by Wells et al, who examined data from 10 validation studies conducted in Britain, Australia, Asia, Greece and the USA.⁶⁷ On the basis of these studies, 1.7% of current smokers are thought to be misclassified as never-smokers on the basis of self-report. While acknowledging the limits of extrapolating from one population to another, this estimate is felt to provide the best indication of the likely magnitude of misclassification in the study cohort.

3.5.2 Correcting for misclassification of SHS exposure

Correction for misclassified SHS exposure requires two additional pieces of information - ie the sensitivity and specificity of SHS exposure classification. Since there is no 'gold standard' test for long-term SHS exposure, it is not possible to derive precise estimates of the sensitivity and specificity of a particular method for classifying SHS exposure. Nevertheless, by testing a range of values we may gain a sense of how sensitive or robust our risk estimates are with respect to misclassification of SHS exposure.

The method used in this study is similar to that described by Greenland.^{64 72} The 'true' values for exposed and unexposed cohorts are calculated on the basis of the observed data plus assumed values for the sensitivity and specificity of SHS exposure classification.

The formulae for calculating ‘true’ data are derived using basic algebra. These are:

$$C = \frac{E(1-S_p) - S_p G}{(1-S_e)(1-S_p) - S_e S_p} \quad A = \frac{G - S_e C}{1 - S_p}$$

Where:

True Data	Deaths	Person-time	Observed Data	Deaths	Person-time
Unexposed	A	B	Unexposed	E	F
Exposed	C	D	Exposed	G	H

and sensitivity = S_e , specificity = S_p .

From first principles, we can see that:

$$E = S_p A + (1 - S_e) C \quad G = S_e C + (1 - S_p) A$$

The second equation can be rearranged to give the following:

$$A = \frac{G - S_e C}{1 - S_p}$$

By substituting this equation (for value A) into the first equation (for value E), the equations are then rearranged to yield the above formula for value C.

3.5.2.1 Sources of misclassification of SHS exposure

There are three main sources of misclassification with respect to SHS exposure:

1. Other household members misreporting their personal smoking status.
2. SHS exposure outside the home.
3. Changes in SHS exposure over time.

I will discuss each of these sources in turn, and provide a rough estimation of the likely misclassification arising from each. (The purpose of this is to provide a rationale for the sensitivity and specificity estimates used in the sensitivity analysis, rather than to give an accurate measure of misclassification from each source.)

3.5.2.1.1 Misclassification due to misreported smoking status amongst other household members.

We can make an approximate estimation of misclassification due to the first source on the basis of misclassification rates for personal smoking status. For example, if 1.7% of actual current smokers misreport themselves as never-smokers (as suggested by Wells et al⁶⁷) we can deduce that around 98.3% of non-smokers with smoking partners were correctly classified as having SHS exposure – in other words, the sensitivity of domestic SHS exposure classification was around 98%. Similarly, if 1% of actual never-smokers misreport their smoking status as current smokers, the specificity of partners' SHS exposure classification will be 99%. (I have assumed that never-smokers are around half as likely as current-smokers to misreport their smoking status.) These values have been used in the first iteration of the sensitivity analysis.

3.5.2.1.2 Misclassification due to SHS exposure outside the home.

The second source of misclassification arises from our inability to measure background SHS exposure. In this study we are unable to measure SHS exposure occurring outside the home, although it is actually total exposure (rather than domestic exposure) that will drive the mortality effect from passive smoking. Categorising SHS exposure on the basis of household smoking status will thus introduce an element of misclassification, to the extent that total SHS exposure does not reflect domestic exposure.

This source of misclassification will alter the sensitivity but not the specificity of our SHS exposure categorisation. This can be demonstrated using the familiar 2x2 table. All those with domestic SHS exposure (a + b) are in the true exposed group, since all individuals with domestic exposure have some SHS exposure and are thus 'true exposed'. (In this analysis we are assuming that imputed domestic SHS exposure is

accurate, and is sufficient to place an individual in the SHS exposed category.) Since there are no ‘false exposed’ individuals (ie $b = 0$), the *specificity* of our exposure classification is 100%. However some of those without domestic SHS exposure ($c + d$) will in fact be exposed (c), due to SHS sources outside of the home. This proportion will drive the *sensitivity* of our exposure classification (ie $a / [a + c]$).

		Actual (total) SHS exposure	
		Exposed	Unexposed
Reported (domestic) SHS exposure	Exposed	a true exposed	b false exposed
	Unexposed	c false unexposed	d true unexposed

$$\text{Sensitivity} = a / (a + c)$$

$$\text{Specificity} = d / (b + d)$$

Thus in the second iteration of the sensitivity analysis I have kept the specificity of SHS exposure categorisation constant at 99% (the level set in the first iteration). I have assumed that 5% of individuals from non-smoking households have significant exposure to SHS in other settings, thus reducing the sensitivity of SHS exposure classification by a further 5%. (NB: This figure of 5% is a ‘best-guess’ estimate used for modelling purposes.)

3.5.2.1.3 *Misclassification due to changes in SHS exposure over time.*

The importance of the third source of misclassification will depend on both the outcome of interest and the duration of follow-up. In studies of fairly short duration, this misclassification will be relatively small for diseases with a short latency (such as ischaemic heart disease and stroke). Misclassification will be greater for diseases with a long latency (such as lung cancer), where SHS exposure at study baseline may be a poor marker of exposure at the relevant stage of disease development (some 20 years prior to death). Misclassification from changing SHS exposure will also be greater in studies of long duration.

This study uses a fairly short follow-up period (ie three years). For most diseases contributing to overall mortality, misclassification from changing SHS exposure will

be relatively small. We might estimate that recent SHS exposure (eg over the past five years) differed from domestic SHS exposure status on the night of the census for around 5% of study participants. This degree of misclassification would reduce both the sensitivity and specificity of SHS exposure categorisation by a further 5%.

It should be noted that misclassification will be greater for mortality from lung cancer and other diseases of long duration. These diseases are therefore more susceptible to negative bias from misclassified SHS exposure, and it will be harder to demonstrate a significant mortality effect in a study such as this.

Chapter 4: Results

Chapter Outline

This chapter presents the results of crude, standardised and multivariable analyses, examining mortality (all-cause and disease-specific) amongst non-smokers according to domestic SHS exposure. Sensitivity analyses for misclassification bias are presented at the end of the chapter.

At all stages of analysis, data were analysed separately for the two census cohorts and for males and females. Each census cohort comprises those respondents aged 45-74 years on census night who identified themselves as never-smokers. Cohort members are categorised by household smoking status (a proxy measure of domestic exposure to SHS).

The structure and characteristics of the study cohorts are presented first. This provides an overview of study numbers and the number of deaths (both all-cause and disease-specific). The demographic profiles of the exposed and unexposed cohorts give an indication of the potential for confounding by demographic and socio-economic factors.

Phase I of the analysis looks at crude and standardised mortality rates by participants' household smoking status. Crude mortality data are presented, stratified into two age bands (45-64 year olds and 65-77 year olds). Age-standardised mortality data are then presented, stratified by ethnicity. Finally, age- and ethnicity-standardised mortality data are presented by age group and by cause of death.

Phase II of the analysis uses Poisson regression to adjust relative risk (RR) estimates for potential confounders, including age, ethnicity, marital status, and various measures of socio-economic position. RR estimates are presented for several different regression models, starting with the simplest model (adjusting for age and ethnicity only) and finishing with the most comprehensive model.

Finally, the results of sensitivity analyses are presented. These analyses show how the RR estimates are affected by differing degrees of misclassification bias, and thus provide an indication of the robustness of the observed association between SHS exposure and all-cause mortality.

4.1. Structure & characteristics of cohorts

The cohorts used in this study are subsets of the 1981 and 1996 census cohorts. A series of restriction steps was followed to derive the cohorts used in standardised and regression analyses.

The first step in this restriction process was to select those census respondents in the relevant age group – ie 45-74 years old at baseline (on census night). The second step was to select out those individuals who identified themselves as never-smokers. Identifying these individuals required them to have completed the smoking question in the census questionnaire. Fortunately, the response rate for this question is very high: within the age group of interest the response rate was 98.0% in 1981 and 92.5% in 1996 (Table 5). Never-smokers comprised 43.5% of this cohort in 1981 and 49.9% in 1996.

The next step in the restriction process was to identify those non-smoking individuals for whom data was available on the smoking status of all other household members. This step required that all adults normally resident in the relevant household were present at that address on census night, and had completed the smoking question in their own individual census form. (Individuals away from their usual residence should still have completed an individual census form, but this could not be traced back to their usual household.) Individuals were also excluded if their usual residence was not a private dwelling (eg individuals living in boarding houses, hospitals, prisons or residential homes).

The cohorts derived through this process were those used in calculating standardised mortality data. The number in each ‘standardisation’ cohort was 286,800 for the 1981 census cohort and 381,462 for the 1996 cohort. Thus amongst self-identified never-smokers the proportion with complete data on household smoking status was 87.0% in 1981 and 85.3% in 1996.

One further restriction was applied in deriving the cohorts used for multivariable regression analysis. The cohorts used in regression analysis were restricted to those individuals whose records included data for all the covariates of interest. This restriction reduced the cohorts by a further 15% (1981) and 9% (1996), so that the cohorts used in regression analysis comprised 72% (1981) and 77% (1996) of the full never-smoking census cohorts.

Numbers in the cohort at each point in this restriction process and the overall ‘response rates’ are presented in Table 5 below.

Table 5: Number of respondents and percentage of full non-smoking cohort for sequential restrictions of study cohorts

Sequential restrictions	Males		Females		Total	
	Number	% full cohort	Number	% full cohort	Number	% full cohort
1981 census cohort						
Census respondents 45-74 years	377,316	(100.0%)	395,694	(100.0%)	773,010	(100.0%)
With data on personal smoking status	370,551	(98.2%)	387,129	(97.8%)	757,680	(98.0%)
Never-smokers	106,623	100.0%	222,993	100.0%	329,616	100.0%
Living in private dwelling	101,589	95.3%	215,583	96.7%	317,172	96.2%
With data on household smoking status (standardisation cohort)	92,082	86.4%	194,715	87.3%	286,800	87.0%
With data on all covariates (regression cohort)	76,398	71.7%	159,786	71.7%	236,184	71.7%
1996 census cohort						
Census respondents 45-74 years	476,757	(100.0%)	491,661	(100.0%)	968,418	(100.0%)
With data on personal smoking status	441,171	(92.5%)	454,551	(92.5%)	895,722	(92.5%)
Never-smokers	180,822	100.0%	266,310	100.0%	447,135	100.0%
Living in private dwelling	171,120	94.6%	253,329	95.1%	424,446	94.9%
With data on household smoking status (standardisation cohort)	152,613	84.4%	228,846	85.9%	381,462	85.3%
With data on all covariates (regression cohort)	137,445	76.0%	205,551	77.2%	342,999	76.7%

Numbers are random rounded to nearest or second nearest multiple of three, as per Statistics New Zealand (SNZ) protocol. Total numbers may not add exactly due to random rounding process.

‘Household smoking status’ was based on the smoking status of all adults (15 years and over) who normally resided in that household. Household smoking status is used as a proxy marker of domestic exposure to second-hand smoke. Never-smokers were thus divided into two SHS exposure groups: those from smoking households (exposed) and those from non-smoking households (unexposed).

Total person-years of observation and the number of deaths are shown for each cohort, sex and cause of death (Table 6).

Table 6: Person-years of observation and deaths (unweighted and weighted) for standardisation cohorts by sex, cohort and cause of death

	Household smoking status	1981		1996	
		Unweighted	Weighted	Unweighted	Weighted
Males					
Person-years of observation	Non-smoking	214,047	211,852	389,120	387,292
	Smoking	57,824	57,344	63,555	63,244
Number of deaths					
All cause	Non-smoking	2,376	3,240	2,982	3,684
	Smoking	579	846	522	687
Disease-specific					
Cardiovascular	Non-smoking	1,380	1,845	1,260	1,563
	Smoking	321	459	228	303
IHD	Non-smoking	1,056	1,395	879	1,080
	Smoking	216	300	147	192
Cerebrovascular	Non-smoking	174	243	165	210
	Smoking	57	84	39	51
Lung Cancer	Non-smoking	66	87	93	111
	Smoking	18	24	18	21
Respiratory	Non-smoking	78	114	93	114
	Smoking	24	39	21	27
Non-lung Cancer	Non-smoking	513	681	1,032	1,245
	Smoking	132	180	144	180
Females					
Person-years of observation	Non-smoking	438,383	435,423	580,059	578,216
	Smoking	139,400	138,675	100,796	100,507
Number of deaths					
All cause	Non-smoking	3,555	4,902	3,333	4,026
	Smoking	855	1,200	591	756
Disease-specific					
Cardiovascular	Non-smoking	1,716	2,358	993	1,212
	Smoking	357	498	177	231
IHD	Non-smoking	1,083	1,458	564	681
	Smoking	216	300	90	111
Cerebrovascular	Non-smoking	399	585	216	267
	Smoking	69	102	33	45
Lung Cancer	Non-smoking	48	69	102	129
	Smoking	15	21	21	27
Respiratory	Non-smoking	87	126	111	138
	Smoking	30	45	27	36
Non-lung Cancer	Non-smoking	1,191	1,572	1,596	1,875
	Smoking	321	435	264	321

Numbers are random rounded to nearest or second nearest multiple of three, as per SNZ protocol.

In the 1981 standardisation cohort there were 0.84 million person-years of observation and 10,188 deaths during follow-up (weighted data). In the 1996 cohort there were 1.13 million person-years of observation and 9,153 deaths during follow-up.

For both cohorts and both sexes, person-years of observation are higher in the unexposed group. This reflects the distribution of non-smokers by household smoking status – ie the majority of non-smokers lived in households with no smoking

adults. In the 1981 census cohort, the exposed group (never-smokers living in smoking households) accounts for around 23% of total person-time. In the 1996 cohort this proportion is even smaller at around 15% of total person-time.

Person-years and deaths have been weighted at the unit level. Weighting adjusts for under-counting of deaths due to linkage bias in the original census-mortality cohort from which these data are drawn (see Chapter 3: 3.2.1). The effect of weighting is to increase the number of deaths but decrease the person-years of observation in each cohort. The impact of weighting is slightly greater for those from smoking households, suggesting that these individuals were less likely to have their mortality records linked back to their census record. All data presented hereafter have been weighted to adjust for linkage bias.

Table 7 shows the characteristics of never-smokers from non-smoking and smoking households.

Table 7: Characteristics of standardisation cohorts by sex and household smoking status

	1981 cohort				1996 cohort			
	Males		Females		Males		Females	
Household smoking status:	non-smk	smoking	non-smk	smoking	non-smk	smoking	non-smk	smoking
Total number	72,504	19,578	147,822	46,893	131,163	21,450	194,958	33,891
Age at census:								
45-64 years	74.2%	85.6%	64.7%	81.8%	77.6%	86.0%	68.9%	83.2%
65-74 years	25.8%	14.4%	35.3%	18.2%	22.4%	14.0%	31.1%	16.8%
Ethnicity:								
Māori	3.8%	12.1%	2.6%	6.3%	5.0%	14.9%	4.1%	10.2%
Pacific	1.2%	2.5%	0.8%	2.5%	2.1%	5.9%	2.0%	7.9%
Non-Māori non-Pacific	95.0%	85.4%	96.6%	91.2%	92.9%	79.2%	93.9%	81.9%
Marital status:								
Currently married	81.6%	87.1%	64.7%	85.4%	80.9%	86.0%	69.7%	80.7%
Previously married	9.3%	7.2%	27.6%	12.4%	9.8%	7.8%	23.3%	15.3%
Never married	8.8%	4.8%	7.6%	1.9%	7.5%	4.2%	5.0%	2.2%
missing	0.3%	0.8%	0.2%	0.3%	1.9%	2.0%	2.0%	1.8%
Highest qualification:								
Post-school	26.8%	21.6%	15.0%	11.3%	44.6%	36.0%	29.4%	22.5%
School	10.6%	10.1%	10.0%	9.7%	20.1%	19.4%	25.8%	25.0%
None	61.1%	66.5%	72.9%	77.1%	34.7%	43.5%	43.8%	51.3%
missing	1.5%	1.7%	2.0%	1.9%	0.7%	1.1%	1.0%	1.2%
Household income tertile:								
1 (highest)	25.3%	26.9%	18.3%	22.5%	28.0%	26.4%	20.4%	21.4%
2	19.6%	21.4%	15.6%	20.3%	20.6%	22.5%	18.1%	21.7%
3	17.0%	16.2%	14.7%	17.0%	16.9%	19.7%	16.1%	20.6%
4	15.4%	11.5%	17.6%	14.1%	15.2%	10.4%	23.2%	12.6%
5 (lowest)	11.8%	6.8%	22.9%	10.3%	13.5%	9.7%	16.6%	12.6%
missing	10.9%	17.0%	10.8%	15.8%	5.8%	11.2%	5.7%	11.1%
NZ Deprivation decile:								
1-2 (least deprived)	23.9%	19.7%	21.3%	18.1%	29.6%	21.8%	26.7%	20.4%
3-4	22.3%	20.1%	21.3%	20.2%	23.5%	20.2%	22.9%	19.5%
5-6	20.7%	19.4%	21.3%	21.0%	19.5%	19.2%	20.5%	19.9%
7-8	18.8%	20.1%	20.0%	20.7%	15.9%	19.0%	17.5%	20.0%
9-10 (most deprived)	14.2%	20.5%	16.0%	20.0%	11.5%	19.7%	12.4%	20.2%
missing	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%

Numbers are random rounded to nearest or second nearest multiple of three, as per SNZ protocol.

Never-smokers living in smoking households tended to be younger than those in non-smoking households. They were also more likely to be married, and less likely to be widowed, divorced or separated. There was a higher prevalence of Māori and Pacific peoples in smoking households.

Never-smokers in smoking households were more likely to have no formal qualifications, and slightly less likely to have post-school qualifications than those in non-smoking households. The distribution of household income was broadly similar across smoking and non-smoking households (allowing for a greater proportion of missing data in smoking households). Smoking households were evenly distributed across NZDep deciles, while non-smoking households were skewed slightly in favour of less deprived areas (this pattern was more marked in the 1996 cohort).

In both census cohorts, 65-74 year olds made up a greater proportion of females compared with males. In other words, the female cohorts had an older age structure than the male cohorts. This pattern was particularly marked in women from non-smoking households.

4.2. Phase I: Crude and Standardised Mortality Rates

Crude, age-standardised and age- and ethnicity-standardised mortality data are presented for the standardisation cohorts by sex and census year.

4.2.1 Crude and age-standardised mortality

Table 8: Crude mortality for 45-77 year old never-smokers by age and household smoking status

Age Group	Household smoking status	Deaths	Person-years of observation	Mortality rate (per 100,000 per year)	(95% CI)	Rate Ratio
Males 1981 cohort						
45-64	Non-smoking	1,170	149,801	782.1	(737.3 - 826.9)	1.00
	Smoking	498	47,549	1,047.7	(955.7 - 1,139.7)	1.34
65-77	Non-smoking	2,070	62,051	3,332.9	(3,189.3 - 3,476.5)	1.00
	Smoking	348	9,796	3,555.0	(3,181.6 - 3,928.4)	1.07
all ages (crude)	Non-smoking	3,240	211,852	1,529.2	(1,476.5 - 1,581.9)	1.00
	Smoking	846	57,344	1,476.0	(1,376.6 - 1,575.4)	0.97
all ages (age-standardised)	Non-smoking	3,240	211,852	1,483.5	(1,422.4 - 1,544.6)	1.00
	Smoking	846	57,344	1,814.9	(1,650.0 - 1,979.8)	1.22
Males 1996 cohort						
45-64	Non-smoking	1,404	286,560.5	489.6	(464.0 - 515.2)	1.00
	Smoking	369	52,572.4	706.6	(634.7 - 778.5)	1.44
65-77	Non-smoking	2,283	100,731.9	2,265.0	(2,172.1 - 2,357.9)	1.00
	Smoking	318	10,671.8	2,967.6	(2,640.8 - 3,294.4)	1.31
all ages (crude)	Non-smoking	3,684	387,292.4	951.4	(920.7 - 982.1)	1.00
	Smoking	687	63,244.2	1,088.1	(1,006.8 - 1,169.4)	1.14
all ages (age-standardised)	Non-smoking	3,684	387,292.4	1,002.2	(965.3 - 1,039.1)	1.00
	Smoking	687	63,244.2	1,443.5	(1,303.6 - 1,583.4)	1.44
Females 1981 cohort						
45-64	Non-smoking	1,344	260,743	515.0	(487.5 - 542.5)	1.00
	Smoking	588	108,470	540.7	(496.9 - 584.5)	1.05
65-77	Non-smoking	3,561	174,680	2,037.6	(1,970.7 - 2,104.5)	1.00
	Smoking	612	30,205	2,025.3	(1,864.8 - 2,185.8)	0.99
all ages (crude)	Non-smoking	4,902	435,423	1,125.8	(1,094.3 - 1,157.3)	1.00
	Smoking	1,197	138,675	864.1	(815.2 - 913.0)	0.77
all ages (age-standardised)	Non-smoking	4,902	435,423	961.8	(928.2 - 995.4)	1.00
	Smoking	1,197	138,675	1,033.7	(956.2 - 1,111.2)	1.07
Females 1996 cohort						
45-64	Non-smoking	1,311	374,284.1	350.2	(331.2 - 369.2)	1.00
	Smoking	369	80,512.9	460.4	(413.5 - 507.3)	1.31
65-77	Non-smoking	2,715	203,931.8	1,331.8	(1,281.7 - 1,381.9)	1.00
	Smoking	384	19,994.1	1,924.7	(1,732.4 - 2,117.0)	1.45
all ages (crude)	Non-smoking	4,026	578,216.0	696.4	(674.9 - 717.9)	1.00
	Smoking	756	100,507.1	751.7	(698.1 - 805.3)	1.08
all ages (age-standardised)	Non-smoking	4,026	578,216.0	646.6	(624.1 - 669.1)	1.00
	Smoking	756	100,507.1	958.8	(872.2 - 1,045.4)	1.48

Numbers are random rounded to nearest or second nearest multiple of three, as per SNZ protocol.

Table 8 shows that the relationship between household SHS exposure and mortality is confounded by age. As would be expected, mortality rates in both men and women are higher in older age groups – so age is clearly associated with mortality. It can also be seen that the proportion of non-smokers living in smoking households is greater in younger age groups – so domestic SHS exposure also differs by age. Finally, the crude mortality rate ratio (comparing those living in smoking vs non-smoking households) is significantly higher within each age group (45-64 and 65-77 year olds) than for the two age groups combined (45-77 year olds). This suggests that age-related confounding has reduced the apparent association between household SHS exposure and mortality in crude analyses.

For 45-77 year olds in both cohorts, the age-standardised mortality rate ratio is significantly higher than the crude RR. This confirms the presence of confounding by age. All results presented hereafter are standardised by five-year age strata.

Finally, Table 8 also shows that the estimate of association between household SHS exposure and mortality is different for the two census cohorts. In the 1996 cohort, the age-standardised RR of mortality amongst those from smoking households is 1.44 in men and 1.48 in women. The corresponding estimates for the 1981 cohort are 1.22 in men and 1.07 in women. Possible reasons for these differences will be explored in the next chapter. The differing RR estimates confirm that data from the two census cohorts should be analysed separately, at least at this stage of the analysis.

Table 9 shows age-standardised mortality rates for each ethnic group: Māori, Pacific and non-Māori non-Pacific (the third group being predominantly Pakeha / New Zealand European).

Table 9: Age-standardised* mortality for 45-77 year old never-smokers by ethnicity and household smoking status

Ethnicity	Household smoking status	Number of deaths	Person-years	Mortality rate (per 100,000 per year)	Rate Ratio	(95% CI)
Males 1981 cohort						
Māori	Non-smoking	204	7,938	2,929.6	1.00	
	Smoking	204	6,833	3,984.6	1.36	(1.01 - 1.83)
Pacific	Non-smoking	33	2,646	1,922.4	1.00	
	Smoking	24	1,439.3	1,743.2	0.91	(0.42 - 1.95)
non-Māori, non-Pacific	Non-smoking	3,003	201,269	1,428.7	1.00	
	Smoking	618	49,072	1,533.3	1.07	(0.96 - 1.20)
all ethnicities (crude)	Non-smoking	3,240	211,852	1,483.5	1.00	
	Smoking	846	57,344	1,814.9	1.22	(1.11 - 1.35)
all ethnicities (ethnicity-std)	Non-smoking	3,240	211,852	1,530.4	1.00	
	Smoking	846	57,344	1,683.6	1.10	(0.99 - 1.22)
Males 1996 cohort						
Māori	Non-smoking	381	19,053.5	2,189.5	1.00	
	Smoking	237	9,238.0	3,201.1	1.46	(1.18 - 1.82)
Pacific	Non-smoking	126	8,213.7	1,792.8	1.00	
	Smoking	66	3,706.0	2,438.8	1.36	(0.89 - 2.07)
non-Māori, non-Pacific	Non-smoking	3,180	360,025.1	926.8	1.00	
	Smoking	384	50,300.2	1,043.4	1.13	(0.99 - 1.28)
all ethnicities (crude)	Non-smoking	3,684	387,292.4	1,002.2	1.00	
	Smoking	687	63,244.2	1,443.5	1.44	(1.30 - 1.60)
all ethnicities (ethnicity-std)	Non-smoking	3,687	387,292.4	1,024.6	1.00	
	Smoking	690	63,244.2	1,198.3	1.17	(1.05 - 1.31)
Females 1981 cohort						
Māori	Non-smoking	210	11,158	1,959.8	1.00	
	Smoking	168	8,604	2,462.6	1.26	(0.93 - 1.69)
Pacific	Non-smoking	45	3,635	1,521.2	1.00	
	Smoking	30	3,396	1,175.9	0.77	(0.40 - 1.50)
non-Māori, non-Pacific	Non-smoking	4,644	420,630	934.6	1.00	
	Smoking	1,002	126,675	948.8	1.02	(0.93 - 1.11)
all ethnicities (crude)	Non-smoking	4,902	435,423	961.8	1.00	
	Smoking	1,197	138,675	1,033.7	1.07	(0.99 - 1.17)
all ethnicities (ethnicity-std)	Non-smoking	4,902	435,423	1,009.8	1.00	
	Smoking	1,200	138,675	1,050.4	1.04	(0.96 - 1.13)
Females 1996 cohort						
Māori	Non-smoking	363	23,275.1	1,539.0	1.00	
	Smoking	180	10,078.3	2,071.3	1.35	(1.06 - 1.71)
Pacific	Non-smoking	117	11,410.9	1,353.1	1.00	
	Smoking	102	7,856.3	1,778.7	1.31	(0.87 - 1.98)
non-Māori, non-Pacific	Non-smoking	3,543	543,530.0	601.2	1.00	
	Smoking	474	82,572.4	750.7	1.25	(1.11 - 1.40)
all ethnicities (crude)	Non-smoking	4,026	578,216.0	646.6	1.00	
	Smoking	756	100,507.1	958.8	1.48	(1.35 - 1.63)
all ethnicities (ethnicity-std)	Non-smoking	4,026	578,216.0	671.6	1.00	
	Smoking	756	100,507.1	854.8	1.27	(1.15 - 1.41)

* Standardised by 5 year age strata

Numbers are random rounded to nearest or second nearest multiple of three, as per SNZ protocol.

These data demonstrate that the association between household SHS exposure and mortality is positively confounded by ethnicity. The relative risk of mortality within each ethnic stratum differs from the RR estimate for all three ethnic groups combined. For example, within the 1996 female cohort the RR of mortality is 1.35 in Māori, 1.31 in Pacific, and 1.25 in non-Māori non-Pacific, while the (non-ethnicity standardised) RR for all three ethnic groups combined is 1.48. The presence of confounding is confirmed by comparing the ethnicity-standardised RR with the non-ethnicity standardised RR for all ethnicities combined. Standardisation by ethnicity decreases the RR estimate for both cohorts and in both sexes.

This confounding arises from an association between Māori and Pacific ethnicity, and household exposure to SHS. From the distribution of person-years by ethnicity (Table 6) it can be seen that household SHS exposure is more common amongst Māori and Pacific non-smokers than amongst non-Māori non-Pacific. Māori and Pacific also have significantly higher mortality than non-Māori non-Pacific. The presence of these two (presumably) independent associations leads to confounding of the relationship between household SHS exposure and mortality.

The relative risk of mortality amongst those with household SHS exposure is slightly different for each ethnic group. This may indicate the presence of effect measure modification by ethnicity. This difference is particularly noticeable in males from the 1996 cohort, and in both sexes from the 1981 cohort. In the 1996 male cohort, the RR of mortality with household SHS exposure is 1.46 in Māori, 1.36 in Pacific, and 1.13 in non-Māori non-Pacific.

The presence of effect measure modification can be statistically tested using Wald's test of homogeneity (as described by Rothman & Greenland⁷²).ⁱⁱ For the above data this test does *not* reject the null hypothesis of homogeneity in the RR estimates across different ethnic groups (p=0.09 for 1996 males, 0.84 for 1996 females, 0.30 for 1981 males and 0.27 for 1981 females). Thus on the basis of these data and this test we

ⁱⁱ ie $X^2_{\text{Wald}} = \text{Sum} [\{ \ln \text{RR}(\text{stratum specific}) - \ln \text{RR}(\text{total standardised}) \}^2 / \text{Variance}(\text{stratum specific})]$;
 X^2 has a distribution with degrees of freedom one less than the number of strata.

cannot conclude that ethnicity acts as an effect measure modifier in the relationship between household SHS exposure and mortality.

4.2.2 Standardised Mortality Rates and Rate Ratios

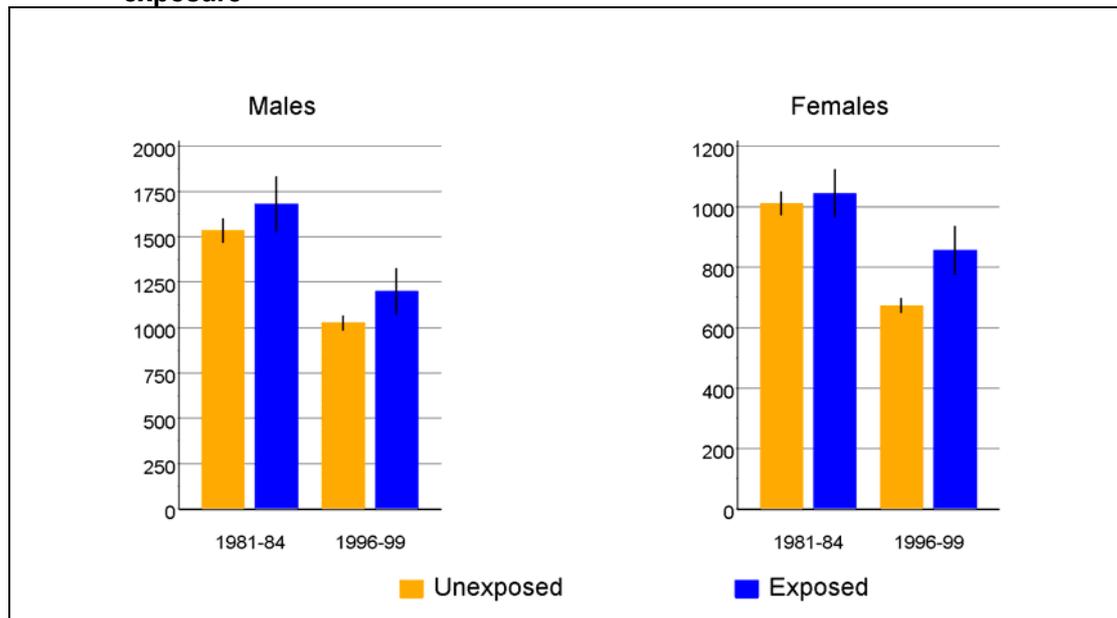
Table 10 presents age- and ethnicity-standardised mortality data for the two cohorts by two age groups (45-64 and 65-77 year olds). Standardised all-cause mortality rates are also presented in Figure 10 by sex, census cohort and domestic SHS exposure.

Table 10: Standardised* mortality for 45-77 year old never-smokers by age and household smoking status

Age Group	Household smoking status	1981			1996		
		Mortality rate (per 100,000 per year)	RR	(95% CI)	Mortality rate (per 100,000 per year)	RR	(95% CI)
Males							
45-64	Non-smoking	767.7	1.00		498.0	1.00	
	Smoking	981.2	1.28	(1.12 - 1.46)	604.8	1.21	(1.06 - 1.40)
65-77	Non-smoking	3,505.1	1.00		2,388.1	1.00	
	Smoking	3,502.4	1.00	(0.86 - 1.16)	2,735.2	1.15	(0.98 - 1.34)
all ages	Non-smoking	1,530.4	1.00		1,024.6	1.00	
	Smoking	1,683.6	1.10	(0.99 - 1.22)	1,198.3	1.17	(1.05 - 1.31)
Females							
45-64	Non-smoking	475.2	1.00		338.7	1.00	
	Smoking	547.0	1.15	(1.01 - 1.31)	415.2	1.23	(1.07 - 1.40)
65-77	Non-smoking	2,214.9	1.00		1,422.0	1.00	
	Smoking	2,185.2	0.99	(0.88 - 1.10)	1,845.9	1.30	(1.13 - 1.49)
all ages	Non-smoking	1,009.8	1.00		671.6	1.00	
	Smoking	1,050.4	1.04	(0.96 - 1.13)	854.8	1.27	(1.15 - 1.41)

* Standardised by 5 year age strata and ethnicity

Figure 10: All-cause mortality (standardised) by sex, census cohort and domestic SHS exposure



Mortality is expressed as deaths per 100,000 per year. 95% confidence intervals are indicated by vertical black lines.

In all four cohorts, mortality is higher amongst those from smoking households. This difference is reflected in elevated mortality rate ratios for those from smoking compared with non-smoking households. The mortality difference by household smoking status is most pronounced in females from the 1996 census cohort, and least marked in females from the 1981 cohort.

For people exposed to SHS (compared to those without exposure), confidence intervals around the RR estimate exclude one for the 1996 but not the 1981 cohort. Within the 1981 cohort, the RR estimate for males from smoking households is 1.10 (95% CI 0.99-1.22) and for females is 1.04 (0.96-1.13). For the 1996 cohort the RR estimate is 1.17 in men (1.05-1.31) and 1.27 in women (1.15-1.41).

The association between household smoking and mortality is generally more marked in the younger age group. Amongst 45-64 year olds with domestic SHS exposure, confidence intervals about the mortality rate ratio exclude one in all four cohort groups. For the older age group (65-77 year olds) the 95% confidence limits exclude one only in females from the 1996 cohort (this is also the only group in which the magnitude of the RR estimate is higher in the older age group).

Overall, these data suggest the presence of a small positive association between household exposure to SHS and mortality. This association is more marked in the later (1996) cohort, and in the younger age group.

The data presented here have been standardised by age and ethnicity. There is still potential for the RR estimates to be confounded by other factors, such as socio-economic position. Controlling for these other potential confounders is most practically achieved using multivariable regression analysis (ie Phase II of analysis).

Table 11 shows age- and ethnicity-standardised mortality data by cause of death, for 45-77 year olds combined.

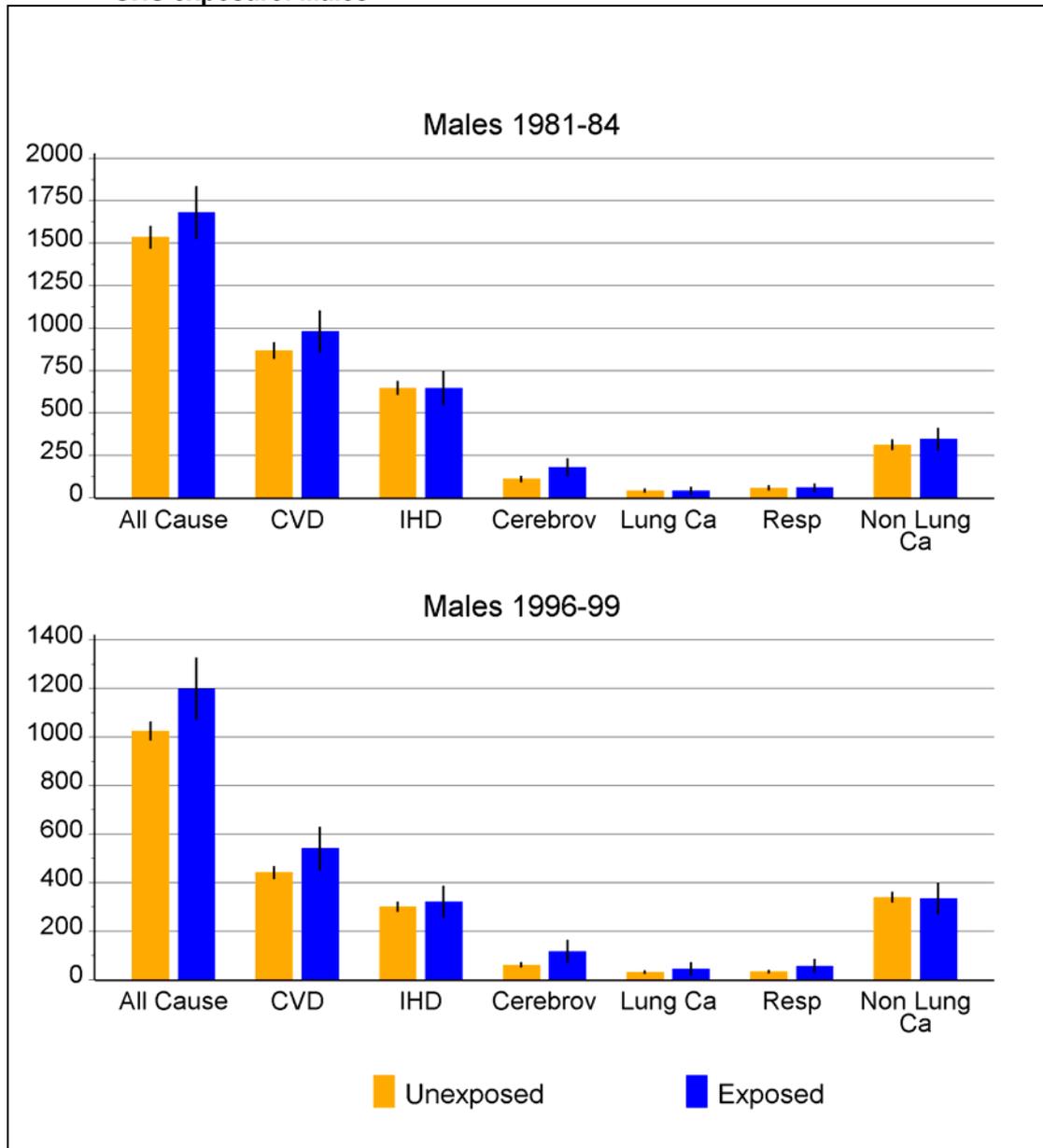
Table 11: Standardised* mortality and mortality rate ratio by sex, cohort, household smoking status and cause of death (45-77 year olds never-smokers)

		1981			1996		
	Household smoking status	Mortality rate (per 100,000 per year)	RR (95% CI)		Mortality rate (per 100,000 per year)	RR (95% CI)	
Males							
All-cause	Non-smoking	1,530.4	1.00		1,024.6	1.00	
	Smoking	1,683.6	1.10	(0.99 -1.22)	1,198.3	1.17	(1.05 -1.31)
Disease-specific							
Cardiovascular	Non-smoking	864.9	1.00		441.2	1.00	
	Smoking	982.8	1.14	(0.99 -1.30)	540.3	1.22	(1.03 -1.46)
IHD	Non-smoking	646.9	1.00		300.2	1.00	
	Smoking	646.7	1.00	(0.85 -1.18)	320.8	1.07	(0.86 -1.32)
Cerebrovascular	Non-smoking	112.3	1.00		60.9	1.00	
	Smoking	178.5	1.59	(1.14 -2.21)	116.3	1.91	(1.23 -2.96)
Lung Cancer	Non-smoking	42.6	1.00		30.2	1.00	
	Smoking	41.4	0.97	(0.53 -1.77)	43.8	1.45	(0.75 -2.81)
Respiratory	Non-smoking	58.1	1.00		32.4	1.00	
	Smoking	59.3	1.02	(0.62 -1.67)	55.8	1.72	(0.99 -2.98)
Non-lung Cancer	Non-smoking	312.2	1.00		339.8	1.00	
	Smoking	347.8	1.11	(0.90 -1.38)	333.4	0.98	(0.80 -1.20)
Females							
All-cause	Non-smoking	1,009.8	1.00		671.6	1.00	
	Smoking	1,050.4	1.04	(0.96 -1.13)	854.8	1.27	(1.15 -1.41)
Disease-specific							
Cardiovascular	Non-smoking	475.4	1.00		205.0	1.00	
	Smoking	469.8	0.99	(0.87 -1.12)	269.4	1.31	(1.09 -1.58)
IHD	Non-smoking	286.8	1.00		113.6	1.00	
	Smoking	279.8	0.98	(0.83 -1.15)	143.3	1.26	(0.98 -1.63)
Cerebrovascular	Non-smoking	116.0	1.00		45.1	1.00	
	Smoking	101.9	0.88	(0.66 -1.17)	52.2	1.16	(0.75 -1.79)
Lung Cancer	Non-smoking	17.5	1.00		20.9	1.00	
	Smoking	17.4	1.00	(0.49 -2.01)	24.3	1.16	(0.70 -1.92)
Respiratory	Non-smoking	30.3	1.00		24.6	1.00	
	Smoking	36.1	1.19	(0.74 -1.92)	43.2	1.75	(0.99 -3.10)
Non-lung Cancer	Non-smoking	319.0	1.00		305.4	1.00	
	Smoking	344.6	1.08	(0.94 -1.24)	374.7	1.23	(1.06 -1.42)

* Standardised by age (5 year age strata) and ethnicity

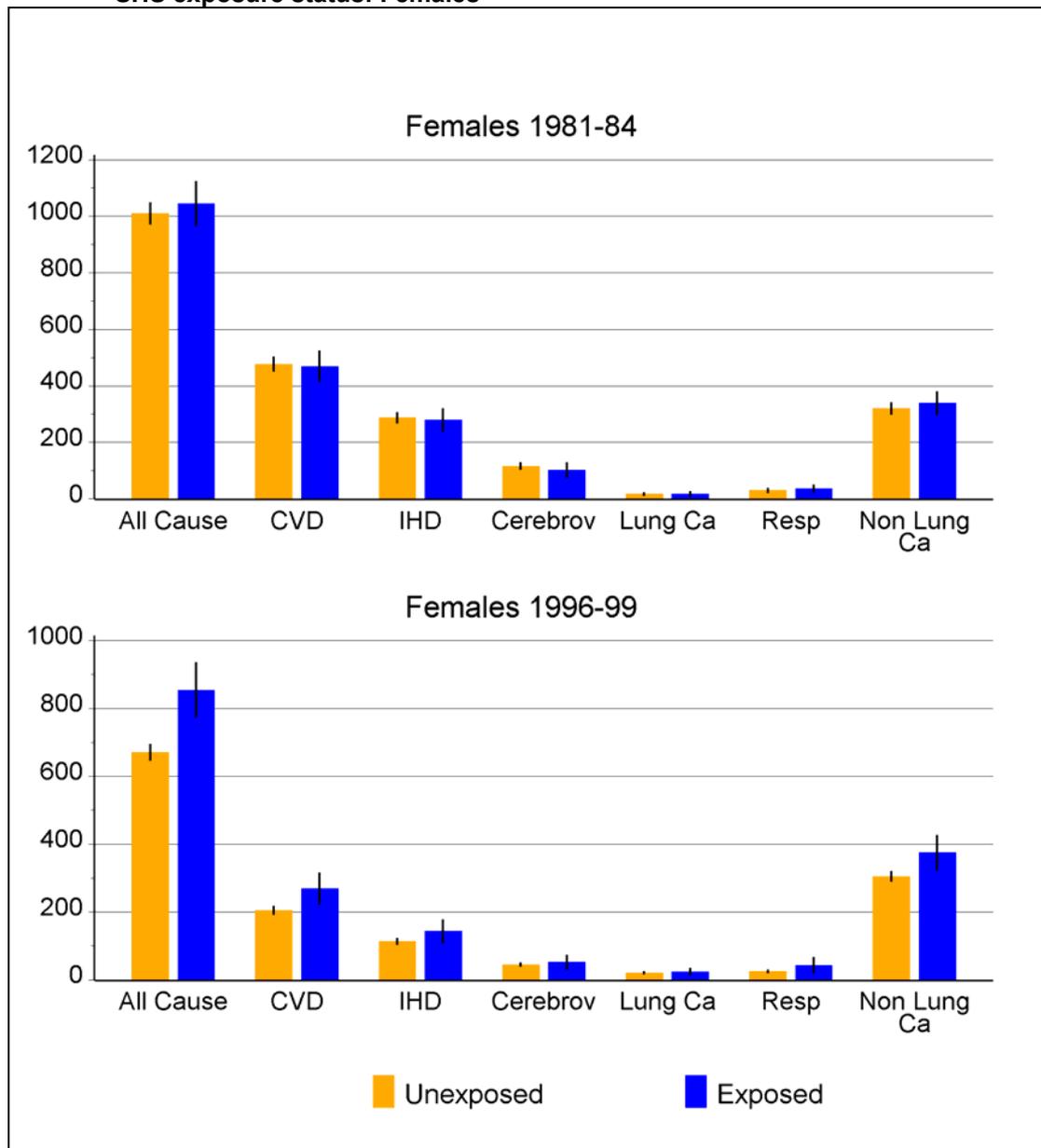
'Cardiovascular disease' includes ischaemic heart disease (IHD) and cerebrovascular disease.

Figure 11: Disease-specific mortality (standardised) by census cohort and domestic SHS exposure: Males



Mortality is expressed as deaths per 100,000 per year.
 95% confidence intervals are indicated by vertical black lines.
 Cause of death is abbreviated as follows: CVD = cardiovascular disease (includes ischaemic heart disease and cerebrovascular disease); IHD = ischaemic heart disease; Cerebrov = cerebrovascular disease; Lung Ca = lung cancer; Resp = respiratory disease; Non Lung Ca = non-lung cancer.

Figure 12: Disease-specific mortality (standardised) by census cohort and domestic SHS exposure status: Females



Mortality is expressed as deaths per 100,000 per year. 95% confidence intervals are indicated by vertical black lines. Cause of death is abbreviated as follows: CVD = cardiovascular disease (includes ischaemic heart disease and cerebrovascular disease); IHD = ischaemic heart disease; Cerebrov = cerebrovascular disease; Lung Ca = lung cancer; Resp = respiratory disease; Non Lung Ca = non-lung cancer.

For ischaemic heart disease, cerebrovascular disease and total cardiovascular disease, mortality is generally higher in those from smoking households. Thus the mortality rate ratio for these conditions is generally greater than one. These diseases appear to make the greatest contribution to elevated all-cause mortality amongst those with domestic exposure to SHS.

The association between household smoking and mortality from cardiovascular diseases shows variable statistical significance. For all cardiovascular disease (CVD), the association reaches statistical significance in both men and women from the 1996 but not the 1981 cohort. For cerebrovascular disease, the association between household SHS exposure and mortality reaches statistical significance in males from both cohorts. The association between household smoking and IHD mortality does not reach statistical significance in any of the four cohort groups.

The association between household smoking and mortality is less clear for other causes of death. Few diseases are associated with an increased RR of mortality in both cohorts. In most cases, confidence intervals around the RR estimate include the null. This may reflect the absence of an association between household SHS exposure and disease-specific mortality, but it is also possible that the study has insufficient statistical power to demonstrate a small but real association. For some diseases (such as lung cancer) there were a relatively small number of deaths during follow-up (Table 6 pg 78).

As in Table 11, RR estimates for those in smoking compared with non-smoking households are generally higher for the 1996 cohort than for the 1981 cohort. The 1996 cohort with household SHS exposure shows increased mortality for both lung cancer and non-lung cancer, although neither association reaches statistical significance. Women in the 1981 cohort show the least association between household SHS exposure and disease-specific mortality, with RR estimates exceeding one only for respiratory disease and non-lung cancer.

Overall, these results suggest that cardiovascular and cerebrovascular disease are the major contributors to excess mortality in those with household exposure to SHS. There is some inconsistency between the two census cohorts and (to some extent) between men and women, possibly due to low study power at a disease-specific level.

Controlling for potential confounders other than age and ethnicity is undertaken in the next stage of analysis.

4.3. Phase II: Adjusted Rate Ratios

The data presented in Phase I of this chapter have been standardised to adjust for age and ethnicity. There are, of course, a number of other factors that may confound the relationship between household smoking status and mortality. Since it is not practical to adjust for these potential confounders through further stratification and standardisation, the next stage of the analysis involves multiple regression techniques. The results of Poisson regression analysis are presented here.

Regression analysis was undertaken on a slightly more restricted cohort than that used in calculating standardised mortality rates and rate ratios (see regression cohort in Table 5 pg 77). This restriction introduces the potential for some selection bias between standardised and multivariable analyses. The extent of this selection bias may be assessed by comparing standardised RR estimates with those derived from regression analysis adjusting for the same covariates (ie age and ethnicity).

Poisson regression analysis was undertaken to control for the following factors: age, ethnicity, marital status, education (highest qualification), income (household equivalised), car access, NZ deprivation index, housing tenure, and labour force status. Apart from basic demographic factors, socio-economic status was considered the main potential confounder in the relationship between household SHS exposure and mortality.

4.3.1 RR estimates for all-cause mortality

Table 12 summarises the results of Poisson regression for all-cause mortality. Relative risk estimates are for non-smokers living in smoking households (ie with domestic SHS exposure), compared with those living in non-smoking households.

Table 12: Adjusted all-cause mortality rate ratios for 45-77 year old never-smokers living in smoking households, by sex, cohort and cause of death

	1981		1996	
	RR	(95% CI)	RR	(95% CI)
Males				
Standardised (age and ethnicity)	1.10	(0.99 -1.22)	1.17	(1.05 -1.31)
Adjusted (multivariable regression)				
R1: Age & ethnicity	1.15	(1.04 -1.28)	1.15	(1.04 -1.29)
R2: Age, ethnicity & MS	1.17	(1.05 -1.31)	1.19	(1.06 -1.32)
R3: Age, ethnicity, MS & SEP	1.17	(1.05 -1.30)	1.16	(1.04 -1.30)
Females				
Standardised (age and ethnicity)	1.04	(0.96 -1.13)	1.27	(1.15 -1.41)
Adjusted (multivariable regression)				
R1: Age & ethnicity	1.05	(0.97 -1.15)	1.28	(1.16 -1.41)
R2: Age, ethnicity & MS	1.06	(0.97 -1.16)	1.31	(1.18 -1.45)
R3: Age, ethnicity, MS & SEP	1.06	(0.97 -1.16)	1.28	(1.16 -1.42)

Standardised RR estimates have been calculated from the standardisation cohort, and are standardised by age (5 year age strata) and ethnicity. Multivariable adjusted RR estimates have been calculated from the regression cohort, and are adjusted (using Poisson regression) for the following variables: R1: age and ethnicity; R2: age, ethnicity and marital status (MS); R3: age, ethnicity, marital status and socio-economic position (SEP) - ie education, income, car access, small area deprivation, housing tenure and labour force status.

For each sex in Table 12, the first line of data shows standardised RR estimates for all-cause mortality in each (standardisation) cohort. These may be compared with the second lines of data (R1), which show RR estimates adjusted for the same variables (ie age and ethnicity) for the regression cohort. For the 1996 cohort the two estimates are very similar, indicating there is no significant selection effect in restricting from the standardisation to the regression cohorts. The estimates are slightly less similar for the 1981 cohort. This may be because standardised rate ratios for the 1981 cohort were calculated using the 1996 census population as the standard, thus introducing a small degree of distortion. There may also be a small element of selection bias in the 1981 regression cohort.

The third line of data (R2) shows RR estimates adjusted for age, ethnicity and marital status. The addition of marital status to the regression model makes very little difference to the RR estimates. For the 1981 cohort, these increase slightly from 1.15

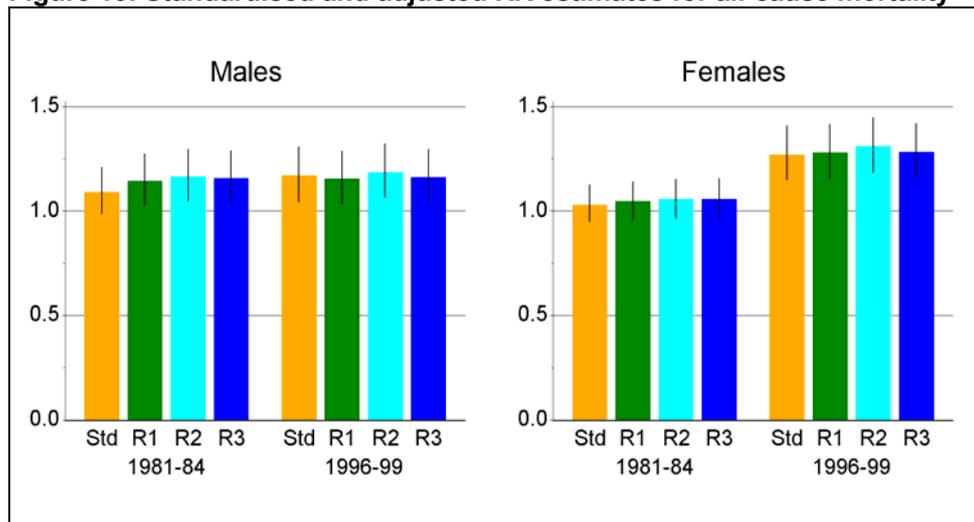
to 1.17 in men and from 1.05 to 1.06 in women. The RR estimates also increase in the 1996 cohort, from 1.15 to 1.19 in men and from 1.28 to 1.31 in women. This small increase suggests that marital status acts as a very minor negative confounder in the relationship between domestic SHS exposure and all-cause mortality.

The fourth line of data (R3) shows RR estimates adjusted for age, ethnicity, marital status and socio-economic position. The variables included in this last adjustment were: education (highest level qualification), income (household equivalised), car access, small area deprivation index (NZ Dep), housing status and labour force status.

Adjustment for socio-economic position makes very little difference to the RR estimates. In the 1981 cohort these remain unchanged with the addition of socio-economic position to the regression model. For the 1996 cohort there is a modest decrease in the RR estimate, from 1.19 to 1.16 in men and from 1.31 to 1.28 in women. This indicates that there is very little confounding by socio-economic position in the association between household SHS exposure and mortality, once age and ethnicity have been controlled.

Standardised and adjusted RR estimates are also shown in Figure 13 below:

Figure 13: Standardised and adjusted RR estimates for all-cause mortality



Column labels are abbreviated as follows: Std = standardised RR estimate; R1 = first regression model (controlling for age and ethnicity); R2 = second regression model (controlling for age, ethnicity and marital status); R3 = third regression model (controlling for age, ethnicity, marital status and socio-economic position).

4.3.2 RR estimates for disease-specific mortality

Multivariable-adjusted relative risk estimates are presented in Table 13 by cause of death. (These RR estimates are based on the regression cohort.) RRs for all-cause mortality (first column) are included for comparison.

Due to small numbers, regression analyses could not be undertaken for disease-specific mortality in two subgroups from the 1981 cohort: men who died from cerebrovascular disease, and women who died from lung cancer.

The effect of multivariable adjustment across most causes of death is similar to that seen for all-cause mortality. Adjustment for age and ethnicity produces RR estimates similar to those obtained from mortality rates standardised by the same two covariates. The addition of marital status to the regression model produces RR estimates very slightly higher than the above, and the further addition of socio-economic position produces a slight reduction in the RR estimates. Thus the final RR estimates (adjusted for age, ethnicity, marital status and socio-economic position) are largely unchanged compared with the standardised RR estimates.

As with standardised RR estimates (Table 11), adjusted RR estimates are generally somewhat higher for the 1996 compared with the 1981 cohort. Possible reasons for this pattern are discussed in the following chapter (Chapter 5: Discussion).

The diseases that show the most consistent elevation in mortality RR are cardiovascular and cerebrovascular disease. (Cardiovascular disease includes both cerebrovascular and ischaemic heart disease.) The RR for cardiovascular and cerebrovascular mortality is elevated amongst passive smokers in all groups except 1981 females. In men, 95% confidence intervals exclude the null for both cardiovascular and cerebrovascular disease; in 1996 women, confidence limits around the RR are >1.0 for cardiovascular disease.

Table 13: Adjusted* mortality rate ratios for non-smokers living in smoking households, by sex, cohort and cause of death

Cause of Death	All Cause		All cardiovascular		IHD		Cerebrovascular		Lung Cancer		Respiratory		Non-lung Cancer	
	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)	RR	95% CI
Males 1981 cohort														
Standardised (age and ethnicity)	1.10	(0.99 -1.22)	1.14	(0.99 -1.30)	1.00	(0.85 -1.18)	1.59	(1.14 -2.21)	0.97	(0.53 -1.77)	1.02	(0.62 -1.67)	1.11	(0.90 -1.38)
Adjusted (multivariable regression)														
R1: Age & ethnicity	1.15	(1.04 -1.28)	1.18	(1.02 -1.36)	1.03	(0.87 -1.22)			1.22	(0.64 -2.33)	1.47	(0.85 -2.57)	1.17	(0.94 -1.47)
R2: Age, ethnicity & MS	1.17	(1.05 -1.31)	1.20	(1.04 -1.38)	1.05	(0.88 -1.24)			1.21	(0.63 -2.31)	1.43	(0.82 -2.50)	1.19	(0.95 -1.49)
R3: Age, ethnicity, MS & SEP	1.17	(1.05 -1.30)	1.19	(1.04 -1.38)	1.04	(0.88 -1.23)			1.08	(0.56 -2.09)	1.38	(0.79 -2.42)	1.19	(0.95 -1.49)
Males 1996 cohort														
Standardised (age and ethnicity)	1.17	(1.05 -1.31)	1.22	(1.03 -1.46)	1.07	(0.86 -1.32)	1.91	(1.23 -2.96)	1.45	(0.75 -2.81)	1.72	(0.99 -2.98)	0.98	(0.80 -1.20)
Adjusted (multivariable regression)														
R1: Age & ethnicity	1.15	(1.04 -1.29)	1.25	(1.06 -1.47)	1.17	(0.96 -1.42)	1.79	(1.19 -2.69)	0.79	(0.40 -1.56)	1.58	(0.88 -2.85)	1.00	(0.82 -1.21)
R2: Age, ethnicity & MS	1.19	(1.06 -1.32)	1.28	(1.09 -1.51)	1.20	(0.98 -1.46)	1.85	(1.23 -2.79)	0.80	(0.41 -1.58)	1.67	(0.93 -3.02)	1.00	(0.82 -1.22)
R3: Age, ethnicity, MS & SEP	1.16	(1.04 -1.30)	1.25	(1.06 -1.47)	1.18	(0.96 -1.44)	1.82	(1.20 -2.77)	0.74	(0.37 -1.47)	1.81	(1.00 -3.28)	0.98	(0.80 -1.20)
Females 1981 cohort														
Standardised (age and ethnicity)	1.04	(0.96 -1.13)	0.99	(0.87 -1.12)	0.98	(0.83 -1.15)	0.88	(0.66 -1.17)	1.00	(0.49 -2.01)	1.19	(0.74 -1.92)	1.08	(0.94 -1.24)
Adjusted (multivariable regression)														
R1: Age & ethnicity	1.05	(0.97 -1.15)	1.01	(0.89 -1.16)	1.02	(0.86 -1.21)	0.88	(0.66 -1.17)			1.28	(0.79 -2.07)	1.04	(0.90 -1.19)
R2: Age, ethnicity & MS	1.06	(0.97 -1.16)	1.02	(0.89 -1.17)	1.00	(0.84 -1.19)	0.91	(0.68 -1.22)			1.41	(0.86 -2.30)	1.03	(0.89 -1.19)
R3: Age, ethnicity, MS & SEP	1.06	(0.97 -1.16)	1.01	(0.88 -1.16)	0.98	(0.83 -1.17)	0.90	(0.67 -1.21)			1.34	(0.81 -2.21)	1.04	(0.90 -1.21)
Females 1996 cohort														
Standardised (age and ethnicity)	1.27	(1.15 -1.41)	1.31	(1.09 -1.58)	1.26	(0.98 -1.63)	1.16	(0.75 -1.79)	1.16	(0.70 -1.92)	1.75	(0.99 -3.10)	1.23	(1.06 -1.42)
Adjusted (multivariable regression)														
R1: Age & ethnicity	1.28	(1.16 -1.41)	1.32	(1.09 -1.59)	1.26	(0.97 -1.63)	1.15	(0.75 -1.76)	1.45	(0.83 -2.51)	1.68	(1.01 -2.77)	1.22	(1.05 -1.40)
R2: Age, ethnicity & MS	1.31	(1.18 -1.45)	1.36	(1.13 -1.65)	1.29	(0.99 -1.68)	1.19	(0.77 -1.83)	1.48	(0.85 -2.57)	1.73	(1.04 -2.87)	1.23	(1.06 -1.42)
R3: Age, ethnicity, MS & SEP	1.28	(1.16 -1.42)	1.35	(1.11 -1.64)	1.27	(0.98 -1.66)	1.17	(0.76 -1.82)	1.38	(0.78 -2.41)	1.59	(0.95 -2.68)	1.21	(1.05 -1.40)

*Standardised RR estimates are standardised by age (5 year age strata) and ethnicity.

Multivariable adjusted RR estimates are adjusted for age, ethnicity, marital status (MS) and socio-economic position (SEP) - ie education, income, car access, small area deprivation, housing tenure and labour force status.

Mortality RR estimates for ischaemic heart disease are elevated for both sexes in the 1996 cohort but not the 1981 cohort. Confidence intervals include one in all four subgroups. Mortality from lung cancer likewise shows an elevated risk in the 1996 but not the 1981 cohort, although in all cases numbers are small and confidence intervals include the null (Table 6 pg 78).

The RR estimate for mortality from respiratory disease is elevated in all four subgroups. This effect is more pronounced in the 1996 cohort, in whom confidence limits only just include the null. Confidence limits are fairly wide in both cohorts, again reflecting small numbers (Table 6).

Amongst a few subgroups there is a suggestion of some selection effect in the more restricted cohort that underwent regression analysis. For mortality from lung cancer, RR estimates adjusted for age and ethnicity differ from those obtained through standardisation. This is likely to be a consequence of the small numbers involved. Similar selection effects are also seen for death from ischaemic heart disease in 1996 men, and death from respiratory disease in 1981 men. In both cases the RR estimate adjusted for age and ethnicity is somewhat higher to that obtained from mortality rates standardised by the same two variables. Caution should be taken in interpreting the adjusted RR estimates for these subgroups.

Finally, the RR estimate for mortality from non-lung cancer is slightly elevated in several subgroups, with the association reaching statistical significance in women from the 1996 cohort. (Note that 1996 men had no such association.) Regression analysis was undertaken for the risk of breast cancer mortality amongst 1996 females with household SHS exposure. This effectively showed no association (RR 1.05, 95% CI 0.79-1.39). Data was not available to undertake regression analysis for cervical cancer mortality.

4.4. Phase III: Sensitivity Analyses

The final step in data analysis was to explore the effect of possible exposure misclassification through sensitivity analyses.

The following tables show the results of sensitivity analyses conducted on crude data for 1996 males. (Data has been weighted to adjust for linkage bias, but is non-standardised so that mortality rates correspond with count data for deaths and person-time.) Analyses explore the effects of two different sources of misclassification: misclassification of personal smoking status and misclassification of SHS exposure. Two slightly different methods have been used for sensitivity analyses; these are presented in separate tables.

Table 14 shows the results of sensitivity analysis using Method A to correct for misclassified personal smoking status. This method assumes a constant mortality rate amongst current and ex-smokers, regardless of SHS exposure (see Chapter 3: 3.5.1 for methodology). The ‘best guess’ estimate for misclassification (underlined) yields an adjusted RR estimate of 1.18. This is slightly higher than the unadjusted estimate of 1.14, and suggests that the overall effect of misclassification is to reduce the observed association between SHS exposure and mortality.

Table 15 gives the results of sensitivity analysis using Method B, which assumes a constant RR effect from SHS exposure regardless of personal smoking status. Compared with Method A, the second method produces a greater reduction in the RR estimate with adjustment for each level of misclassification. Using this method, the ‘best guess’ level of misclassification yields an adjusted RR estimate of 1.09, which is slightly lower than the unadjusted estimate.

Table 14: Method A. RR estimates adjusted for misclassification of personal smoking status and SHS exposure status*

Misclassified current- and ex-smokers as a proportion of self-reported never-smokers			Sensitivity and specificity of SHS exposure classification									
			1		2		3		4		5	
			Se	Sp	Se	Sp	Se	Sp	Se	Sp	Se	Sp
			100%	100%	98%	99%	88%	99%	88%	94%	88%	90%
A	Current smokers	0%	1.14		1.15		1.16		1.24		1.45	
	Ex-smokers	0%										
B	Current smokers	0.8%	1.10		1.11		1.11		1.18		1.45	
	Ex-smokers	6.5%										
C	Current smokers	1.5%	1.04		1.05		1.05		1.09		1.37	
	Ex-smokers	11.5%										

* Based on crude data for male never-smokers living in smoking vs non-smoking households, 1996 (see Table 6). The sensitivity and specificity of SHS exposure classification are determined by three sources of error (see Chapter 3: 3.5.2.1). Column 2 represents misclassification arising from misreported smoking status amongst household members; Column 3 adds the effect of misclassification due to SHS exposure outside the home; and Columns 4 and 5 include misclassification due to changes in SHS exposure over time.

Table 15: Method B. RR estimates adjusted for misclassification of personal smoking status and SHS exposure status*

Misclassified current- and ex-smokers as a proportion of self-reported never-smokers			Sensitivity and specificity of SHS exposure classification									
			1		2		3		4		5	
			Se	Sp	Se	Sp	Se	Sp	Se	Sp	Se	Sp
			100%	100%	98%	99%	88%	99%	88%	94%	88%	90%
A	Current smokers	0%	1.14		1.15		1.16		1.24		1.45	
	Ex-smokers	0%										
B	Current smokers	0.8%	1.05		1.05		1.05		1.09		1.22	
	Ex-smokers	6.5%										
C	Current smokers	1.5%	0.99		0.99		0.99		0.98		0.93	
	Ex-smokers	11.5%										

* Based on crude weighted data (as shown in Table 6) SHS exposure misclassification is determined by three sources of error (see footnote to Table 14 above).

4.4.1.1.1 Interpretation of tables

Table *rows* indicate different rates of *misclassification of personal smoking status*. Rows are labelled along the left-hand side of the table (A, B and C). Misclassification rates for *current* and *ex-smokers* refer to the proportion of current and ex-smokers in the study population who inaccurately report themselves as never-smokers. The least misclassification (0%) is represented by Row A in each table; misclassification rates increase going from Row A to Row C.

Table *columns* refer to different rates of *misclassification of SHS exposure*. Columns are labelled across the top of the table (1-5). The least misclassification (100% sensitivity and specificity) is shown in the first column. Misclassification rates then increase going from Column 1 to Column 5.

The RR estimate in each cell has thus been ‘corrected’ for both misclassification of personal smoking status and misclassification of SHS exposure status. The original (unadjusted) RR estimate is shown in cell A1. ‘Best guess’ values for misclassification of personal smoking status and misclassification of SHS exposure are shown in italics (Row B and Column 4 respectively), with the intersection of the two underlined (cell B4).

4.4.1.1.2 *Effect of each type of misclassification*

Looking down the table from Rows A to C, it may be seen that adjustment for misclassification of personal smoking status reduces the RR estimate. (For example, in the first column of Table 14 the RR estimate diminishes from 1.14 to 1.04 as one looks from top to bottom.) This reflects the positive bias arising from differential misclassification of current and ex-smokers by domestic SHS exposure status. Current or ex-smokers who are misclassified as never-smokers will have higher mortality than true never-smokers; if this misclassification is greater amongst those with SHS exposure, the association between SHS exposure and mortality will be exaggerated.

Looking across the table from Column 1 to Column 5, the RR estimate increases with adjustment for misclassification of SHS exposure. (For example, in the first row of Table 14 the RR estimate increases from 1.14 to 1.45 going from Column 1 to Column 5.) This mirrors the effect of non-differential misclassification of SHS exposure, which biases the observed RR estimate towards the null. Correcting for this misclassification removes the negative bias and so increases the RR estimate amongst those with SHS exposure.

In correcting for misclassified SHS exposure it can be seen that the *specificity* of exposure categorisation is the strongest driver of misclassification bias. Even a modest reduction in specificity produces a significant bias towards the null, so that adjustment for this level of misclassification produces a much stronger association measure for SHS exposure and mortality.

From these tables it may be seen that the two types of misclassification (personal smoking status and SHS exposure) bias the RR estimate in opposite directions. The net effect of misclassification depends on the underlying nature of the SHS-mortality association. The two methods used in these sensitivity analyses are based on different assumptions about the nature of this association.

In terms of misclassified personal smoking status, Method A indicates that even a high level of misclassification would be insufficient to explain all of the apparent association between SHS exposure and mortality. Using Method B, an overall misclassification rate of 13% amongst self-reported never-smokers would be sufficient to fully explain the apparent association between passive smoking and mortality.

Both methods produce a $RR > 1.0$ after adjustment for the 'best guess' level of misclassification. In other words, the apparent association between domestic SHS exposure and mortality persists after adjusting for likely misclassification bias.

Chapter 5: Discussion

Chapter Outline

In evaluating the results of any study, it is important to take account of study limitations and potential sources of error. These include possible random error and threats to internal validity. Having explored the likely limitations of this study, its results can then be interpreted in the context of previous research on passive smoking and mortality. This includes an evaluation of the evidence for causality and the implications for future research and health policy.

Study precision is reflected in confidence intervals for effect measure estimates (presented in the previous chapter). The precision of effect measure estimates depends on study power in relation to the size of the effect under investigation. In this study, measures of association are more precise for all-cause mortality than for disease-specific mortality.

An evaluation of internal validity requires a more qualitative approach. Sensitivity analyses provide an indication of the likely direction and magnitude of exposure misclassification bias. Internal validity may also be limited by selection bias, outcome misclassification and residual confounding. I have discussed these causes of systematic error and explored the effect they may have had on the observed association between domestic SHS exposure and mortality.

The results of this study are then examined in the context of previously published research on SHS exposure and mortality. Effect measure estimates for all-cause mortality show a high degree of consistency with those reported previously (particularly those from higher-powered studies). The biological plausibility of passive smoking as a risk factor for some fatal diseases and the consistency between these results and the active smoking-mortality relationship provide further support for a causal association. Such an association has important implications for future health research and for public policy in relation to the supply and use of tobacco products.

5.1. Summary of study results

Results from this study demonstrate a positive association between passive smoking and mortality which (in my view) is not accounted for by either confounding or exposure misclassification. Mortality from all causes was elevated amongst 45-77 year old never-smokers with domestic exposure to second-hand smoke in both 1981-84 and 1996-99. Comparing never-smokers from smoking and non-smoking households, age- and ethnicity-standardised mortality rate ratios were 1.10 (95% CI 0.99-1.22) in 1981 men, 1.17 (1.05-1.31) in 1996 men, 1.04 (0.96-1.13) in 1981 women, and 1.27 (1.15-1.41) in 1996 women.

At a disease-specific level, mortality from cardiovascular and cerebrovascular disease showed the most consistent association with household SHS exposure. Rate ratios for cardiovascular and cerebrovascular mortality were elevated amongst passive smokers in all groups except 1981 females. Ischaemic heart disease and lung cancer mortality rates were elevated amongst passive smokers in the 1996 but not the 1981 cohort. Mortality from respiratory disease was elevated in SHS-exposed individuals from all cohorts (although the number of respiratory deaths was small and RR estimates may be affected by random error). Mortality from non-lung cancer was elevated in 1996 females with domestic SHS exposure.

5.2. Study limitations

This section discusses possible sources of non-random error in this study, including the potential for selection bias, misclassification of exposure and outcome, and confounding of the relationship between domestic passive smoking and mortality. The limitations of a cohort study with relatively short follow-up are also discussed. Finally, I have considered the generalisability of study results to other populations and time periods.

5.2.1 Selection of study cohorts and potential for selection bias

The cohorts used in the study were subsets of the New Zealand Census-Mortality Study, a dataset comprising four census cohorts linked for mortality over the three years following each census. Cohorts consisted of those respondents from the 1981 and 1996 censuses who were aged 45-74 years on the night of the census, reported their smoking status as never-smokers, and for whom data on household smoking status was complete.

It was decided to limit the study cohort to never-smokers in order to minimise the risk of confounding due to active tobacco smoke exposure. Exposure to SHS may well produce adverse health effects in both ex- and current smokers, but such effects are likely to be clouded by the relatively stronger health impact of active smoking. If an association between passive smoking and mortality were observed amongst ex- or current smokers, it would be difficult to rule out the effects of confounding from heavier active smoking (either past or present) in the SHS-exposed group. By limiting the study cohort to never-smokers the cohort size and study power were reduced in favour of greater internal validity.

Selection bias is unlikely to be a significant source of error in this study. Both censuses had a high response rate for smoking questions; within the 45-74 year age group, data on personal smoking status was complete for 98% of respondents in 1981

and 92% in 1996. Amongst self-reported never-smokers, data on household smoking status was complete for a high proportion of subjects (87% in 1981 and 85% in 1996). There is therefore relatively limited potential for selection bias in the cohorts used to calculate standardised mortality data. A small selection effect is theoretically possible (for example, less well individuals may have been more likely to be at their usual residence on census night and thus be included in the study cohort), but the scope for such selection bias is not great.

The restricted cohort used for multivariable analyses comprised a more selected group than that used for standardised analyses. In the 1981 cohort, 72% of 45-74 year old never-smokers had full data on household smoking status and all covariates of interest; in the 1996 cohort this proportion was slightly higher at 77%. There is therefore some potential for a selection effect in moving from standardised to multivariable-adjusted rate ratios. The magnitude of this effect may be gauged by comparing standardised and adjusted mortality rate ratios controlled for the same variables. For three out of four cohorts, the age- and ethnicity-controlled relative risk values are very similar for both the standardised and the regression cohorts. The only exception to this is the 1981 male cohort, in whom the age- and ethnicity-controlled RR increases from 1.10 in the standardised cohort to 1.15 in the regression cohort. Thus the 1981 male cohort used in regression analyses may represent a more selected group than that used in standardised analyses, resulting in a slight inflation of the multivariable-adjusted RR estimate for this cohort. The effect of such selection bias appears to be small, however.

5.2.2 Misclassification

Misclassification may apply to both the exposure and the outcome under investigation. In this study, likely sources of misclassification include current- and ex-smokers who self-report as never-smokers, misclassification of SHS exposure, and misclassification of vital status and cause of death. Two major sources of exposure misclassification were explored using sensitivity analyses, which provide an indication of how mortality rate ratios observed in this study may have been affected by exposure misclassification bias.

5.2.2.1 Self-reported never-smokers: potential for misclassification of smoking status

As discussed above, the study cohorts consisted of census respondents who self-reported their smoking status as never-smokers.

As with any self-reported characteristic, there is potential for misclassification of respondents' smoking status. Evidence from the published literature suggests that smokers who self-report as never-smokers are more likely to be found in households with other smokers. In other words, misclassification of personal smoking status is likely to be differential by household SHS exposure. This form of misclassification is therefore likely to produce a positive bias in the observed association between passive smoking and mortality. (This possibility was explored in sensitivity analyses, discussed later in this chapter.)

5.2.2.2 SHS exposure status and potential for misclassification of exposure

The exposure status of study subjects was based on SHS exposure occurring in the home. The existence of a dataset based on census records made it possible to categorise smoking behaviour at both an individual and a household level. Thus it was possible not only to identify the self-reported smoking status of each census respondent, but also to identify the self-reported smoking behaviour of all other adults with whom they lived.

Cohort members were categorised as SHS exposed or unexposed according to the 'smoking status' of their household. Households were classified as 'non-smoking' if no adult members identified themselves as current smokers; where at least one member self-identified as a current smoker, the household was classified as 'smoking'.

This method of determining SHS exposure status has a number of limitations. The most significant limitation is the inability to take account of SHS exposure occurring in settings outside the home. There is also potential for misclassification of domestic SHS exposure, due to 1. inaccurate self-reporting of smoking status by other household members; 2. unmeasured changes in household smoking status (due to changing smoking behaviours or changing household composition); 3. smoking by household members less than 15 years old (for whom smoking data is not recorded in the census); and 4. smokers who do not smoke inside their homes.

Inaccurate reporting of smoking status by household members and unmeasured SHS exposure outside the home are both addressed in sensitivity analyses. Other sources of error are discussed briefly below.

5.2.2.2.1 Unmeasured changes in household smoking status

Households were classified as ‘smoking’ or ‘non-smoking’ according to the smoking status of household members *at the time of the census*. Thus households with no *current* smokers were classified as non-smoking, even if some household members were ex-smokers. Where a non-smoking household included ex-smokers, members of that household may well have experienced domestic SHS exposure in the (possibly very recent) past. In other words, never-smokers from households consisting of all never-smokers are likely to represent a group with lower SHS exposure than those from households of never-smokers plus ex-smokers.

In theory it would have been possible to stratify non-smoking households into ‘never-smoking’ and ‘ex-smoking’, in which case one might have expected to see a difference in mortality between these two exposure groups. I decided not to make this distinction since in practice any mortality difference was likely to be small, and further stratification of exposure status would increase measurement error. For similar reasons I also decided against stratifying the SHS-exposed cohort according to the number of smokers in the household.

Changing household composition represents another unmeasured change that may affect household smoking status. A household that was 'non-smoking' at the time of the census may have included smoking members in the recent past; conversely, a household that had been non-smoking for the past 20 years would be classified as 'smoking' if a smoker had moved in the week before. In both cases, household smoking status on the night of the census would not provide an accurate indication of domestic SHS exposure in the recent past.

Misclassification due to changing household composition could have been reduced by restricting the study cohort to individuals from households of stable composition. For example, it would have been possible to exclude individuals from households in which one or more of the adult residents had been living for less than five years. The trade-off for reducing misclassification in this way is that the study cohorts would have been smaller and more restricted, thus reducing study power and increasing the potential for selection bias. For these reasons I decided against this further restriction of the study cohort.

5.2.2.2.2 Smokers less than 15 years of age

The 1981 and 1996 censuses collected data on smoking behaviour only for respondents aged 15 years or older. Smokers aged less than 15 could therefore not be identified in determining household smoking status. In practice, this omission is unlikely to have significantly increased mismeasurement of household smoking status. While there are undoubtedly some smokers amongst children less than 15 years,¹²⁵ most of their tobacco consumption is likely to occur in settings outside the home¹²⁶ and will not contribute to household SHS exposure. Young smokers who do smoke at home would change the smoking status of their household only if there were no adult smokers in residence.

5.2.2.2.3 Smokers who restrict their smoking to outside the home

In determining household smoking status I have assumed that all current smokers do in fact smoke in their homes, thus exposing other household members to SHS. In

practice this is not always the case; some current smokers may smoke only in settings away from home, while others may be careful to always smoke outside.

Unmeasured differences in smokers' behaviour may mean that some census respondents were classified as SHS-exposed when their domestic exposure to SHS was actually minimal. Such misclassification is probably fairly small, however. Biomarker studies show that children of smoking parents have similar levels of hair nicotine, regardless of whether their parents report smoking inside or outside the house.¹²⁷ Non-smoking members of smoking households are unlikely to avoid exposure altogether, even when smokers do not smoke inside the house.

5.2.2.2.4 Misclassification of currently-smoking cohabitants as ex-smokers

Another source of error in determining household smoking status is misreporting of current smokers as ex-smokers. This form of misclassification has not been included in sensitivity analyses, but is likely to further reduce the sensitivity of SHS exposure classification. Households are categorised as non-smoking if members self-report as ex- but not current-smokers; where these households contain current smokers misclassified as ex-smokers, their never-smoking members will be misclassified with respect to domestic SHS exposure.

The end result of these different sources of exposure misclassification is a negative bias of study results. Misclassification of SHS exposure is likely to be non-differential – in other words, the exposed/unexposed distinction is blurred in both directions – so any real mortality difference between the two exposure groups will be diluted. Although it was not possible to measure or correct for the above sources of error, I am confident that they have not inflated the observed association between domestic passive smoking and mortality.

5.2.2.3 Mortality and cause of death: potential for misclassification of outcome

5.2.2.3.1 *Misclassification of vital status*

There is some potential for misclassification of outcome in this study. The primary outcome of interest is death, which is seldom misdiagnosed; however there is potential for misclassification of subjects' vital status, since documentation of death in the study cohort relies on linkage of census and mortality records.

Misclassification of vital status is unlikely to significantly bias the results of this study, as this form of misclassification has been minimised through the application of linkage weights. Linkage weights correct study data for undercounting of deaths due to unlinked mortality records (see Chapter 3: 3.2.1 for methodology and underlying rationale). Since all study analyses are based on weighted data, the potential for misclassification of mortality outcome is minimal.

The impact of linkage weighting was slightly greater for subjects with domestic SHS exposure, suggesting that misclassification of vital status (in unweighted data) was greater for the exposed part of the cohort. This effect was expected, as the cohort with household SHS exposure represented a younger population group with a higher proportion of Māori and Pacific peoples (see Table 7 pg 79). These characteristics are associated with lower linkage of census and mortality records, and thus attract higher linkage weights to account for undercounting of deaths.¹¹⁷

5.2.2.3.2 *Misclassification of cause of death*

It is possible that cause of death was misclassified for a portion of study subjects. For those subjects who died during follow-up, cause of death was derived from the relevant mortality record, which in turn was informed by the death certificate (completed by a medical doctor). Post-mortem examination is undertaken in around 8% of deaths in New Zealand;¹²⁸ for the remaining 92%, cause of death is determined solely on the basis of past medical history and clinical findings. A New Zealand study comparing data from death certificates and a population disease register found

that death certificates in the early 1980s had a sensitivity of 91% in identifying ischaemic heart disease as the cause of death for decedents less than 65 years old.¹²⁹ Even where death certificates have a high degree of accuracy there will inevitably be a proportion of decedents for whom cause of death is misclassified.

Misclassification of cause of death will not affect the association between domestic SHS exposure and all-cause mortality, but it may bias the association with mortality from specific causes. This bias is unlikely to be differential by domestic SHS exposure itself (which in many cases will be unknown to the doctor completing the death certificate); however there may be some differentiation by other factors associated with passive smoking, such as lower socio-economic position. For example, individuals from an advantaged socio-economic position may be more likely to have health symptoms investigated and diagnosed, and so may be more likely to have a particular cause of death (such as lung cancer) recorded on their death certificate.

Since mortality rate ratios have been adjusted for most recognised sources of confounding in the passive smoking-mortality relationship, misclassification of cause of death is unlikely to be substantially differential by domestic SHS exposure. If misclassification is indeed non-differential, it will tend to dilute any true passive smoking-mortality association at the disease-specific level. The extent of such misclassification bias in this study is probably small.

5.2.2.4 Quantifying misclassification: sensitivity analyses

Sensitivity analyses were undertaken in order to gain an idea of the likely magnitude of misclassification bias and its effect on the observed association between domestic passive smoking and mortality. Results of these analyses are presented in Table 14 and Table 15 (pg 99).

As discussed above, there are many potential sources of misclassification error in this study. In undertaking sensitivity analyses I sought to model the effect of the two

sources most likely to distort study results: ie misclassification of personal smoking status and misclassification of SHS exposure status.

5.2.2.4.1 Correcting for misclassified personal smoking status

Misclassification of personal smoking status is likely to be differential by household smoking status, and therefore inflate the relative risk estimate for never-smokers with domestic exposure to SHS. Correction for this misclassification thus reduces the magnitude of the RR estimate. Two different methods of correction were used: the first of these assumes a *constant mortality rate* amongst active smokers regardless of SHS exposure, and the second assumes a *constant RR effect* regardless of personal smoking status. The true situation is likely to lie somewhere between these two positions; thus the outcomes of the two correction methods may be seen as bracketing the likely true effect of correcting for misclassified personal smoking status.

Correction for misclassification of personal smoking status reduces but does not eliminate the excess risk of mortality observed in those with domestic SHS exposure. The most likely value for misclassification of personal smoking status was based on empirical estimates from studies in several countries outside New Zealand.⁶⁷ Thus it was assumed that 1.7% of current smokers misreport their smoking status as never-smokers, and that 6.8% of ex-smokers misreport as never-smokers. Using these estimates, correction for misclassified smoking status by the first method reduced the excess mortality estimate for passive smokers by around a third. Correction by the second method reduced the estimate by almost two thirds. These results suggest that misclassification of personal smoking status is likely to account for less than half of the excess mortality seen in those with SHS exposure.

5.2.2.4.2 Correcting for misclassified passive smoking exposure

Misclassification of SHS exposure will negatively bias the observed association between passive smoking and mortality, since this form of bias is likely to be non-differential by exposure status. Correction for this misclassification therefore

increases the relative risk estimate for those with household passive smoking exposure.

It is difficult to make an informed estimate of the likely degree of misclassification with respect to SHS exposure. As discussed above (section 5.2.2.2), there are multiple potential sources of misclassification in attempting to delineate those with and without exposure to SHS. In many ways, the distinction between 'exposed' and 'unexposed' individuals is an artificial one, since virtually everyone has some degree of SHS exposure and the best one can hope for is to determine who is more and who is less exposed.

For the purposes of sensitivity analysis, I have assumed that SHS exposure classification in this study had a sensitivity around 88% and a specificity around 94%. (For justification of these estimates see Chapter 3: 3.5.2.) These values do not take account of all possible sources of measurement error, and may therefore underestimate the degree of exposure misclassification. Nevertheless, sensitivity analyses based on these values indicate the likely magnitude of bias arising from misclassification of SHS exposure.

Correction for misclassification of SHS exposure increases the relative risk estimate for mortality amongst those with passive smoking exposure. Based on the figures given above, the estimated excess risk of mortality amongst those with domestic SHS exposure increased by over two thirds. This suggests that exposure misclassification results in a significant underestimation of the association between passive smoking and mortality.

In conclusion, misclassification bias (considered for all sources simultaneously) is very unlikely to produce a false association between SHS exposure and mortality, and may actually result in the association being underestimated. Misclassification of personal smoking status and misclassification of SHS exposure will bias study results in opposite directions, so each tends to cancel out the other. While sensitivity analyses cannot exactly quantify the effect of misclassification bias, they do strengthen the evidence for a true association between passive smoking and mortality independent of such bias.

5.2.3 Confounding

Using regression analysis, study data were adjusted for most factors recognised as potential confounders in the passive smoking-mortality relationship. There may still be some residual confounding from lifestyle factors not patterned by socio-economic position, and from unknown confounders. Residual confounding could have produced a positive bias in study results; if such bias is present, however, its magnitude is probably small.

5.2.3.1.1 Age and ethnicity

All study data were controlled for age and ethnicity. Data in Table 8 (pg 81) and Table 9 (pg 83) show that both these factors are potential confounders in the relationship between domestic SHS exposure and mortality. Age acts as a negative confounder, since mortality increases with age and never-smokers from smoking households tended to be younger than those from non-smoking households. Ethnicity acts as a positive confounder, since the group with domestic SHS exposure contained a higher proportion of Māori and Pacific peoples in whom mortality is higher than for non-Māori non-Pacific.

5.2.3.1.2 Marital status and household composition

Marital status was controlled using regression analysis. Marital status differed by domestic SHS exposure, with current marriage more common in those from smoking households and previous or no marriage more common in those from non-smoking households. This pattern reflects categorisation of household smoking status; never-smokers living alone or with no other adults would invariably be classified as unexposed with respect to domestic SHS, while those in the exposed group must (by definition) be living with other adults 15 years or over.

The above pattern creates the possibility of confounding by household composition. All subjects living alone must logically have been classified as unexposed. Thus if there were an independent association between living alone and health status, this could confound the relationship between household SHS exposure and mortality.

In practice, any confounding by household composition has probably been minimised through controlling for marital status. The potential for such confounding could have been further reduced by restricting the study cohort to those subjects living with at least one other adult. The benefits of such a restriction (in terms of reduced potential for confounding) are probably outweighed by the reduction in study power.

5.2.3.1.3 Socio-economic position

The use of census data made it possible to measure and control for a variety of factors related to socio-economic position (SEP). Low socio-economic position is a potential confounder in the relationship between passive smoking and mortality, since those with SHS exposure generally represent a more materially deprived group than those without exposure. This was true of the cohorts in this study: never-smokers living in smoking households were more likely to have no formal qualifications and to live in a more deprived neighbourhood compared to those in non-smoking households. (Interestingly, household income showed a broadly similar distribution across the exposed and unexposed cohorts, although this variable was more likely to be missing for smoking households.) Socio-economic indicators included in the regression model were education, household income (equivalised for number of household members), car access, housing tenure, labour force status and small area deprivation (New Zealand Deprivation index).

Interestingly, the addition of socio-economic position to the regression model made very little difference once relative risk estimates had been controlled for age, ethnicity and marital status. There are three possible explanations for this observation:

- i) In limiting the study cohort to never-smokers I selected a restricted group in whom socio-economic variability was less than for the general population;

- ii) The correlation between socio-economic position and passive smoking is less pronounced than that for socio-economic position and active smoking;
- iii) Within the study cohort, socio-economic position may be largely patterned by other factors (such as ethnicity) for which control had already been applied. (Socio-economic variables were not included in any regression model without age, ethnicity and marital status, so it was not possible to examine the effect of SEP independent of these other factors.)

The first explanation is supported by Table 7 (pg 79), which shows a broadly similar income distribution for both smoking and non-smoking households. Elements of the second and third explanations may also apply.

5.2.3.1.4 Unmeasured confounders

Overseas studies have found that never-smokers with SHS exposure tend to have less healthy lifestyles than those without exposure, creating the potential for confounding of the passive smoking-mortality relationship.¹⁴ It was not possible to control directly for lifestyle differences between the two SHS exposure groups in this study, as information on diet and other behaviours was not included in census records. In controlling for socio-economic position, however, at least some of the potential confounding from differential lifestyle has probably been controlled by proxy, since lifestyle factors (such as diet) tend to be distributed in parallel with SEP.^{84 85}

The use of socio-economic position as a proxy marker of lifestyle is supported by studies undertaken in Italy and the United States,^{28 89 90} which found little evidence of lifestyle differences between non-smokers with and without household SHS exposure once adjustment had been made for socio-economic position. Matanoski found that non-smoking women whose husbands smoked were more likely to have poor diets and heavy alcohol consumption compared with those whose husbands did not smoke; after controlling for education, these associations all but disappeared.²⁸ It should be noted, however, that the SEP-mortality relationship may differ slightly from one country to the next, so that evidence from overseas studies may not be directly applicable to the New Zealand population.

There may be some residual confounding where behaviours such as diet are not patterned by socio-economic factors included in the regression model. It seems unlikely that such confounding would have a substantial effect, however, since the adjusted relative risks changed very little with each iteration of the regression model (see Table 12 pg 93). This suggests that factors added in later models (such as marital status and socio-economic position) exerted little confounding once age and ethnicity (included in earlier models) had been controlled. In other words, the two exposure groups appear similar in most other respects once differences in age and ethnicity have been taken into account.

In observational studies there is always the potential for confounding due to unrecognised or unmeasured characteristics that are distributed differentially by the exposure of interest. The effect of such unmeasured confounding cannot be excluded in this study, but it is unlikely to be great (for reasons given above).

5.2.4 Summary: potential sources of systematic error

Table 16 summarises potential sources of systematic error. The likely direction and magnitude of resulting biases are indicated in the second and third columns.

Table 16: Sources and effects of systematic error

Type of Error	Likely direction of bias on RR estimates	Likely magnitude of effect
Selection bias	?	+
Misclassification of personal smoking status	↑	++
Misclassification of SHS exposure status	↓	+++
Misclassification of death / cause of death	↓	+
Residual confounding	↑	+

5.2.5 Short duration of follow-up

Another potential limitation of this study is the relative short duration of follow-up. Cohort members were followed for mortality during the three years after the census - a relatively short period compared with seven- to 12-year follow-up for most other studies of SHS exposure and mortality (Table 1 pg 7).

Cohort studies with short follow-up run the risk of measuring outcomes too soon after measuring exposure. Diseases such as cancer and ischaemic heart disease develop over years or even decades; where these conditions are the most likely sources of excess mortality, the exposure of interest (in this case passive smoking) should ideally be measured several years before.¹¹¹ SHS exposure at the time of the 1981 and 1996 censuses will have been too recent to influence many of the deaths occurring in the subsequent three years. In this study, passive smoking exposure at the time of the census essentially represents a proxy measure of an individual's historical passive smoking exposure.

This limitation may be regarded as a type of misclassification error. Cohort members will be misclassified with respect to exposure if their SHS exposure on the night of the census differs from their exposure over the preceding years or decades. Exposure misclassification will be greater for diseases of long latency (such as lung cancer), and less where tobacco exposure exerts late-stage effects (eg in cardiovascular disease). (Disease processes are discussed in section 2.2.4.1 of the Literature Review, pg 41.)

In both cases, the effect of exposure misclassification will be to reduce the observed association between household SHS exposure and mortality. Exposure misclassification will be non-differential (ie 'true exposed' and 'true non-exposed' groups will be equally affected); thus any true association between SHS exposure and mortality will be diluted. In terms of disease-specific mortality, this effect will be greatest for diseases of long latency.

Despite the short duration of follow-up, this study demonstrates an association between household SHS exposure and mortality. If follow-up had continued for more

than three years, it is possible that I might have found a stronger association between SHS exposure and mortality (since follow-up would more closely resemble the latency period of tobacco-related diseases, thus reducing exposure misclassification). This benefit should be weighed against the likelihood of less complete follow-up with a longer study. Interestingly, the British Doctors' Study revealed an association between active smoking and mortality only three years after it was started (by which time only 789 deaths had occurred in a cohort of 24,389 male doctors aged 35 years or more).¹

5.2.6 Generalisability

The results of this study reflect the experience of a particular population at two particular points in time. While the effects of SHS exposure are likely to be consistent (regardless of where exposure occurs), potential differences should be borne in mind when applying results from this study to populations experiencing SHS exposure in non-domestic settings. Care should also be taken in applying these results to populations in other countries and at different points in time.

Exposure to SHS in the home is likely to produce the same qualitative health effects as exposure occurring in other settings. The *strength* of these effects may differ where the intensity of exposure varies: with less intense exposure one would expect the effects to be less pronounced, and *vice versa*. Biomarker studies from the USA have shown that non-smokers exposed to SHS in the workplace experience a similar average intensity of exposure to non-smokers living in smoking households.^{60 61} The intensity of workplace SHS exposure in other populations will be influenced by local regulations and practices governing smoking in the workplace, and may differ between occupational groups.¹³⁰ SHS exposure in other environments will be influenced by the size of the space in which exposure occurs, the number of people present (both smoking and non-smoking), the amount of ventilation, proximity to the smoking source, and the duration of exposure.⁵¹ These factors should be borne in mind when extrapolating the results of this study to SHS exposure in non-domestic settings.

Results from this study are likely to be broadly applicable to other developed countries, with a few reservations. Since it includes all New Zealand census records, the NZCMS has a study cohort very close to the entire population of New Zealand (Statistics New Zealand estimates the 1996 census was completed by 98.4% of all NZ residents¹³¹). The results of this study may therefore be seen as representing the experience of all New Zealand never-smokers in the 45-77 year age group. This experience is likely to be broadly similar to that of populations in other developed countries. Discrepancies may exist, however, where there are differences in patterns of tobacco usage, living and working conditions, and background risk factors and mortality rates.

The effect of domestic SHS exposure may also vary for different points in time. Temporal differences in effect may arise from the same sources that produce inter-country variation – ie changing tobacco usage (including intensity of consumption), changing social and occupational circumstances, and changes in the underlying risk profile of the population. These possibilities prompted the independent analysis of data from the 1981 and 1996 census cohorts. Differences between the two cohorts are discussed in the next section.

5.3. Interpretation of study results

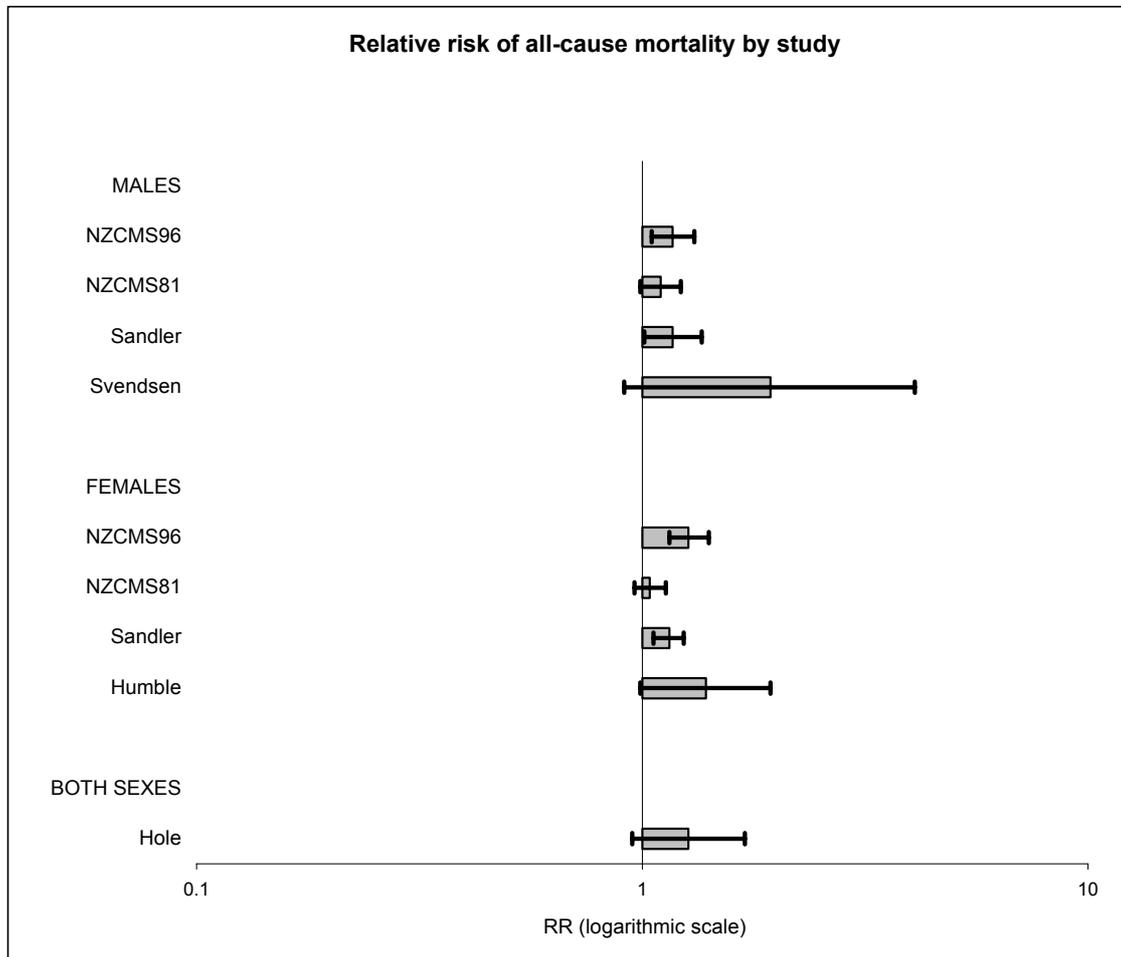
This section discusses the results of this study in the context of existing evidence on passive smoking and mortality. Study power is greatest for the primary outcome of interest – all-cause mortality – for which this is the largest study to date. Results for all-cause mortality are credibly consistent for both study cohorts and both sexes. Power is somewhat less for disease-specific mortality, but consideration of overall patterns provides some insight into which conditions are likely to make the greatest contribution to excess mortality in those with passive smoking exposure.

5.3.1 All-cause mortality

This study provides good evidence for a positive association between domestic exposure to SHS and mortality. In both cohorts and both sexes, all-cause mortality was higher in never-smokers with domestic SHS exposure. Mortality rate ratios (standardised by age and ethnicity) were 1.10 (95% CI 0.99-1.22) for 1981 males, 1.17 (1.05-1.31) for 1996 males, 1.04 (0.96-1.13) for 1981 females and 1.27 (1.15-1.41) for 1996 females. This association is very unlikely to be accounted for by systematic error (including misclassification bias and residual confounding).

These results make a significant contribution to the existing evidence for a passive smoking-mortality association. Figure 14 shows results from this study alongside results from published studies of SHS exposure and all-cause mortality (presented earlier in Chapter 2: Figure 1 pg 8).

Figure 14: Relative risk estimates for all-cause mortality in non-smokers with SHS exposure - published studies plus NZCMS data



The null value (no association) is indicated by the vertical line at RR = 1. Error bars indicate 95% confidence intervals around the RR estimate. RRs for NZCMS are standardised rate ratios (standardised by age and ethnicity); RRs for other studies are multivariable-adjusted relative risk estimates.

Results from this study are very similar to those reported by Sandler et al, who conducted the largest previous study of all-cause mortality in passive smokers. In Sandler's study, the relative risk of mortality amongst never-smokers with domestic SHS exposure was 1.17 (95% CI 1.01-1.36) in males and 1.15 (1.06-1.24) in females.²¹ Taken together, these studies show a consistent effect from household passive smoking exposure, with excess mortality in the order of 15%.

5.3.1.1 Differences between 1981 and 1996 cohorts

The association between household SHS exposure and mortality was generally stronger for the 1996 than for the 1981 cohort. In the 1981 cohort, standardisedⁱⁱⁱ mortality rate ratios were 1.10 and 1.04 for males and females respectively, compared with corresponding values of 1.17 and 1.27 in the 1996 cohort.

There are three possible explanations for this effect difference between the earlier and later cohorts: i) The different estimates may simply reflect random error (note that confidence intervals for the two cohorts are overlapping); ii) The difference may be artefactual, due to the greater influence of bias in one or other cohort; iii) The different RR estimates may reflect real differences in the effect or intensity of SHS exposure at these two periods in time.

5.3.1.1.1 *Differential misclassification by census cohort*

There is reason to suppose that misclassification of SHS exposure may have been greater in the earlier cohort. In 1981, smoking was relatively ubiquitous and most non-smokers would have been exposed to SHS in a number of settings. The introduction of smoking restrictions in public areas in the early 1990s and a general decline in the social acceptability of smoking during the 1980s and 90s meant that SHS exposure outside the home was likely to be considerably less by 1996.¹³² Household smoking status may therefore provide a more accurate proxy for overall SHS exposure in 1996 than it did in 1981. Greater misclassification of SHS exposure in the 1981 cohort may have caused greater negative bias of the association between household smoking status and mortality.

Another way of describing this ‘misclassification’ is to consider the amount of passive smoking experienced by the reference group (ie never-smokers from non-smoking households). In 1981, smoking was common in most social settings (including the workplace), and almost all adults would have experienced significant SHS exposure. Thus in the 1981 cohort, the reference group would have had a significant degree of

ⁱⁱⁱ Standardised by age and ethnicity.

SHS exposure and (probably) SHS-related mortality. The effect of this is to diminish any mortality difference between the 'reference' and 'exposed' cohort groups. By 1996, changing regulations and social expectations meant that smoking had become a more segregated activity, with non-smokers less likely to be exposed to SHS in workplace or social settings. Thus in the 1996 cohort, the reference group was probably more truly 'unexposed', creating a clearer distinction between the groups with and without SHS exposure with a clearer difference in mortality.

5.3.1.1.2 Different SHS effects across time

It is possible that the effect of domestic SHS exposure was greater in 1996 than in 1981, although this would contradict expected changes in exposure intensity. Average tobacco intake declined during the 1980s and 90s,¹³³ so the amount of second-hand smoke produced by each smoker was probably less in 1996 than in 1981. Furthermore, one would expect that smokers in the late 1990s were less inclined to smoke in the presence of non-smokers, due to growing public awareness of the possible health effects of passive smoking. Differences in cigarette production may possibly have changed the quality of second-hand smoke from 1981 to 1996.

On balance, I believe that greater exposure misclassification is the most likely reason for a smaller effect size in the 1981 cohort. Although confidence limits are overlapping, it seems unlikely that both males and females from the 1981 cohort would show a weaker SHS-mortality effect due to chance alone. A greater SHS effect in 1996 would be counterfactual to the expected pattern of exposure intensity. It is worth noting that the census smoking question was slightly different in 1981 and 1996 (see pg 53), although the effect of this difference on exposure classification is difficult to predict.

5.3.2 Disease-specific mortality

A secondary aim of this study was to measure the association between domestic exposure to SHS and disease-specific mortality. Study power is limited by relatively few outcomes at the disease-specific level, and 95% confidence limits include 1.0 for most relative risk estimates. Nevertheless, by looking at patterns of mortality over both cohorts and sexes it is possible to gain a sense of which diseases are likely to account for the elevated mortality risk seen in those with domestic SHS exposure.

The following discussion refers to data presented in Chapter 4: Table 11 (pg 88), Figure 11 (pg 89), Figure 12 (pg 90), and Table 13 (pg 96).

5.3.2.1 Cardiovascular disease

Cardiovascular disease appears to make the most significant contribution to excess mortality amongst passive smokers. Amongst never-smokers with domestic SHS exposure, mortality from cardiovascular disease was elevated in all groups except females from the 1981 cohort. The age- and ethnicity-standardised RR for cardiovascular mortality in these groups was 1.14 (95% CI 0.99-1.30) for 1981 males, 1.22 (1.03-1.46) for 1996 males, 0.99 (0.87-1.12) for 1981 females, and 1.31 (1.09-1.58) for 1996 females.

‘Cardiovascular disease’ refers to both cerebrovascular and ischaemic heart disease, as well as other diseases of the circulatory system such as peripheral vascular disease and venous thromboembolism (see Table 4 pg 60 for ICD codes). By grouping together deaths from all these conditions the number of outcomes is increased, enhancing study power and thus its ability to demonstrate a non-random association with passive smoking. The disadvantage of this approach is that one cannot distinguish between cardiovascular diseases of differing aetiology which may differ in their relationship with passive smoking.

5.3.2.1.1 *Ischaemic heart disease*

The majority of cardiovascular deaths are due to ischaemic heart disease (IHD). The risk of IHD mortality was elevated in passive smokers from the 1996 but not the 1981 cohort (although confidence limits around the rate ratio include 1.0 for all four study groups). In females from 1996, the association between domestic SHS exposure and IHD mortality was of similar magnitude to that reported for passive smoking and incident IHD,^{6 7 32 40} with a standardised RR of 1.26 (95% CI 0.98-1.63). Males from the 1996 cohort showed a somewhat weaker association between domestic SHS exposure and IHD mortality, with a standardised RR of 1.07 (95% CI 0.86-1.32). The absence of any difference between exposed and unexposed groups in the 1981 cohort may reflect greater misclassification bias in this cohort.

Results for IHD mortality in this study are presented alongside the results of published studies in Figure 15 (at the end of this section).

5.3.2.1.2 *Cerebrovascular disease*

Cerebrovascular disease was the next most significant component of cardiovascular mortality. Mortality from cerebrovascular disease was significantly elevated in males from both cohorts, with a standardised RR of 1.59 (95% CI 1.14-2.21) in 1981 men and 1.91 (1.23-2.96) in 1996 men. These compare with reported relative risk estimates of around 1.8 for incident stroke.^{43 44} The association between SHS exposure and cerebrovascular mortality was much weaker in women, in whom the standardised RR was 0.88 (95% 0.66-1.17) in 1981 and 1.16 (0.75-1.79) in 1996.

In this study it was not possible to distinguish between ischaemic and haemorrhagic stroke as a cause of death, since these were grouped together under cerebrovascular mortality. The two forms of stroke have different aetiologies, with ischaemic stroke bearing a closer resemblance to other atherosclerotic conditions such as ischaemic heart disease. The two forms of stroke may therefore differ in their relationship with SHS exposure. In future studies it may be useful to distinguish between ischaemic and haemorrhagic stroke so that the association with passive smoking may be examined independently for each.

5.3.2.2 Lung cancer

Lung cancer mortality was elevated amongst passive smokers in the 1996 but not the 1981 cohort. The small number of lung cancer deaths is reflected in relatively wide confidence intervals around RR estimates for all four study groups. Results are shown alongside RR estimates from published studies in Figure 15 (pg 131).

In 1996 cohort members with household SHS exposure the standardised RR for lung cancer mortality was 1.45 in men and 1.16 in women. These values are broadly comparable with the relative risk of incident lung cancer in passive smokers (around 1.3).^{5 38 39} This finding is perhaps rather surprising, given the short duration of study follow-up relative to the latency period for lung cancer development. Since clinical lung cancer is thought to appear some 20 or so years after the relevant tobacco smoke exposure, one might expect a relatively weak association between lung cancer mortality and domestic SHS exposure at the last census. By restricting the study cohort to census respondents aged 45 years or more, I may have selected a relatively stable population in whom recent domestic SHS exposure bears a reasonably close correlation with exposure some 20 years earlier.

Notwithstanding the above, one would still expect misclassification of SHS exposure to be more significant for lung cancer than for diseases of shorter latency (such as cardiovascular disease). Thus it may be that the rate ratio of lung cancer mortality is underestimated in this study (more so than the RRs for cardiovascular outcomes). Misclassification may account for the absence of an association between household SHS exposure and lung cancer mortality in the 1981 cohort.

5.3.2.3 Respiratory disease

While there were relatively few respiratory deaths in the study cohort, respiratory mortality showed a fairly consistent association with domestic SHS exposure (although confidence intervals include the null value for all groups). In the 1996 cohort, the standardised RR of respiratory death in domestic passive smokers was 1.72 (95% CI 0.99-2.98) for men and 1.75 (0.99-3.10) for women.

Other studies have also found an association between passive smoking and respiratory mortality. Sandler and Helsing reported relative risk estimates of 1.44 (95% CI 0.75-2.75) in men and 1.21 (0.87-1.69) in women.²¹ In the recently published paper by Enstrom and Kabat, chronic obstructive respiratory disease was the only disease to show elevated mortality in non-smokers married to smoking spouses, with RR estimates of 1.28 (95% CI 0.72-2.27) in men and 1.13 (0.80-1.58) in women. These data suggest that respiratory disease is a possible cause of elevated mortality in passive smokers. Future studies should include respiratory disease and mortality as outcomes of interest.

5.3.2.4 Non-lung cancer

Mortality from non-lung cancer was slightly elevated amongst passive smokers in several groups. Females from the 1996 cohort showed the greatest association between domestic SHS exposure and non-lung cancer mortality, with a standardised RR of 1.23 (95% CI 1.06-1.42) in those from smoking households.

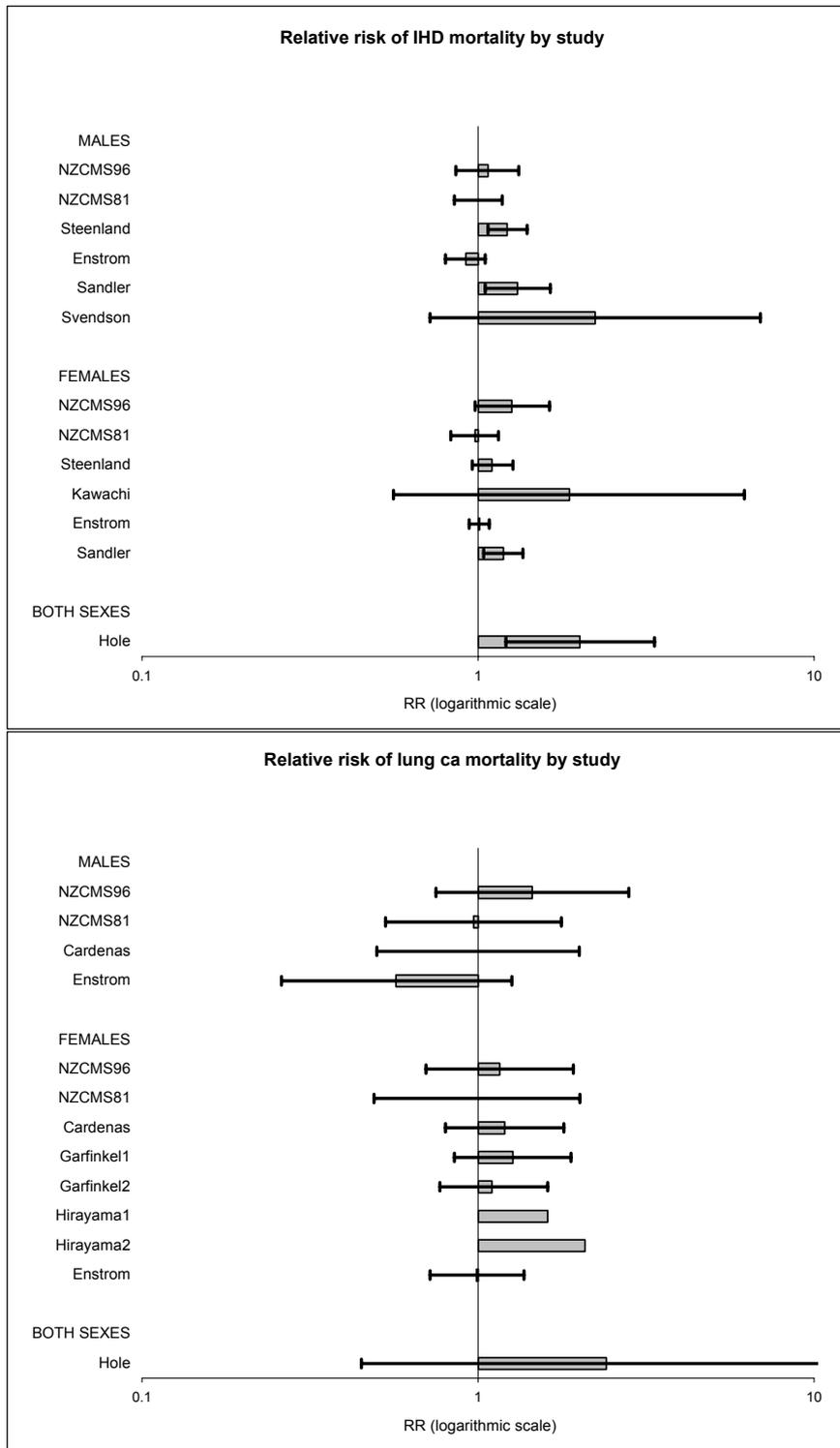
Apart from being a chance finding, there are two possible explanations for the apparent association between passive smoking and non-lung cancer in the 1996 female cohort. While lung cancer is the malignancy most commonly coupled with active smoking, there are other forms of cancer for which tobacco exposure is a risk factor. These may give rise to a true association between SHS exposure and non-lung cancer. The alternative explanation is that the apparent association is artefactual and has arisen from residual confounding of the passive smoking-mortality relationship.

Active smoking is known to increase the risk of many non-lung cancers. Tobacco exposure is a major risk factor for cancers of the kidney, mouth, pharynx, oesophagus, larynx, pancreas and bladder, with relative risks >3 in active smokers.²⁷ Active smoking is a lesser risk factor for cancers of the lip, nose, stomach and liver, increasing the incidence of these malignancies up to twice that in non-smokers.²⁷ (The risk of cervical and breast cancer in smoking women is still in contention.¹³⁴⁻¹³⁷) Around 30% of all fatal cancers in the United Kingdom are thought to be attributable to active smoking.²⁷

Given the association between active smoking and non-lung cancer, it seems plausible that these cancers may also have a modestly increased incidence in those with SHS exposure. Non-lung cancers are many times more common than lung cancer, so even a small increase in risk amongst passive smokers may make a substantial contribution to the excess mortality observed in those with SHS exposure. With reference to the US population, Glantz and Parmley estimate that non-lung cancers account for a greater proportion of passive smoking deaths than lung cancer.⁴² It is interesting that the association between SHS and non-lung cancer was observed in women but not men from the 1996 cohort. Possible reasons for this gender difference include: i) chance; ii) an association between SHS and female-specific cancers (such as cervical and breast cancer); and iii) possible gender-specific biases (such as male never-smokers experiencing greater SHS exposure outside the home).

It is possible that the apparent association between domestic SHS exposure and non-lung cancer is due to residual confounding by lifestyle factors. In addition to age and ethnicity, adjustment has been made for several measures of socio-economic status. Lifestyle characteristics such as diet will be controlled for to the extent that they are patterned by socio-economic factors included in the regression model. Without independent data on these lifestyle factors, one cannot exclude the presence of residual confounding due to less healthy behaviour patterns in the SHS-exposed group. In my view, residual confounding is probably minimal in this study (for reasons discussed in section 5.2.3) and is therefore an unlikely explanation for the observed association between passive smoking and non-lung cancer mortality in 1996 women.

Figure 15: Relative risk estimates for IHD and lung cancer mortality in non-smokers with SHS exposure - published studies plus NZCMS data



The null value (no association) is indicated by the vertical line at RR = 1.
 Error bars indicate 95% confidence intervals around the RR estimate.
 RRs for NZCMS are standardised rate ratios (standardised by age and ethnicity);
 RRs for other studies are multivariable-adjusted relative risk estimates.
 In lower graph (lung cancer mortality), upper 95% confidence limit for Hole's RR estimate is 12.8

5.4. Passive smoking and mortality: evidence for causality?

The observed association between passive smoking and mortality may be causal or non-causal. Principles suggested by Bradford Hill provide a useful framework for assessing causality. These principles are: strength, consistency, specificity, temporality, dose-response, biological plausibility, coherence, experimental evidence, and analogy.⁷² Temporality (ie the precedence of exposure to disease) is generally viewed as the most important and only necessary criterion.

5.4.1.1 Temporal relationship

Most studies of passive smoking and mortality are cohort studies, in which SHS exposure is determined at baseline and mortality occurs some months or years later. An element of reverse causality is not impossible – for example, the development of disease in one household member may prompt other members to take up or resume smoking in response to stressful domestic circumstances. In the vast majority of households, however, SHS exposure will precede the development of disease and eventual death. (This criterion is not entirely satisfied in cohort studies of short duration – such as my own – where disease development will often have started prior to exposure measurement.)

5.4.1.2 Strength of association

The association between SHS exposure and all-cause mortality is not a strong one, with relative risk estimates converging around 1.15. While this effect is reported fairly consistently (Figure 14 pg 123), such a small association inevitably remains in the shadow of doubt cast by the lurking bogeymen of bias and confounding.

5.4.1.3 Consistency of evidence

The association between passive smoking and all-cause mortality has been reported in several different populations and time periods. Published data come from studies in the United States and the United Kingdom, spanning the period 1960 to 1982.^{11 12 21 24} The NZCMS study extends this evidence base to include the New Zealand population during the early 1980s and late 1990s. Results from this study are consistent with those from the previous largest study of SHS exposure and all-cause mortality, which reported excess mortality in the order of 15% amongst passive smokers.²¹

5.4.1.4 Specificity

Passive smoking is associated with several diseases, including ischaemic heart disease, stroke, lung cancer and respiratory disease. All these diseases are linked to active smoking, and in this instance the association is widely accepted as causal. The lack of specificity for passive smoking is therefore neither surprising nor inconsistent with causality.

5.4.1.5 Dose-response relationship

A dose-response relationship for passive smoking and mortality has not been demonstrated, and indeed would be difficult to demonstrate given the small effect size and the difficulties involved in quantifying SHS exposure. Hackshaw et al report a dose-response relationship between SHS exposure and lung cancer, with risk proportional to both the number of cigarettes consumed in the passive smoker's presence and the duration of regular exposure.⁵ The association between SHS exposure and cardiovascular disease may be non-linear, with tobacco smoke exposure appearing to exert a threshold effect on some atherogenic processes (such as platelet aggregation).^{6 92} Such a relationship is not inconsistent with causality.⁷²

5.4.1.6 Biological plausibility

In my view, there is very good biological evidence for a causal relationship between passive smoking and mortality. Active smoking is a well-established cause of lung cancer, ischaemic heart disease, chronic obstructive pulmonary disease and other fatal

conditions.² Following active smoking, components of cigarette smoke (including nitrogen oxide, carbon monoxide, nicotine and respiratory particles) are present in the indoor environment,¹³⁸ and metabolites of tobacco smoke (such as cotinine) can be measured in non-smokers exposed to that environment.¹³⁹ Thus there is good evidence that passive smokers are exposed to harmful substances similar to those inhaled by active smokers, albeit at a lower dose.

Based on biological markers of tobacco exposure, passive smokers are estimated to have around 1% of the exposure experienced by active smokers of 20 cigarettes per day.^{5,52} The risk of lung cancer observed in passive smokers is very similar to that seen in light active smokers with equivalent exposure from active smoking.⁵ The relationship between smoke exposure and ischaemic heart disease is less linear, but (as with lung cancer) the risk observed in passive smokers is very similar to that seen in light active smokers.⁶ This evidence supports the premise that tobacco smoke exposure carries the same health risks regardless of whether it occurs through active or passive smoking.

Finally, biological processes leading to disease development have been demonstrated in passive smokers. Non-smokers exposed to second-hand smoke have been shown to have increased platelet aggregation, decreased oxygen delivery capacity, and decreased antioxidant levels.^{92,93} Experimental work has found that passive smoke exposure reduces arterial dilatation (a sign of impaired endothelial function).⁵⁶ Increased levels of carcinogenic substances have been found in the body fluids of passive smokers.⁹⁷⁻¹⁰⁰

5.4.1.7 Coherence

The epidemiological, biological and experimental evidence for a causal association between passive smoking and mortality is broadly coherent. Although there are alternative explanations for the observed association between SHS exposure and mortality (such as confounding and bias), there is no evidence that directly conflicts with a causal relationship.

5.4.1.8 Experimental evidence

Human experimental studies of SHS exposure and mortality would be unethical and untenable. There is experimental evidence of impaired physiology in individuals exposed to tobacco smoke either actively or passive (see 5.4.1.6: 'Biological plausibility' above).

5.4.1.9 Analogy

The relationship between passive smoking and mortality is analogous to that between active smoking and mortality. As discussed above, the observed risk of diseases such as lung cancer and ischaemic heart disease in passive smokers is consistent with that seen in light active smokers. Thus it seems highly plausible that passive smoking will produce health effects that are weaker but qualitatively the same as those seen in active smokers.

Mengersen et al provide an alternative assessment of the Bradford-Hill criteria in relation to the health effects of passive smoking.¹⁴⁰ In evaluating the evidence for causality between passive smoking and ischaemic heart disease, the authors conclude that biological plausibility is (probably) satisfied; strength, consistency and specificity are not; and there is insufficient data to judge the remaining criteria. My own view leans more in favour of causality; in considering all the existing evidence on passive smoking and mortality, I believe a causal association is far more likely than a non-causal association.

5.5. Implications for future research and policy

This study makes a substantial contribution to the existing evidence for an association between passive smoking and mortality. There is good reason to believe that this association reflects a causal relationship. These findings therefore have implications for future research, and for tobacco-related public policy.

5.5.1 Future research

5.5.1.1 Health effects of passive smoking

By focussing on all-cause mortality as the main outcome of interest, this study has included diseases other than those traditionally associated with passive smoking. Most studies of passive smoking and mortality have looked solely at deaths from lung cancer and ischaemic heart disease. Few have examined the association between SHS exposure and all-cause mortality, and even fewer have looked at mortality from other tobacco-related diseases. Sandler's is the only published study to include cerebrovascular mortality as an outcome of interest, and Enstrom is the only other author to have considered mortality from respiratory disease.^{10 21}

As well as the association with lung cancer and ischaemic heart disease, results from this study suggest that passive smoking may also be associated with mortality from cerebrovascular disease, respiratory disease and possibly some non-lung cancers. These outcomes should be included in future studies of passive smoking and mortality. It may also be useful to distinguish between haemorrhagic and ischaemic stroke in future studies, as these two conditions have different epidemiological patterns and may differ in their relationship with SHS exposure.

5.5.1.2 Meta-analysis

A formal meta-analysis was beyond the scope of this thesis, but could add much to our understanding of the passive smoking-mortality relationship. Individual studies of

SHS exposure and mortality tend to be constrained by limited study power relative to the small effect size, and many relative risk estimates have wide confidence limits. A pooled estimate would have greater statistical power and would thus provide a more precise measure of the association between passive smoking and mortality (both all-cause and disease-specific). The limitations of published observational studies should be borne in mind in any meta-analysis. For instance, the possibility of publication bias should be acknowledged and accounted for (as far as possible) in examining studies of IHD and all-cause mortality.

5.5.1.3 New Zealand Census-Mortality Study

This study provides further evidence for the value of the New Zealand Census-Mortality Study as a research tool. The NZCMS was originally created in order to examine socio-economic gradients in mortality within New Zealand,¹¹³ but has since become an invaluable source of data for a variety of other research topics including ethnic disparities in mortality,¹⁴¹ historical undercounting of deaths amongst Māori New Zealanders,^{142 143} the association between unemployment and suicide¹⁴⁴, mortality from active smoking in New Zealand,¹²⁴ and the association between bicycle access and mortality.

These research outputs also testify to the value of linked datasets as health research tools, particularly where these datasets are based on comprehensive and high-quality sources such as a national census. Linked datasets based on routinely collected data can provide the study power needed to investigate associations of small size. It is interesting that the largest previous study of passive smoking and all-cause mortality was also based on a linked dataset comprising census and mortality records for a defined population.²¹

5.5.2 Tobacco-related policy

Further evidence of a causal relationship between passive smoking and mortality highlights the need for public protection from second-hand smoke. A relative risk of 1.15 is small in epidemiological terms, but significant in terms of population impact.

Because a large proportion of the population is exposed to second-hand smoke, the resulting burden of disease and mortality is considerable.⁴⁸

Exposure to passive smoking is widespread in New Zealand. A 1996 survey found that household SHS exposure affected 15% of non-smoking men and 17% of non-smoking women, while exposure in the workplace (during working hours) affected 19% of non-smoking men and 6% of non-smoking women.¹³⁰ These figures are similar to those observed in the 1996 NZCMS cohort of never-smokers, in which 14% of men and 15% of women lived in smoking households (see Table 7 pg 79).

In 1990 the New Zealand Parliament passed the Smokefree Environments Act, thus imposing legal restrictions on smoking in public areas and workplaces.^{132 145} While this decreased workplace exposure to second-hand smoke, many workers were (and are) still exposed during working hours, particularly those working in non-office workplaces.¹³⁰ The New Zealand Parliament has just passed an amendment to the original Act which will extend smoking restrictions to all work places (including bars and restaurants).¹⁴⁶ Such an extension is clearly supported by the results of this study, since there is no reason to believe that exposure to SHS outside the home is any less harmful than exposure within the home.

A more problematic issue is the possible imposition of smoking restrictions in private settings. While there is now widespread public support for smokefree workplaces, people are generally less accepting of regulation in their private lives.^{147 148} The introduction of smoking restrictions in private cars could be seen as analogous to the legal requirement for use of seatbelts and child passenger restraints (particularly as deaths in New Zealand from passive smoking are thought to be of the same magnitude as deaths from road crashes⁴⁸). Support for such measures may increase as awareness of the health consequences of passive smoking extends beyond the research community and into the public arena.

Chapter 6: Summary and Conclusions

A number of previous studies have explored the relationship between passive smoking and mortality, but most have been hampered by limited study power, potential (unexplored) bias from exposure misclassification, and uncontrolled confounding. These difficulties are to be expected when investigating any association of small magnitude.

In this study I have attempted to address all three of these limitations. The availability of linked census-mortality records provided a cohort dataset with significant statistical power. The two population cohorts included a total of 668,262 cohort members contributing 19,341 deaths and almost two million person-years of observation. Census records included data on a range of socio-economic factors, making it possible to control for potential differences between the exposure groups in terms of socio-economic position and (by proxy) diet and lifestyle. Finally, sensitivity analyses were undertaken to explore the likely effects of misclassification (for both personal smoking status and SHS exposure status). These analyses suggest that misclassification bias is very unlikely to produce a false association between SHS exposure and mortality, and more probably causes an underestimation of the true association.

The most important finding from this study is that mortality is increased by about 15% in those with domestic exposure to second-hand smoke. The rate ratio of age- and ethnicity-standardised mortality was 1.10 (95% CI 0.99-1.22) in 1981 men, 1.17 (1.05-1.31) in 1996 men, 1.04 (0.96-1.13) in 1981 women and 1.27 (1.15-1.41) in 1996 women. Further adjustment for marital status and socio-economic position had little effect on these relative risk estimates. Cardiovascular disease appears to be the main driver of excess mortality in those with domestic SHS exposure.

The association between domestic SHS exposure and mortality is very unlikely to be due to confounding by factors associated with socio-economic status. It is unlikely (in my view) that residual confounding or misclassification could be that sole explanation for the study findings. Further evidence for causality is provided by the common findings across gender and time, bolstered by existing epidemiological evidence for an increased risk of tobacco-related disease in non-smokers with SHS exposure, and by biological and experimental evidence of physiological disturbance in those exposed to SHS. The likely presence of a causal association between SHS exposure and mortality highlights the need for public protection from the health effects of passive smoking.

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Chapter 7: Appendix

7.1.1 Worked example of correction for misclassified personal smoking status

(see Chapter 3: 3.5.1)

Sensitivity analyses were undertaken using crude data for 45-77 year old males from the 1996 cohort. Within this sub-population, self-reported smoking prevalence was 20.2% current smokers, 39.1% ex-smokers and 40.7% never-smokers. Crude mortality rates (per 100,000 per year) were 1,645 amongst smokers, 1,397 amongst ex-smokers and 788 amongst never-smokers, yielding crude mortality rate ratios of 2.09, 1.77 and 1.00 respectively.¹²⁴

Observed data for self-reported never-smokers are shown below:

	Deaths	Person-time	Mortality*	Mortality RR
Unexposed	3,684	387,292	951	
Exposed	687	63,244	1,086	1.14
Total	4,371	450,536		

*Mortality is expressed as deaths per 100,000 population per year

(Note that in the following calculations, ‘persons’ or ‘numbers’ refer to person-time of observation.)

Misclassification rates are described as in the following table:

		Actual smoking status		
		Current	Ex	Never
Self-reported smoking status	Current	A true smokers		
	Ex	B misclassified smokers	C true ex-smokers	
	Never	D misclassified smokers	E misclassified ex-smokers	F true never-smokers

Misclassification amongst actual current smokers (M_C) is simplified as $D / [A + D]$

Misclassification amongst actual ex-smokers ($M_E = E / [C + E]$)

Misclassification amongst self-reported never-smokers ($M_N = [D + E] / [D + E + F]$)

(Misclassification amongst self-reported never-smokers (M_N) is the sum of

misclassification due to current smokers ($M_{NC} = D / [D + E + F]$) and

misclassification due to ex-smokers ($M_{NE} = E / [D + E + F]$).

Step 1. The misclassification rate amongst actual current smokers in the study population was set.

This example uses a misclassification rate of 1.7% amongst actual current smokers – that is, I have assumed that 1.7% of actual current smokers inaccurately self-reported their smoking status as never-smokers ($D / [A + D]$).

Step 2. Numbers of misclassified current and ex-smokers in the observed cohort were calculated, based on the number of self-reported never-smokers, the prevalence of never, current and ex-smoking in the study population, and the misclassification ratio for actual ex-smokers vs actual current-smokers.

Never-smokers are known to comprise 40.7% of the study sub-population. There are 450,536 (self-reported) never-smokers in the observed cohort; this number of never-smokers corresponds to a total sub-population of 1,106,968 (ie $450,536 / 40.7\% = 1,106,968$). Within the total sub-population, current smokers will comprise 223,608 (ie $20.2\% \times 1,106,968 = 223,608$) and ex-smokers will comprise 432,825 (ie $39.1\% \times 1,106,968 = 432,825$).

The misclassification rate amongst actual current smokers ($D / [A + D]$) has been set at 1.7%. This means that the number of misclassified smokers in our observed cohort is 1.7% of all current smokers in the study sub-population, or $1.7\% \times 223,608 = 3,801$ misclassified smokers.

Misclassification amongst ex-smokers ($E / [C + E]$) is assumed to be four times the rate in current smokers; thus misclassified ex-smokers will number $4 \times 1.7\% \times 432,825 = 29,432$.

(Note that the prevalence rates for the three smoking groups are based on self-reported smoking status, and will thus be affected by misclassification. The above estimates could therefore be improved slightly by iterative recalculation using improved estimates of actual smoking status. However the marginal gain in accuracy from this process would be negligible.)

Step 3. Rates of misclassified current and ex-smokers were calculated for each exposure group in the observed cohort. This was undertaken using basic algebra, based on the (known) total numbers in each exposure group, misclassification rates within the self-reported non-smoking cohort for current and ex-smokers (from Step 2), and the ratio of misclassification in exposed vs unexposed participants.

On the basis of the figures calculated in Step 2, misclassified smokers make up 0.844% of the self-reported never-smoking cohort (3,801 / 450,536) and misclassified ex-smokers make up 6.533% (29,432 / 450,536).

Using basic algebra, misclassification rates are calculated for the SHS-exposed and SHS-unexposed cohorts. The formula for the misclassification rate amongst the unexposed cohort is as follows (the algebraic derivation for this formula is outlined in section 7.1.2):

$$M_U = \frac{M_T C}{A + RB}$$

Where:

	Person-time	
Unexposed	A	M_U = misclassification rate in unexposed cohort
Exposed	B	M_T = misclassification rate in total cohort
Total	C	R = ratio of misclassification in exposed vs unexposed cohorts (assumed to be 3:1)

Using this formula, misclassified current- and ex-smokers are calculated as a percentage of self-reported never-smokers in each SHS exposure category (ie M_{NC} and M_{NE}). In the SHS unexposed cohort, misclassified actual smokers make up 0.659% of self-reported never-smokers - ie $[0.844\% \times 450,536] / (387,292 + [3 \times 63,244]) = 0.659\%$. In the SHS exposed cohort, misclassified actual smokers make up three times this amount – ie $3 \times 0.659\% = 1.977\%$.

In the SHS unexposed cohort, misclassified ex-smokers make up 5.101% of self-reported never-smokers - ie $[6.533\% \times 450,536] / (387,292 + [3 \times 63,244]) = 5.101\%$). In the SHS exposed cohort, misclassified ex-smokers make up 15.303% of self-reported never-smokers ($3 \times 5.101\% = 15.303\%$).

Step 4. Numbers of misclassified current and ex-smokers and true never-smokers were calculated for each exposure group in the observed cohort, based on the misclassification rates calculated in Step 3.

Person-time by smoking status of individuals in observed cohort				
	Total observed	Current-	Ex-	Never-smokers
SHS Unexposed	387,292	2,551	19,754	364,986
SHS Exposed	63,244	1,250	9,678	52,316

Within the unexposed cohort, misclassified smokers number $(0.659\% \times 387,292) = 2,551$. Misclassified ex-smokers are $(5.101\% \times 387,292) = 19,754$.

Within the exposed cohort, misclassified smokers are $(1.977\% \times 63,244) = 1,250$. Misclassified ex-smokers are $(15.303\% \times 63,244) = 9,678$.

Person-time in the true never-smoking cohort can now be calculated by simple subtraction. True never-smokers without SHS exposure number 364,986 ($= 387,292 - 2,551 - 19,754$). True never-smokers with SHS exposure number 52,316 ($= 63,244 - 1,250 - 9,678$).

Method A (assumes that mortality amongst current and ex-smokers is constant regardless of SHS exposure):

Step 5. The numbers of deaths amongst misclassified current and ex-smokers were calculated, based on the numbers in each group and the (known) mortality rates for current and ex-smokers within the same study population.

This step is most easily shown using 2x3 tables.

Misclassified smokers

	Deaths	Person-time	Mortality*
Unexposed	42	2,551	1,645
Exposed	21	1,250	1,645

Misclassified ex-smokers

	Deaths	Person-time	Mortality*
Unexposed	276	19,754	1,397
Exposed	135	9,678	1,397

*Mortality is expressed as deaths per 100,000 population per year

The numbers (ie person-time) in each category have been calculated in Step 4 above. Mortality rates are known; from these it is possible to calculate the number of deaths in each exposure group for misclassified current and misclassified ex-smokers.

Step 6. Finally, the numbers of deaths amongst true never-smokers (with and without SHS exposure) were calculated, followed by the mortality rate for each exposure group and the true relative risk for those with SHS exposure.

For the true never-smoking cohort, the numbers of deaths in each SHS exposure group are calculated by subtracting deaths in the misclassified current- and ex-smoking cohorts from total deaths in the observed cohort (see below).

Observed data

	Deaths	Person-time	Mortality*
Unexposed	3,684	387,292	951
Exposed	687	63,244	1,086

True never-smokers

	Deaths	Person-time	Mortality*
Unexposed	3,366	364,986	922
Exposed	531	52,316	1,015

*Mortality is expressed as deaths per 100,000 population per year

Using death and person-time counts in the true never-smoking cohort it is then possible to calculate the mortality rate in each exposure group, and so the true mortality rate ratio for exposed compared with unexposed non-smokers. This is equal to $1,015 / 922 = 1.10$.

Method B (assumes that the relative risk of mortality from SHS exposure is constant regardless of personal smoking status):

Step 5. The numbers of deaths amongst misclassified current and ex-smokers were calculated, based on the numbers in each group, the numbers of observed deaths in each exposure group and the (known) mortality rate ratios for current and ex-smokers within the same study population.

Within each SHS exposure group, the number of deaths in each smoking category is calculated according to the following formulae (the algebraic derivation for these formulae is outlined in section 0):

$$D_C = \frac{D_T}{1 + \frac{P_E RR_E}{P_C RR_C} + \frac{P_N}{P_C RR_C}} \quad D_E = \frac{D_T}{1 + \frac{P_C RR_C}{P_E RR_E} + \frac{P_N}{P_E RR_E}}$$

Where:

Smoking Status of individuals in observed cohort

	Total	Current-smokers	Ex-smokers	Never-smokers
Deaths	D_T	D_C	D_E	D_N
Person-Time	P_T	P_C	P_E	P_N
Mortality Rate Ratio	RR_T	RR_C	RR_E	RR_N

We know the total number of deaths (D_T) in each SHS exposure category, and the mortality rate ratios (RR) for both current- and ex-smokers. Since we have calculated person-time (P) for each subgroup in Step 4 above, we can solve the above equations to give the number of deaths in each SHS exposure group within each smoking category.

Misclassified smokers

	Deaths	Person-time	Mortality RR*
Unexposed	48	2,551	2.09
Exposed	25	1,250	2.09

Misclassified ex-smoker

	Deaths	Person-time	Mortality RR*
Unexposed	318	19,754	1.77
Exposed	164	9,678	1.77

*Mortality rate ratios refer to true never-smokers as the reference group.

Step 6. Finally, the numbers of deaths amongst true never-smokers (with and without SHS exposure) were calculated, followed by the mortality rate for each exposure group and the true relative risk for those with SHS exposure.

The number of deaths amongst true never-smokers is now calculated by simple subtraction. For true never-smokers without SHS exposure, the number of deaths is 3,317 (= 3,684 – 48 – 318). For those without SHS exposure, deaths are equal to 499 (= 687 – 25 – 164). The true mortality rates amongst never-smokers with and without SHS exposure can now be calculated. These yield a RR of 953/909 = 1.05.

Observed data				True never-smokers			
	Deaths	Person-time	Mortality*		Deaths	Person-time	Mortality*
Unexposed	3,684	387,292	951	Unexposed	3,317	364,986	909
Exposed	687	63,244	1,086	Exposed	499	52,316	953

*Mortality is expressed as deaths per 100,000 population per year

7.1.2 Formula for calculating misclassified smokers and ex-smokers as a proportion of self-reported never-smokers

Section 7.1.1 above demonstrates the method used to correct observed data for misclassification of personal smoking status. Step 3 of this method involves calculating the misclassification rates for actual current- and ex-smokers as a proportion of self-reported never-smokers, according to SHS exposure status. This process uses the following formula:

$$M_U = \frac{M_T C}{A + RB}$$

Where:

	Observed Data	Misclassified current or ex-smokers
	Person-time	
Unexposed	A	D
Exposed	B	E
Total	C	F

And: M_U = misclassification rate in unexposed cohort

M_E = misclassification rate in exposed cohort

M_T = misclassification rate in total cohort

R = ratio of misclassification in exposed vs unexposed cohorts

From the above, it can be seen that:

$$1. M_U = \frac{D}{A} \quad 2. M_E = \frac{E}{B} \quad 3. M_T = \frac{F}{C} \quad 4. D + E = F \quad 5. M_E = RM_U$$

By rearranging and substituting equation 4 into equation 1, and equation 5 into equation 2, we can derive the following:

$$6. M_U = \frac{F - E}{A} \quad 7. E = RBM_U$$

Similarly, by rearranging and substituting equation 3 into equation 6 we get the following:

$$8. M_U = \frac{M_T C - E}{A}$$

Finally, we can substitute equation 7 into equation 8 and rearrange this to create the formula for misclassification amongst the unexposed cohort:

$$9. M_U = \frac{M_T C}{A + RB}$$

7.1.3 Formulae for calculating number of deaths amongst misclassified current- and ex-smokers, Method B

Observed data is corrected for misclassification of personal smoking status, as outlined in section 7.1.1 above. Method B uses known mortality rate ratios for current- and ex-smokers to calculate the number of deaths amongst misclassified current- and ex-smokers in the observed cohort (Step 5). This step uses the following formulae:

$$D_C = \frac{D_T}{1 + \frac{P_E RR_E}{P_C RR_C} + \frac{P_N}{P_C RR_C}} \quad D_E = \frac{D_T}{1 + \frac{P_C RR_C}{P_E RR_E} + \frac{P_N}{P_E RR_E}}$$

Where:

Smoking Status of individuals in observed cohort				
	Total	Current-smokers	Ex-smokers	Never-smokers
Deaths	D_T	D_C	D_E	D_N
Person-Time	P_T	P_C	P_E	P_N
Mortality Rate Ratio	RR_T	RR_C	RR_E	RR_N

From the above, it can be seen that:

$$RR_C = \frac{D_C / P_C}{D_N / P_N} \quad \rightarrow \quad 1. \quad \frac{D_C}{P_C} = \frac{D_N}{P_N} \times RR_C$$

$$RR_E = \frac{D_E / P_E}{D_N / P_N} \quad \rightarrow \quad 2. \quad \frac{D_E}{P_E} = \frac{D_N}{P_N} \times RR_E$$

$$3. \quad D_N = D_T - D_C - D_E$$

Equation 1 can be rearranged and substituted into equation 2, which is then rearranged to yield the following:

$$4. \quad D_E = \frac{D_C P_E RR_E}{P_C RR_C}$$

Equation 1 is further rearranged to yield the following:

$$5. \quad D_N = \frac{D_C P_N}{P_C RR_C}$$

Equations 4 and 5 are then substituted into equation 3, which is solved for D_C :

$$6. \quad D_C = \frac{D_T}{1 + \frac{P_E RR_E}{P_C RR_C} + \frac{P_N}{P_C RR_C}}$$

The formula for D_E is derived in a similar way to that for D_C . Equation 2 is rearranged and substituted into equation 1, which is solved for D_C :

$$7. \quad D_C = \frac{D_E P_C RR_C}{P_E RR_E}$$

Equation 2 is rearranged to yield the following:

$$8. \quad D_N = \frac{D_E P_N}{P_E RR_E}$$

Equations 7 and 8 are then substituted into equation 3, which is solved for D_E :

$$9. \quad D_E = \frac{D_T}{1 + \frac{P_C RR_C}{P_E RR_E} + \frac{P_N}{P_E RR_E}}$$

