EVALUATION OF REPEATED MEASURES OUTCOMES IN EPIDEMIOLOGY

HALEH GHAEM MARALANI

(B.Sc, Tehran Medical Azad University, Iran; MSc, Shiraz University of Medical Sciences, Iran)

A THESIS SUBMITTED

FOR THE DEGREE OF DOCTORATE OF PHILOSOPHY

SAW SWEE HOCK SCHOOL OF PUBLIC HEALTH

NATIONAL UNIVERSITY OF SINGAPORE

2013

DECLARATION

I hereby declare that this thesis is my original work and it has been written by me in its entirety. I have duly acknowledged all the sources of information which have been used in the thesis.

This thesis has also not been submitted for any degree in any university previously.

Haleh Ghaem Maralani

11 October 2013

“The universe is full of magical things, patiently waiting for our wits to grow sharper.”

Eden Phillpotts

ACKNOWLEDGEMENT

This thesis would not have been completed without the help and support, both moral and material, of many persons. In particular, I wish to express my deepest gratitude and sincere thanks to my main supervisor Associate Professor Bee-Choo Tai, Saw Swee Hock School of Public Health, National University of Singapore, for her profound interest, support and expert guidance throughout the period of my graduate stay at the National University of Singapore, especially supporting me through my difficult times with understanding and care. Her humor, friendship and encouragement made my stay a fulfilling and enjoyable journey. The countless hours I spent with her discussing scientific issues will remain a constant source of inspiration for the rest of my life.

I would like to extend my sincere thanks and appreciation to my co-supervisor Professor Tien Yin Wong, Department of Ophthalmology, National University of Singapore for his excellent support, and inspiring guidance. Without his expertise, vision and, enthusiasm this thesis simply would not have been possible.

I would also like to express my thanks to my co-supervisor Associate Professor Jialing Li, from the Department of Statistics and Applied Probability, National University of Singapore, for his precious advice and support regarding to statistical issues.

I wish to convey my heartfelt thanks to Associate Professor E Shyong Tai, from the Department of Medicine, National University of Singapore, for his scientific guidance and precious comments on my papers.

I would like to gratefully acknowledge Professor Jie-Jin Wang and Professor Paul Mitchell from University of Sydney, for giving me this opportunity to access the data base from the Blue Mountains Eye Study to fulfill my PhD study research and also for their profound suggestions on my papers.

I am grateful to Ms Elena Rochtchina and Ms Ava Grace Tan from Centre for Vision Research Westmead Millennium, Institute University of Sydney, Australia, for helping me to access the database of the Blue Mountains Eye Study.

I also thank Associate Professor Rob M. van Dam, Associate Professor Jeanette Lee and Associate Professor Ecosse Lamoureux for sitting in my PhD Qualifying Examination Committee, to Associate Professor E Shyong Tai (Chairman) and Associate Professor Bee-Choo Tai and Professor Tien-Yin Wong for sitting in my Thesis Advisory Committee, to Associate Professor Rob M. van Dam and

Assistant Professor Chuen Seng Tan for sitting in my Final Oral Defence Committee and last but not least to Professor Ronald Klein for agreeing to be my external thesis examiner. Also, I would like to thank Assistant Professor Mohammad Kamran Ikram for agreeing to be my thesis opponent and Assistant Professor Wei-Yen Lim for sitting as my chairman Oral Defence Committee.

Next, I would like to offer my regards and blessings to Dr. Khin Lay Wai and Chen Zhaojin for their emotional support and helping me with epidemiological and statistical programming.

Special thanks to all faculty members and staff of the Saw Swee Hock School of Public Health, National University of Singapore, especially to all staff and students of Level 5, for providing a peaceful, calm and happy place for students to pursue research.

Finally, I am grateful for the award and the opportunity to pursue the PhD as a result of the SINGA research scholarship.

This thesis is affectionately dedicated to

My beloved mother and father

Who have taught and shown me how to live

My sister, Hayedeh and my brother, Reza

For their kind, support and understanding

All of them have made this journey possible

TABLE OF CONTENTS

Page

Page

SUMMARY

Background and objective

Many longitudinal studies have been conducted to evaluate the relationship between a variety of exposures and outcomes using only baseline data, due to the simplicity of statistical methods used for implementation. The failure to fully utilize the information that has been collected over time limits the inferences that could have been drawn especially with regards to changes in exposure effect. This thesis aims to evaluate repeated measures outcomes in epidemiology, assuming metabolic syndrome (MetS) as the main exposure of interest.

Methods

The thesis is motivated by data from the Blue Mountains Eye Study, Australia. It is a prospective cohort study of persons aged ≥49 years who were followed over 10 years. A total of 3086 subjects had complete information for the factors we are interested in at baseline contributed to the analysis of this thesis. Among these 3086 subjects, 2133 and 1632 subjects had complete information at the 5- and 10-year follow-up, respectively. The survival status of each subject was evaluated at each follow-up and the exact time of death recorded if it had occurred. MetS components as defined by the International Diabetes Federation criteria, were measured at baseline (1992-1994), 5 (1997-1999) and 10 (2002-2004) years. The outcomes, which include the development of cataract and age-related macular degeneration (AMD), were also assessed at the 5- and 10-year follow-up visits. In this thesis, repeated measures of MetS components were shown to be highly

correlated. To account for intra-subject correlation in the analysis, we apply appropriate statistical methods to unravel the relationship between MetS and its components, with time-to-event outcome involving all-cause and cause-specific mortality, interval-censored outcome involving age-related cataract and binary outcome of AMD. The thesis comprises four studies as described below.

Study 1

This study evaluates the association between MetS and its components with all-cause and cause-specific mortality. These covariates were repeatedly assessed at baseline, 5- and 10-year follow up and found to change with time. We thus evaluated the relationship between MetS (components) with all-cause and cause-specific mortality by applying Cox proportional hazards and competing risks models respectively, and considered MetS and its components as time-dependent covariates. The time-dependent receiver-operating-characteristic curve, integrated-discrimination-improvement and net-reclassification-improvement tests were also performed to assess the predictive abilities of individual and combined MetS components. The effects of MetS on all-cause and cause-specific death changed with time. The discrimination analyses showed that different MetS components were associated with different causes of death.

Study 2

This study determines the relationship between BMI including its 5-year changes and mortality. It has been argued that conventional Cox regression model may overestimate the relationship between exposure of interest such as BMI with

multiple failure endpoints such as different causes of death especially among frail or elderly population. Therefore, we compared the results obtained using Cox and competing risks models. The pattern of the relationship between BMI and mortality was found to depend on age. Amongst the younger subjects, the relationship between baseline BMI and all-cause mortality was U-shaped. Amongst elderly persons, an L-shaped relationship was seen: only low but not excessive BMI was found to be associated with an increased risk of all-cause death. A 5-year reduction in BMI was associated with increased risk of all-cause and cancer mortality. The Cox regression model showed a larger magnitude of effect, and with wider confidence interval, as compared with competing risks model.

Study 3

This study investigates whether the effect of MetS and its components on the incidence of cortical, nuclear and posterior subcapsular cataract (PSC) change with time. In this study, the occurrence of cataract is said to be interval-censored since the event was only known to occur between two assessment periods, that is, between baseline and 5-year or between 5- and 10-year follow-up. To deal with interval-censoring, the random effects complementary log-log model was implemented. Changes in MetS predicted the 5-year incidence of cortical and PSC cataract. Different MetS components predicted the incidence of different cataract sub-types at varying time-intervals.

Study 4

This study investigates the relationship between MetS and its components with the risk of early and late stage AMD. The outcomes and main exposure of interest, namely early or late stage AMD as well as MetS and its components respectively, were measured at baseline, 5- and 10-year follow-up. To explore the relationship between MetS with subsequent development of early or late AMD during 10-year follow-up, the mixed-effects logistic regression was implemented to account for intra-subject correlation which arose with repeated measurement. Changes in MetS, obesity, high glucose and high triglycerides predicted the incidence of late AMD during the 10-year follow-up among subjects aged ≤70 years.

Conclusions

Full utilization of baseline and follow-up information in longitudinal studies provides a more precise and accurate estimate of the exposures on the outcomes of interest. Moreover, for the analysis of multiple-failure endpoints such as different causes of death, the competing risks model yielded a more accurate estimate as compared with the cause-specific Cox regression.

LIST OF ABBREVIATIONS

AMD	age-related macular degeneration
ABS	Australian Bureau of Statistics
AMI	acute myocardial infarction
AUC	area under the curve
BMES	Blue Mountains Eye Study
BMI	body mass index
BP	blood pressure
CI	confidence interval
CVD	cardiovascular disease
EGIR	European Group for the Study of Insulin Resistance
FPG	fasting plasma glucose
FFP	fresh frozen plasma
GA	geographical atrophy
HDL	high density lipoprotein
HR	hazard ratio
ICC	intra-class correlation
ICD	International Classification of Diseases
IDF	International Diabetes Federation
IDI	integrated discrimination improvement
IFG	impaired fasting glucose
K	kappa
MetS	metabolic syndrome
MRI	magnetic resonance imaging
NCEP ATP 3	National Cholesterol Education Program—Third Adult Treatment Panel
NDI	net reclassification improvement
OR	odds ratio
PSC	posterior subcapsular cataract

ROC	receiver operating characteristic
SE	standard error
SD	standard deviation
SHR	subdistribution hazard ratio
TG	triglycerides
WHO	World Health Organization

LIST OF TABLES

Page

Page

LIST OF FIGURES

Page

CHAPTER 1 – Introduction

SUMMARY

Long-term longitudinal studies are the best instrument for exploring changes in effect over time. Although many longitudinal studies have been conducted to evaluate the relationship between a variety of exposures and outcomes, the results were usually evaluated using only baseline data, due to the simplicity of statistical methods used for implementation. The failure to fully utilize the information that had been collected over time limited the inferences that could have been drawn especially with regards to changes in exposure effect. This thesis aims to evaluate repeated measures outcomes in epidemiology, assuming metabolic syndrome (MetS) and its components as the main exposure of interest. In this thesis, MetS and its components, as well as the respective outcomes, age-related cataract and age-related macular degeneration (AMD) were repeatedly measured at baseline, 5- and 10-year follow-up. The survival status of each subject was evaluated at each follow-up and the exact time of death recorded if it had occurred. We apply advanced statistical models that account for possible intra-class correlation to evaluate the longitudinal effect of MetS and its components according to the endpoints of interest. These included time-to-event outcomes involving all-cause and cause-specific mortality, interval-censored outcome involving age-related cataract and binomial outcome involving AMD.

1.1. Examples and defining features of longitudinal studies

In the past decade, many longitudinal studies have been conducted to evaluate the relationship between a variety of exposures and outcomes. However, despite the longitudinal nature of the study design, the relationships were evaluated using only baseline information. These included the Framingham study which examined the association between exercise blood pressure (BP) and the risk of incident cardiovascular disease (CVD) (Lewis et al. 2008), the study by Saczynski et al. (2010) on the relationship between depression syndrome and the risk of dementia, and the Nurses' Health Study which evaluated the relation between smoking, caffeine and alcohol with epilepsy (Dworetzky et al. 2010). These cohort studies assessed the relationship between baseline exposure(s) and the respective disease outcomes without taking into account additional information that were collected at subsequent follow-up visits.

The defining feature of longitudinal studies is that measurements of the same individual, for example, BP levels or occurrence of kidney disease are recorded repeatedly, thereby allowing the direct study of changes over time. With repeated measures on individuals, one can capture within individual changes in the response over time and the factors that influence such changes, which can only be achieved within a longitudinal study design (Crowder and Hand 1990; Fitzmaurice et al. 2004).

There are some advantages of full utilisation of information in longitudinal studies. In practice, missing data cannot be avoided in long term follow-up studies. This results in a reduction in power and biased estimates. In this scenario,

the best solution to overcome this problem is to apply longitudinal panel data analysis. The longitudinal panel data refers to a group of individuals who are surveyed repeatedly over time. Clustering of data arises when the observations are grouped, for example, according to individuals. Moreover, due to repeated measures of exposure within each subject over time, the data are usually correlated in such study design.

The number of participants in this thesis at different visits varies due to loss to follow-up, deaths, migration or refusal to continue to participate in the study, thus resulting in missing observations. Of the 3654 eligible BMES participants at baseline, 501 refused participation. Attrition also occurred during the 5- and 10-year follow-up visits. The response rates were at baseline 82.4%, 5-year 75.8% and 10-year 76.7%. Fuller details on the follow-up of study participants are provided in **Chapter 2**. In the conventional statistical approach, if a person is missing on a covariate, his/her observation will be excluded from the entire analysis. To overcome this problem, the mixed model approach is recommended for analysis of longitudinal data, as only the time point when the observation is missing will be excluded from the analysis. The remaining data will continue to contribute to the analysis of the outcomes.

In this thesis, we define metabolic syndrome (MetS) and its components according to the International Diabetes Federation (IDF) criteria. As shown in **Chapter 2**, the prevalence of MetS and its components changed from visit to visit. For example, the prevalence of MetS increased slightly after 5 years follow-up from baseline, and again decreased by 10-year follow-up. Among the 5-MetS

components, the prevalence of BMI >30 kg/m^2, high glucose, high triglycerides (TG) and high BP levels increased from baseline to 5-year and then decreased by 10-year. However, the prevalence of low high density lipoprotein (HDL) cholesterol decreased from baseline to 5-year and then increased by 10-year. As such, when evaluating the relationship between MetS and its components with the outcomes of interest, we need to consider the time-varying effect of MetS and its components. In addition, the information of MetS or its components at baseline and subsequent follow-up visits were also shown to be highly correlated. Therefore, accounting for intra-subject correlation between MetS (or its components) at different time of assessments would be appropriate.

One approach for analyzing repeated measures data is via the mixed model which includes both the fixed and random effects. Random effect refers to subject-specific effect, while fixed effect refers to population average effect. In the mixed-effects model, the random effects are estimated when the data structure consists of repeated measures over time (Brown and Prescott 2006). The intra-class correlation (ICC), which refers to the within-cluster correlation of the exposure of interest, is usually reported in such instances. The use of a mixed model is clearly desirable to take account of the possible intra-subject correlations between the repeated measurements, as well as to overcome the problem of missing data. Such models are more flexible in terms of repeated measures and they do not need to have same number of observations per subject (Brown and Prescott 2006).

Although conducting longitudinal studies involve a great deal of effort in study design and data collection, they offer several important benefits over cross-sectional study (Lebowitz, 1996; Rothman et al. 2008). These include the recording of incident events such as incidence of age-related cataract or age-related macular degeneration (AMD) and presenting a direct measure of risk in terms of hazard ratio (HR) or relative risk ratio. While cross-sectional study explores the effect of exposure at a particular time point since the exposure and outcome were assessed at the same time, longitudinal study explores the temporal association between the covariate of interest, for example, BP, and the outcome which were measured at different time points (i.e. at baseline, 5- and 10-year follow-up). The cohort study design thus allows us to follow the subjects up till the observation of the outcome regardless of their risk status during the study period. This unique feature is lacking in a cross-sectional study.

1.2 Statistical methods for analyzing longitudinal data

In longitudinal studies involving repeated measures data, different models may be implemented depending on the outcome of interest. In this thesis, we apply appropriate statistical models for analyzing longitudinal data relevant to each outcome of interest.

Time-to-event outcome

In time-to-event analysis, the survival status of each subject is evaluated at each follow-up and the exact time of death recorded if it occurs. In many instances, information on covariates are also collected longitudinally. For example, BP,

weight, disease history, and hospitalization data may be collected at periodic time point, for example, at baseline, 5- and 10-year follow-up. Consequently, it is possible to detect changes in the exposure of interest over time. If such changes occur, then the exposure of interest may be regarded as a time-dependent covariate. In such a situation, one can investigate the usefulness of the temporal covariate information with an appropriate statistical model. The use of time-dependent covariates in a time-to-event analysis offers exciting opportunities for predicting outcomes with quantities that vary over time (Collett 2003).

In the analysis of all-cause mortality, the time-varying effect of the exposure may be accounted for by implementing the Cox proportional hazards models with time-dependent covariate (Collett 2003). In such settings, implementing the conventional Cox regression model without taking into account the time-varying effect of exposure would fail to distinguish between the short and long term effect of an exposure on an outcome (Collett 2003). For example, in studying the association between BP and mortality, utilising only the information of BP at baseline would not be able to clarify whether the earlier or most updated status of BP best predict mortality. In addition, such studies would also fail to quantify the effect of its changes over time.

Studies have shown that a time-dependent Cox regression model has the potential to yield a more precise estimate of exposure effect on outcome than the traditional Cox regression models (Boberg et al. 2002; Hartmann et al. 2012). To illustrate, a study on short-term prognosis in primary sclerosing cholangitis reported that the main exposure of interest, bilirubin, was more significant in

the time-dependent model than in the time-invariant analysis. The time-dependent regression model indicated that once the patients survived beyond the first 5 years, the impact of bilirubin at diagnosis on prognosis ceases. The time-dependent model was superior to the time-invariant model in assigning low 1-year survival probabilities to patients that actually survived less than 1 year (Boberg et al. 2002).

Competing risks outcome

Under the classical competing risks framework, a subject may be simultaneously exposed to several distinct events, but may eventually only fail from one of these. In such settings, the occurrence of a specific event would preclude the competing risks from being observed (Tai et al. 2001, Tai et al. 2010, Tai et al. 2011a; Tai et al. 2011b). In the analysis of cause-specific mortality, a subject may die from any of the following distinct causes: cardiovascular, cancer or other causes. These causes of death are therefore regarded as competing risks, as the failure of one precludes the occurrence of the other.

It has been argued that the cause-specific Cox analysis is not adequate for modelling competing risks data because it censors the competing events. Such censoring is assumed to be non-informative, and this procedure fails to consider that those who have experienced a competing event can never experience the main event of interest (Tai et al. 2011a; Tai et al. 2011b). The key feature that distinguishes competing risks data from the usual survival data is that in the analysis of the former, it is essential to take into account other causes of failure, whereas in a standard time-to-event setting, only a single failure cause is

considered. Thus special methods are required for analyzing competing risks data (Tai et al. 2011a; Tai et al. 2011b).

For the evaluation of outcomes involving multiple failure types such as cardiovascular, cancer and other causes of death, the Cox regression model is adequate when competing risks are rare, such as in younger adults. However, in the presence of strong competing risks, for example, the frail or elderly populations (Koller et al. 2008), the standard Cox regression model may substantially overestimate the absolute risk of event of interest, because subjects with a competing (and thus censored) event are treated as if they could experience the event of interest in the future (Wolbers et al. 2009; Tai et al. 2010; Tai et al. 2011a; Tai et al. 2011b).

In addition, predictions from a standard survival analysis in the presence of competing risks implicitly assumes that the risk of failing from the event of interest is not affected by these competing risks, which can be an unrealistic assumption in a real world setting (Tsiatis 1975; Kalbfleisch and Prentice 2002; Putter et al. 2007). In a clinical decision-making scenario, where competing risks do occur, accounting for these competing risks are often more relevant (Grunkermeier et al. 1997; Grunkemeier et al. 2007). Therefore, for analysis of multiple failure endpoints such as different causes of death, competing risks analysis provides a more robust and precise estimate of exposure on different causes of death in comparison with conventional cause-specific Cox-regression analysis (Wolbers et al. 2009; Tai et al. 2010; Tai et al. 2011a; Tai et al. 2011b).

Interval-censored outcome

When the exact time of occurrence of outcome, such as cataract is not known, but the time-to-event is only known to occur between two assessment periods, for example, between baseline and 5-year follow-up, or between 5- and 10-year follow-up, then interval censoring is said to have occurred. Since the covariate of interest, for example, BP level may also be measured repeatedly at similar predefined time intervals, the repeated measures data which are recorded on each subject are said to be nested within clusters. Within each cluster, the exposure of interest is correlated and this should be accounted for in the analysis as a random effect. When the occurrence of outcome such as cataract is interval-censored, then applying the Cox model to the hazards of events in intervals along with the repeated measures of covariates results in a random-effects complementary log-log regression model (Rabe-Hesketh and Skrondal 2008). In this model, the random-effects account for intra-subject correlation of exposure of interest which frequently arises in studies with repeated measurements. Studies have shown that interval-censored approach performs well for practical situations and would be applicable in real situations in medicine (Tong et al. 2008; Sun et al. 2013). Tong et al. (2008) conducted an experimental study in animals to investigate the relationship between exposure to chloroprene at different concentrations and adrenal tumor growth rate with an interval-censored model. They showed that interval-censored model provided an unbiased estimate in their simulation study. Similarly, in the simulation study, the outcome was regarded as an interval-censored. The results of simulation study suggested that for most situations, the

proposed estimate of the regression parameter seemed unbiased and the estimate of the standard error was close to the sample standard deviation. Both the simulation and experimental study showed that the random-effects interval-censored model would predict the associations in an unbiased manner, when the data were correlated and outcome was interval-censored.

The random-effects complementary log-log regression model can also overcome intra-subject correlation which cannot be accounted for by the conventional logistic regression model. Moreover, the failure to fully utilize the information that have been collected over time limits the inferences that could have been drawn especially with regards to changes in exposure effect (Rabe-Hesketh and Skrondal 2008; Tong et al. 2008; Sun et al. 2013). Therefore, interval-censored modelling provides a more robust and precise estimate of exposure on outcome in comparison with conventional logistic regression analysis.

Binomial outcome

The mixed-effects model can be applied to continuous and categorical outcomes. In study 4 of this thesis, we focus on the mixed-effects logistic regression model, which is appropriate for a binary outcome. When the outcome is binary such as the presence or absence of AMD, and the data are clustered, the mixed effects logistic regression would be appropriate for modeling this outcome. In this situation, the log odds of the event is modeled as a linear combination of the predictor variables based on the clustered data (Agresi 2013). Previous studies

have shown that the mixed-effects model is an appropriate and powerful tool for analysis of longitudinal clustered data (Blasco-Fontecilla et al. 2012; Candel 2012). For example, Blasco-Fontecilla et al. (2012) investigated the trends and correlations of changes in gross domestic product on changes in suicide rates in 10 World Health Organisation (WHO) regions during the past 30 years. They also stated that the mixed-effects model allows conclusions to be drawn on the cluster level based on different countries. Such detailed information on effect sizes based on cluster level (e.g. country) cannot be obtained from standard logistic regression modelling technique.

The mixed-effects model can also overcome intra-subject correlation which cannot be accounted for by a conventional logistic regression model. Therefore, mixed model provides stronger and more robust estimate of exposure on outcome in comparison with the conventional logistic regression model.

1.3 Objectives of the thesis

This thesis aims to evaluate repeated measures outcomes in epidemiology, assuming MetS as the main exposure of interest. In the past decade, many longitudinal studies have evaluated the relationship between MetS and its components with mortality or eye diseases. Despite the longitudinal nature of the study design, the relation between obesity and age-related eye diseases was assessed at a single point in time in the Beaver Dam Eye Study (Klein et al. 2001). Other longitudinal studies on MetS also used only the baseline information to describe its association with all-cause and cause-specific mortality (Jaggers et

al. 2009; Satio et al. 2009; Zambon et al. 2009; Akbaraly et al. 2010; Salminen et al. 2010; Sidorenkov et al. 2010) or age-related cataract (Tan et al. 2008).

This thesis evaluates the longitudinal effect of MetS and its components as defined by the IDF criteria. It includes body mass index (BMI) as a mandatory component for defining MetS. We consider different morbidity and mortality outcomes. These included time-to-event outcomes involving all-cause and cause-specific mortality, interval-censored outcome involving age-related cataract and binomial outcome involving AMD. In this thesis, MetS, its components and the respective outcomes were longitudinally measured over the study period, at baseline and again at the 5- and 10-year examinations after first recruitment. Details of the measurement of MetS components are provided in **Chapter 2**. In this thesis, we seek to provide a more comprehensive understanding of how advanced statistical methods may be used to deal with repeated measures of exposures and outcomes according to relevant situation involving time-to-event, competing risks, interval-censored or binary outcomes.

Specifically, this thesis is divided into four different studies. Within each study, we describe the use of relevant statistical methods for handling the correlation between repeated measures as well as the presence of missing data in order to effectively address the respective objectives of the study. In the section that follows, we describe the specific objective of each study and briefly discuss the statistical models used. Fuller details of the methodology for each study are provided in previous sections as well as in subsequent chapters.

Study 1: Metabolic syndrome and mortality in the elderly: A time-dependent association.

Although MetS increases with age, previous studies have shown inconsistencies regarding its relationship with all-cause and cause-specific mortality especially among elderly subjects (Hu et al. 2004; Hunt et al. 2004). To-date, no study has evaluated whether the relationship between MetS and mortality changes with time. In this study, the status of MetS and the survival status of each subject were evaluated at each follow-up. Further, the exact time of death was recorded if it had occurred. Since it was possible that the status of MetS might change from visit to visit, it was thus regarded as a time-dependent covariate in the analysis. In evaluating the relationship between MetS and its components with all-cause and cause-specific mortality, and determining whether the association changes with time, we appropriately implemented the time-dependent covariate Cox and competing risks models respectively.

As explained earlier, in the analysis of all-cause mortality, we take into account the time-varying effect of MetS and its components by implementing the Cox proportional hazards models with time-dependent covariate (Collett 2003). In this instance, MetS and its components were regarded as time-dependent covariates, whereas possible confounders such as age, sex, smoking status, pre-existing diseases at baseline (namely, cancer, angina, acute myocardial infarction (AMI), stroke and chronic lung disease), whose information were collected at baseline and were not expected to change with time, were considered as fixed covariates.

When MetS and its components were observed to change over study period, the competing risks model with time-dependent covariate was applied for analyzing cause-specific mortality such as cardiovascular-, cancer- and other causes of death (Tai et al. 2010; Tai et al. 2011a; Tai et al. 2011b).

To further evaluate the predictive performance of MetS component with time-to-event outcome namely all-cause and cause-specific mortality, the time-dependent receiver operating characteristic (ROC) curve for censored survival data and the area under the ROC curve (AUC), net reclassification improvement (NRI) and integrated discrimination improvement (IDI) tests were implemented. Fuller details of these methods are provided in **Chapter 3**.

Study 2: The prognostic role of body mass index on mortality amongst the middle-aged and elderly: A competing risks analysis

The relationship between BMI and mortality, especially in the overweight and obese range, amongst the elderly may be different from younger adults (Corrada et al. 2006). Furthermore, there are inconsistencies in reporting with regards to changes in BMI over time and its associations with all-cause and cause-specific mortality (Breeze et al. 2006; Corrada et al. 2006; Bamia et al. 2007; Myrskylä and Chang 2009; Saito et al. 2009; Yun et al. 2010). Moreover, obesity is associated with multiple causes of death, and it has been also argued that the conventional survival model may overestimate the risk of the competing causes of death such as cardiovascular, cancer and other causes of death, especially among the elderly population (Wolbers et al. 2009; Tai et al. 2010; Tai et al. 2011a; Tai

et al. 2011b). Hence, in this study, we aim to determine whether BMI and its changes are associated with all-cause and cause-specific mortality amongst middle-aged and elderly subjects, and compare the results obtained using standard Cox and competing risks models.

Study 3: Metabolic syndrome and risk of age-related cataract over time: An analysis of interval-censored data using random effects model.

So far, few studies have evaluated the relationship between baseline MetS and its components with age-related cataract (Tan et al. 2008d; Sabanayagam et al. 2011). Inconsistencies remain with regards to whether MetS or its components would predict the different types of age-related cataract, namely, cortical, nuclear or posterior subcapsular cataract (PSC). Besides it is questionable whether these associations change with time. In this study, we evaluate the effect of MetS and its components on the incidence of different age-related cataract sub-types, namely cortical, nuclear and PSC, and determine whether these associations change with time, using an interval-censored analysis.

In this thesis, the outcome of interest, cataract occurrence was evaluated at different time-interval between baseline and 5-year follow-up or between 5- and 10-year follow-up. Therefore, the occurrence of cataract is said to be interval-censored. The information of MetS and its components are also available at pre-defined time-intervals. As the within subject MetS components have been shown to be highly correlated in this thesis, we accounted for the intra-subject correlation via the random-effects complementary log-log regression model (Rabe-Hesketh

and Skrondal 2008). This allowed for the detection of a stronger and more robust estimate of MetS on the occurrence of the different types of cataract which was evaluated at pre-defined time-intervals. Repeated measures of MetS and its components were regarded as random effects, whereas age, sex, history of eye disease, pre-existing cardiovascular disease and family history of blindness which were measured at baseline, were regarded as fixed effects.

Study 4: Metabolic syndrome and risk of age-related macular degeneration

Atherosclerosis has long been postulated to be associated with late stage AMD through its effect on the choroidal circulation and possible deposition of lipids in the Bruch membrane (Friedman 2000). The prevalence of AMD and CVD are strongly age-dependent, and there have been conflicting reports about the independent associations of CVD, its risk factors (eg. BP or high serum lipid levels) and the development of AMD (Klein 2005; Klein et al. 2007). To-date, there has not been any study that evaluates the relationship between MetS (as a whole) and AMD. Hence, in this study, we investigate the age-specific relationship between MetS and its components with early and late stage AMD through the application of mixed-effects logistic regression model.

MetS and its components, as well as the endpoints of interest, namely early and late stage AMD, were repeatedly measured at baseline, 5- and 10-year follow-up. Since the outcome, presence or absence of AMD was binary, and the data were clustered within subject due to repeated measurements, the mixed effects logistic regression would be appropriate for modeling this type of outcome

(Agresi 2013). Repeated measures of MetS and its components were regarded as random-effects, whereas age, sex and pre-existing cardiovascular disease which were measured at baseline, were regarded as fixed-effects.

It should be noted that, although age-related cataract and AMD are both binary outcomes, in this thesis, we have modeled the two outcomes using different statistical technique to provide variety in illustrating different methods of handling such data.

1.4 Outline of the thesis

This thesis comprised a total of seven chapters. In the remaining section of this chapter, we outline our contribution to medical research in terms of presentation at conferences and publications. In **Chapter 2**, we describe the Blue Mountains Eye Study, which provides the motivation for this thesis. It covers the study design, epidemiological aspects such as confounding, interaction, collinearity, general statistical methods that apply to most studies, as well as describes the study population and general strengths and limitations of the thesis not specific to individual studies. In **Chapter 3**, we examine the relationship between MetS and its components with all-cause and cause-specific mortality via the application of the Cox and competing risks models that account for MetS and its components as time-dependent covariate. **Chapter 4** evaluates the age-specific relationship between BMI and its 5-year changes with all-cause and cause-specific mortality, and compares the results obtained using Cox regression and competing risks models. In **Chapter 5**, we explore the relationship between MetS and its

components with the incidence of different types of age-related cataract, namely, cortical, nuclear and PSC cataract. Since the exact time when a specific cataract developed was not known, and only the interval between two assessment times were recorded, we therefore implemented the random-effects complementary log-log model to account for interval censoring. **Chapter 6** investigates the relationship between MetS and its components and the development of early and late AMD. As the outcome is binary, and the data are repeatedly measured at baseline and subsequent follow-up visits, the mixed-effects logistic regression model is implemented to account for intra-subject correlation. Finally in **Chapter 7**, we review the important findings reported in the four studies, discuss the statistical methods implemented in this thesis, as well as the strengths and limitations of each study. Last but not least, the thesis concludes with several suggestions for future work. A separate summary is also provided for each chapter.

1.5 Contribution to medical research

To-date, the topics relating to the thesis have resulted in seven presentations at conferences and three publications. A merit and a third prize was awarded for an oral and a poster presentation respectively. Another paper has been submitted for consideration to be published and is currently pending review by the editorial board. The details of these conference presentations and publications are listed below:

Presentation at conferences

1. **Ghaem Maralani H**, Tai BC, Wong TY, Tai ES, Li J, Wang JJ, Mitchell P. The effect of metabolic syndrome on all-cause and cause-specific mortality: The Blue Mountains Eye Study. The Inaugural Yong Loo Lin School of Medicine, Graduate Scientific Congress 2011, Singapore, 25 Jan 2011 (Poster Presentation).

2. **Ghaem Maralani H**, Tai BC, Wong TY, Tai ES, Li J, Wang JJ, Mitchell P. The impact of metabolic syndrome and its components on all-cause and cause-specific mortality: The Blue Mountains Eye Study. 6th Singapore Public Health & Occupational Medicine Conference. 24-26 August 2011, Furama Riverfront Singapore. (Oral presentation) (*Received merit award*)

3. **Ghaem Maralani H**, Tai BC, Wong TY, Tai ES, Li J, Wang JJ, Mitchell P. The effect of baseline body mass index and its changes over 5-year on all-cause and cause-specific mortality in an elderly population: The Blue Mountains Eye Study. 6th Singapore Public Health & Occupational Medicine Conference. 24-26 August 2011, Furama Riverfront Singapore. (Poster presentation) (*Awarded 3rd prize*)

4. **Ghaem Maralani H**, Tai BC, Wong TY, Tai ES, Li J, Wang JJ, Mitchell P. Metabolic syndrome and mortality in the elderly: a time-dependent association. The Inaugural Yong Loo Lin School of Medicine, Graduate Scientific Congress 2012, Singapore, 15 Feb 2012. (Poster Presentation).

5. **Ghaem Maralani H**, Tai BC, Wong TY, Tai ES, Li J, Wang JJ, Mitchell P. Metabolic syndrome and risk of age-related cataract over time: an analysis of interval-censored data. 1st Singapore International Public Health Conference in conjunction with 7th Public Health & Occupational Medicine Conference, 2012, 1-2 October 2012. (Poster Presentation).

6. **Ghaem Maralani H**, Tai BC, Wong TY, Tai ES, Li J, Wang JJ, Mitchell P. Metabolic syndrome and mortality in the elderly: a time-dependent association. 1st Singapore International Public Health Conference in conjunction with 7th Public Health & Occupational Medicine Conference, 2012, 1-2 October 2012. (Poster Presentation).

7. **Ghaem Maralani H**, Tai BC, Wong TY, Tai ES, Li J, Wang JJ, Mitchell P. Metabolic syndrome and risk of age-related macular degeneration: a propensity score analysis. The Inaugural Yong Loo Lin School of Medicine, Graduate Scientific Congress 2013, Singapore, 30 January 2013. (Poster Presentation).

Publications

1. **Ghaem Maralani H**, Tai BC, Wong TY, Tai ES, Li J, Wang JJ, Mitchell P (2013). Metabolic syndrome and mortality in the elderly: a time-dependent association. *Diabetes Research and Clinical Practice* 99:209-216.
2. **Ghaem Maralani H**, Tai BC, Wong TY, Tai ES, Li J, Wang JJ, Mitchell P (2013). Metabolic syndrome and risk of age-related cataract over time:

an analysis of interval-censored data using random effects model. *Investigative Ophthalmology & Visual Science* 54:641-646. [Copyright The Association for Research in Vision and Ophthalmology (ARVO)].

3. **Ghaem Maralani H**, Tai BC, Wong TY, Tai ES, Li J, Wang JJ, Mitchell P (2014). The prognostic role of body mass index on mortality amongst the middle-aged and elderly: a competing risks analysis. *Diabetes Research and Clinical Practice* 103:42-50.

4. **Ghaem Maralani H**, Tai BC, Wong TY, Tai ES, Li J, Wang JJ, Mitchell P. Metabolic syndrome and risk of age-related macular degeneration. *Retina* February 2014, pending review.

All data analyses were done by me and all manuscripts were written by me as the first author.

CHAPTER 2 – The Blue Mountains Eye Study

SUMMARY

The Blue Mountains Eye Study (BMES) is a prospective population-based cohort study of age-related eye diseases and other health outcomes in west of Sydney, Australia. Persons aged ≥49 years were invited to attend a detailed examination at baseline (1992-1994) and after 5- (1997-1999) and 10-years (2002-2004). A detailed history of diseases was recorded at face-to-face interviews conducted by trained interviewers using a standardized questionnaire. Metabolic syndrome (MetS) components as defined by the International Diabetes Federation were measured and recorded at baseline, 5- and 10-year follow-up visits. We included 3086 subjects who had complete information at baseline for our study factors including, MetS, its components, age, sex, smoking status, pre-existing diseases, alcohol intake and physical activity in to the analysis of this thesis. Of these, 2133 had complete information for MetS and its components at 5-year follow-up and another 1632 had complete information for MetS and its components at 10-year follow-up. In this thesis, repeated measures of MetS components over 10-year follow-up were highly correlated. As such, it is important to account for intra-subject correlation in the analysis. We apply relevant statistical methods for time-to-event on all-cause and cause-specific mortality, interval-censored outcome on age-related cataract and or binary AMD outcome, to unravel their relationship with MetS and its components.

2.1 Overview

The Blue Mountains Eye Study (BMES) baseline survey (1992-1994) was conducted to describe the prevalence and identify the risk factors of vision loss and common eye diseases in a typical older Australian. The sampled subjects consisted of permanent residents 49 years of age or older residing in the Blue Mountains area, west of Sydney, New South Wales, Australia. Prospective follow-up at 5- (1997-1999), 10-year (2002-2004) and 15-year (2007-2010) of this population-based sample enabled us to assess the longer-term incidence of vision loss and common eye diseases, and the factors associated with increased risks of these common diseases among older people. So far, the findings of this study include the prevalence and incidence as well as assessment of risk factors for the above outcomes. However, previous studies using the BMES data

examined the relationship between exposures such as smoking, alcohol intake, fibrinogen and retinal vessel caliber and outcomes involving glaucoma, myopia, cataract, AMD, diabetes and stroke only at a single time point. This was despite having collected data at subsequent follow-up visits (http://www.cvr.org.au/bmes.htm). It should be noted that the data set for the 15-year follow-up was not ready at the time of analysis of this thesis. Therefore, in this thesis, we include all available information of our primary exposures of interest, that is, MetS and its components, not only at baseline but also at subsequent follow-up visits at 5 and 10 years to unravel the relationship between MetS (and its components) and subsequent development of outcomes such as mortality, cataract and AMD, after accounting for possible intra-subject correlation that arose when the repeated measurements were taken at each follow-up visit. Advanced statistical methods were implemented to analyze the data with full information and account for intra-subject correlation. This provides a more efficient and accurate estimate of the exposure(s) on the mentioned study outcomes.

2.2 Study design and population

The BMES used a door-to-door census, supplemented by electoral roll data, to identify all community-dwelling subjects aged over 49 years in a single postcode. This comprehensive sampling frame provides a rare opportunity to compare the characteristics of those who could have been recruited with the characteristics of those who could not have been recruited, using either (1) the telephone book only; or (2) the electoral roll only (Smith et al. 1997).

The original sampling frame involved an electronic database which contained the particulars of all residents aged 49 years and over and their postal code list. The study team obtained permission from the Electoral Commission to use the database of the state electoral roll at the time of commencement of the BMES study. As the state election had occurred six months earlier, the roll was thus considered accurate. The following data were included in the listing: name, address, occupation and date of birth. All telephone numbers, subscribers' names and addresses were downloaded from a CD-ROM containing the latest version of the electronic white pages (largest and most updated dictionary for finding people in Australia) at the time of commencement of the study. This was a computerized version of the white pages telephone dictionary, which was updated six-monthly.

One urban postcode area 2780 in Katoomba, Leura and Medlow Bath, in the Blue Mountains region was selected as the target area. This area has a stable and homogeneous population representative of the state of New South Wales with respect to income and socioeconomic status. The population was chosen because its age structure was older than that of the state and it was geographically well-defined, enhancing the potential for publicity, community support and a high response (Smith et al. 1997).

A door-to-door census was conducted by trained interviewers from November to December 1991 in the 28 census collector districts of postcode area 2780. Between March and April 1993, the study was extended to a second postcode area 2782 in Wentworth Falls using similar methods. The census was preceded by local publicity in newspapers and community radio and notification

by mail to all dwellings in the postcode area. All non-institutionalised, permanent residents aged 49 years and over who were born before 1 January 1943 at the time of the census were eligible. Permanent residents were defined as people who had lived in the dwelling for more than six months of the year (Smith et al. 1997).

Call-back visits to each house were made until contact with a resident occurred, usually by door-knock but also by telephone, using an electronic telephone dictionary stored by street name. A final classification as "no contact" was made if at least three door-knock calls to the house, five telephone calls at different times of the day and on different days of the week, and three letters to the household yielded no response (Smith et al. 1997).

The interviewers administered a short questionnaire to each eligible resident at doorstep (Smith et al. 1997). This questionnaire included self-reported vision and hearing problems and any past diagnosis of cataract, glaucoma, macular degeneration, diabetes or hypertension. The last visit to an ophthalmologist or optometrist was also recorded. A detailed information sheet and questionnaire is provided in **Appendix 1**.

The door-to-door census, supplemented by the telephone dictionary and electoral roll, identified 4433 eligible residents. The number of eligible residents differed by only six (0.15%) from the Australian Bureau of Statistics (ABS) Census91 conducted 3 months earlier (Mitchell et al. 1998a). The very small difference between the BMES and ABS census count for the eligible age group provided evidence that the BMES sampling frame covered the target population well (Smith et al. 1997). Of the total 4433 eligible subjects in the BMES, the

complete response rate was 3654 (82.4%) (Figure 2.1), the partial response rate was 353 (8.0%), and the complete refusal rate was 148 (3.3%). The definition of complete response referred to eligible subjects agreeing to participate in both interview and examination. Partial response was defined when eligible subjects received a brief interview, but refused to participate in examination. A complete refusal was defined when the eligible subjects refused to participate in both the interview and examination. When eligible households were contacted for clinic appointment, 68 people (1.5%) had died and 210 (4.8%) had moved out from the area. Thus, an additional 278 (6.3%) persons identified in the census could not be examined (Mitchell et al. 1998a). After excluding the people who could not be examined, the response rate was 3654/(4433-278) = 87.9% (Mitchell et al. 1998a). Overall 779 (353+148+278) subjects were non-participants (Figure 2.1).

Surviving baseline participants were invited to participate in the 5- and 10-year follow-up examinations. Between baseline and 5-year follow-up visit 575 had died. Of the 3079 eligible participants who survived, 745 had refused further follow-up or moved to another area, and so, only 2334 or 75.8% of survivors returned for subsequent follow-up at 5 years. Between the 5- and 10-year follow-up visit, 535 had died. 745 persons who did not participate at the 5-year follow-up were again invited to participate at the 10-year follow-up. Therefore, of the 2544 persons who were eligible for the 10-year follow-up, 592 refused further follow-up or were no longer living in the two selected post code areas. This resulted in a total of 1952 subjects or 76.7% of survivors who returned for follow-up after 10 years (Figure 2.1).

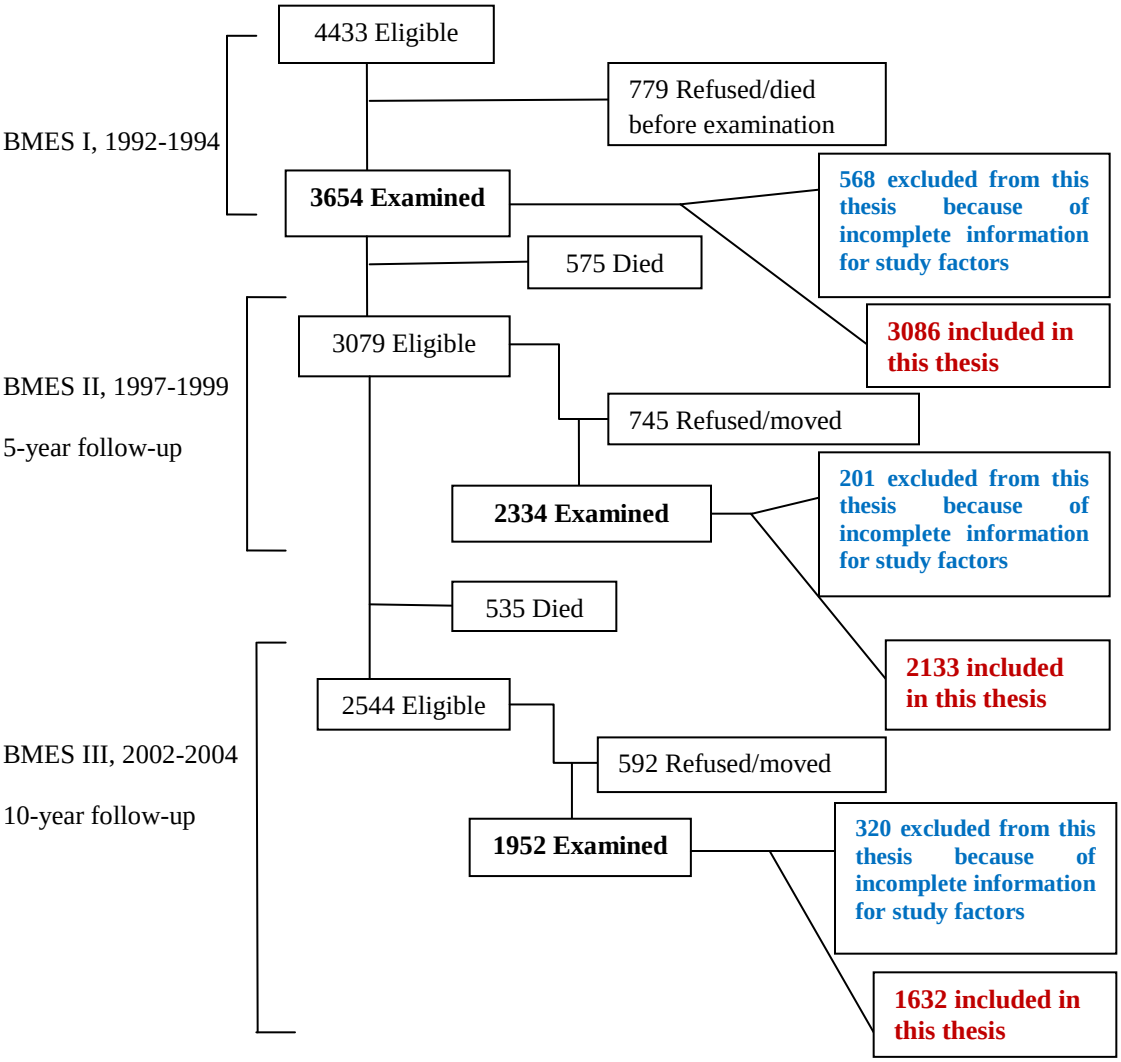


Figure 2.1 Flow chart of study progress of the Blue Mountains Eye Study (BMES)

The original BMES study cohort was 98 percent White, reflecting the community studied. All baseline and follow-up examinations of the BMES were approved by the Human Research Ethics Committees of the University of Sydney and the Western Sydney Area Health Service, and the study was conducted adhering to the tenets of the Declaration of Helsinki. Signed informed consent was obtained from all participants at each examination visit (Mitchell et al. 1998a; Shankar et al. 2007a).

Only 3086 subjects had complete information at baseline for our study factors including, MetS, its components, age, sex, smoking status, pre-existing disease (cancer, hypertension, diabetes, stroke, AMI and angina), alcohol intake and physical activity. Of these, 2133 had complete information for MetS and its components at 5-year follow-up and another 1632 had complete information for MetS and its components at 10-year follow-up. Therefore 568, 201 and 320 subjects who did not have complete information for the predefined study factors at baseline, 5- and 10-year follow-up, respectively, were excluded from this thesis (Figure 2.1).

2.3 Data collection

A detailed history of diseases including cancer, hypertension, diabetes, angina, AMI and stroke was recorded at face-to-face interviews conducted by trained interviewers using a standardized questionnaire (Mitchell et al. 1998a). We defined pre-existing disease(s) as a binary variable based on past history or medication of at least one of the above mentioned diseases. Current smokers were defined as those currently smoking manufactured cigarettes, hand-rolled cigarettes, cigars, or pipe tobacco. Ex-smokers were those who had ever regularly smoked cigarettes, cigars, or a pipe. In addition, information on alcohol consumption (gram per week) was collected (Attebo et al. 1996; Tsang et al. 1998). Participants had their weight (after removal of shoes and heavy clothing) measured by standing on an automated scale, to which a vertical height measure was attached (Younan et al. 2003). BP was measured while seated prior to the

installation of any eye drop using a stethoscope and mercury sphygmomanometer (Younan et al. 2003). In addition, self-reported physical activity based on time spent on activities per week using the International Physical Activity Questionnaire (Craig et al. 2003) were collected. The activities captured included occupational, household and leisure activities. It should be noted that BMES data double entered each time and cleaned the data carefully. Any inconsistency detected would have been fixed before using the data.

Fasting blood specimens and data quality control

Fasting blood specimens were collected in the morning, centrifuged on site, and then transported for laboratory analysis within four hours of collection. All tests were performed by the Institute of Clinical Pathology and Medical Research at Westmead Hospital, Sydney, for hematology and clinical biochemistry assessment. Hematocrit and fasting plasma glucose were measured by spun microhematocrit and hexokinase methods, respectively. HDL cholesterol and TG concentrations were measured on a Reflotron reflectance photometric analyser (Boehringer Mannheim Diagnostics [currently Roche Diagnostics], Germany). The laboratories were fully accredited under the Royal College of Pathologists Australasia/National Association of Testing Authorities Australasia medical registration program appropriate for Australian laboratories (Shankar et al. 2007b). The BMES group identified from the computerized data all subjects who had any missing values or any values above the 97.5th percentile or below the 2.5th percentile for each hematological index. Their original paper records were

checked, and any coding mistakes were rectified to produce the data set used for all analyses (Tsang et al. 1998).

2.4 Metabolic syndrome

The combination of metabolic disturbances now known as the MetS was first described as the clustering of hypertension, hyperglycaemia and gout (Kylin, 1923). It is now agreed that the well established term 'metabolic syndrome' remains the most useful and widely accepted description of this cluster of metabolically related cardiovascular risk factors which also predicts a high risk of developing diabetes (if not already present) (Alberti et al. 2006). General features of MetS include abnormal body fat distribution (obesity), insulin resistance, dyslipidaemia (high TG and/or low HDL) and elevated BP (Alberti et al. 2006).

A number of expert groups have attempted to develop a unifying definition for MetS. The most widely accepted of these definitions are those provided by the World Health Organization (WHO 1999), The European Group for the Study of Insulin Resistance (EGIR) (Balkau et al. 1999) and the National Cholesterol Education Program—Third Adult Treatment Panel (NCEP ATP 3) (NCEP, 2001) (Table 2.1). All groups agree on the core components of MetS: obesity, insulin resistance, dyslipidaemia and hypertension (Alberti et al. 2006).

However, the various definitions of MetS are not as successful in predicting diabetes or CVD as are some of the established predicting models such as the Diabetes Predicting Model and the Framingham Risk Score (Stern et al. 2004). In May 2004, the IDF held an expert workshop to examine how the various available definitions of MetS could be improved and developed with the aim of

reaching a consensus for the introduction of a new, unifying and working worldwide definition. The IDF criteria is a simple diagnostic tool for use in clinical practice and research world-wide. This should facilitate a better understanding of the syndrome and targeting of care to people who would benefit from cardiovascular risk reduction (Alberti et al. 2006).

In this thesis, we define MetS according to the IDF criteria as summarized in Table 2.1. Based on this definition, a person is defined as having MetS if he/she has central obesity (BMI >30 kg/m^2) plus any two of the following four risk factors:

- TG ≥1.7 mmol/l (150 mg/dl)
- HDL-cholesterol <1.03 mmol/l (40 mg/dl) in males and <1.29 mmol/l (50mg/dl) in females or specific treatment for these lipid abnormalities
- Systolic BP ≥130 or diastolic BP ≥85 mmHg or treatment of previously diagnosed hypertension
- Fasting plasma glucose ≥5.6 mmol/l (100 mg/dl) or previously diagnosed type 2 diabetes.

For the measurements of MetS components, all participants were asked to return on a morning within 4 weeks of each interview for fasting pathology tests, including glucose, TG, HDL-cholesterol. Seated BP, height and weight were also measured by trained interviewers. The BMI was calculated as weight (kg)/height (m^2). Information on history of diabetes, hypertension and lipid abnormalities as well as medication used was also measured via questionnaire by trained interviewers.

The baseline MetS components were measured and recorded when the participant entered the study (1992-1994), and again at the 5- (1997-1999) and 10- (2002-2004) year examinations after first recruitment. Data were therefore available on how prevalent MetS and its components changed in each subject throughout the study.

Table 2.1 Definitions of metabolic syndrome

Component	WHO (1999)	EGIR (1999)	NCEP ATP III (2001)	IDF (2004)
	Glucose intolerance, impaired glucose tolerance (IGT) or diabetes and / or insulin resistance* plus two or more of the following:	Insulin resistance (defined as hyperinsulinaemia —top 25% of fasting insulin values among the non-diabetic population) plus any two of the following:	Three or more of the following five risk factors:	Central obesity plus any two of the following risk factors:
Obesity	Men: waist–hip ratio > 0.90 Women: waist–hip ratio > 0.85 and/or body mass index >30 kg/m^2	Men: waist circumference ≥94 cm Women: waist circumference ≥80 cm	Men: waist circumference >102 cm Women: waist circumference >88 cm	If body mass index is >30 kg/m^2 then central obesity can be assumed, and waist circumference does not need to be measured.
Fasting plasma glucose		≥6.1 mmol/l (110 mg/dl) but non-diabetic	≥5.6 mmol/l (100 mg/dl)	≥5.6 mmol/l (100 mg/dl) or previously diagnosed Type 2 diabetes
Blood pressure	≥140 / 90 mmHg	≥140 / 90 mmHg or treatment	≥130 / ≥85 mmHg	≥130 / ≥85 mmHg or treatment
Dyslipidaemia	TG ≥1.7 mmol/l (150 mg/dl) *and/or*	TG > 2.0 mmol/l (178 mg/dl)or treatment *and/or*	TG ≥1.7 mmol/l (150 mg/dl) *and/or*	TG ≥1.7 mmol/l (150 mg/dl) or treatment *and/or*
	Men: HDL <0.9 mmol/l (35 mg/ dl) Women: HDL < 1.0 mmol/l (39 mg/ dl)	HDL <1.0 mmol/l (39 mg/dl) or treatment	Men: HDL <1.03 mmol/l (40 mg/ dl) Women: HDL <1.29 mmol/l (50 mg/ dl)	Men: HDL <1.03 mmol/l (40 mg/dl) Women: HDL <1.29 mmol/l (50 mg/dl) or treatment
Microalbuminuria	Urinary albumin excretion rate ≥ 20 μg/min or albumin:creatinine ratio≥ 30 mg/g			

*Insulin sensitivity measured under hyperinsulinaemic euglycaemic conditions, glucose uptake below lowest quartile for background population under investigation.

2.5 Epidemiological issues

Confounding factors

Confounding is one of the most important problems in observational epidemiological studies. Confounders can be adjusted in many ways: (a) restriction based on subgroup, for example, if smoking status is a confounder, then include only smokers or non-smokers in the study, (b) randomization, (c) matching and (d) stratification. There are three criteria to define confounders. First, a confounding factor has an effect on studied outcome. Second, it is linked or associated with study exposure. Third, it is not a mediator in the causal chain between the main exposure and the outcome. If confounding is not adjusted for, the results may be spurious (Rothman et al. 2008).

In our study, we explore possible confounders by first performing bivariate analysis of all potential independent variables. However, to minimize residual confounding, we further consider other confounders which have been established in other earlier studies. Therefore, based on the statistical and clinical selection, possible confounders in this thesis were thought to include: age, sex, smoking status (never, ex-smoker and current smoker), alcohol intake, physical activity, pre-existing disease(s) at baseline (namely, hypertension, diabetes, angina, AMI, stroke and cancer). For outcomes involving age-related cataract and AMD, covariates such as family history of eye disease (cataract, AMD, myopia, glaucoma and blindness), patient's history of eye disease (cataract, myopia and glaucoma), eye iris color (blue, hazel/ green, tan/ brown, dark brown), and skin sun-tanning characteristics estimated on 4-point scale (always burn, never tan;

usually burn, tan with difficulty; burn and tan above average; rarely burn, tan above average) were further considered as possible confounders. It should be noted that in this thesis covariate such as sex is naturally non-varying, but some covariates, for example, smoking status and pre-existing disease might be time-varying. However, these were considered as fixed covariate in the thesis as they have been shown not to have time-varying effect in the analysis.

Collinearity

Collinearity is one of the major concerns as high inter-correlation between variables might affect our findings. When collinearity happens, small changes in the covariate may result in significant changes in β. Therefore, we also ran collinearity test in our analysis to avoid this problem. For continuous variables, such as TG and HDL cholesterol, Pearson correlation coefficient was used, while for instances which considered one continuous variable and an ordered categorical variable, for example, systolic BP and smoking status (never, former and current smoker), the Spearman rank correlation coefficient was used. Association between two nominal variables, for example, sex and pre-existing disease(s) was tested by a chi-square test.

Interaction

Generally, there is always more than one factor involved in the disease etiology. To consider how multiple factors interact in causing a disease, we need to take into account effect modification. An example of an interaction effect is when the

incidence rate of disease in the presence of two or more risk factors differs from the incidence rate expected to result from their individual effects (Rothman et al. 2008). Initially, we apply bivariate analysis to estimate the effect based on the measured variables such as age, sex, smoking status or pre-existing disease(s) on the main outcomes, namely all-cause/cause specific mortality, age-related cataract and AMD. Then, we perform multivariate analysis based on likelihood ratio tests to compare nested models. During this procedure, we also check for any dramatic changes in effect size as well as standard error (SE) estimates. Subsequently, we also tested for interactions between primary exposures of interest, namely, MetS, its components and BMI with other measured covariates such as age groups, gender, smoking status and pre-existing disease(s) at baseline. Further details are provided in the respective chapters.

2.6 Statistical analyses

This thesis involves repeated measurements of primary exposures, namely MetS and its components, and outcomes of interest such as cataract and AMD, which were measured at baseline and subsequent follow-up visits at 5- and 10-year after recruitment. In the analysis of all-cause and cause-specific mortality, the time-to-event (measured in years) was calculated from recruitment to the time of death. For those who remained alive at the end of study, the follow-up time was censored at the study closure. We use different statistical methods relevant to specific outcome for the analysis. For time-to-event outcome, namely all-cause and cause-specific mortality, we perform Cox-regression and competing risks

models, respectively. However, to account for information on MetS and its components which were repeatedly measured at baseline, 5- and 10-year follow-up, the Cox-regression and competing risks models with time-dependent covariate were implemented. For interval-censored outcome involving age-related cataract, the random effects complementary log-log regression model was applied. The mixed-effects logistic regression model was used in the analysis of binary outcome involving AMD. Fuller details of these methods are provided in the respective chapters.

In the bivariate analysis, independent sample *t*-test was used to evaluate the relationship between continuous covariates (eg. age, alcohol intake and physical activity) with binary outcome such as 10-year cumulative incidence of age-related cataract or AMD. In addition, the chi-square test was used to examine the relationship between categorical covariates (eg. sex, smoking status, pre-existing disease) with the above-mentioned outcomes. All evaluations were made assuming a two-sided test based on a 5% level of significance using STATA version 11 unless otherwise stated.

Table 2.2 Characteristics of the study population by metabolic syndrome (MetS) status at baseline, 5- and 10-year follow-up

		Baseline		5-year		10-year	
	Total (n= 3086)	No MetS (n=2702)	MetS (n=384)	No MetS (n=1772)	MetS (n=341)	No MetS (n=1433)	MetS (n=199)
Mean baseline age, years (SD)	65.9 (9. 5)	66.0(9.6)	65.0 (8.6)	64.8 (8.7)	63.2 (7.9)	63.1 (7.7)	61.0 (6.7)
Sex (%)							
Female	1759 (57.0)	1509 (55.8)	250 (65.1)	1003 (56.6)	217 (63.6)	837 (58.4)	130 (65.3)
Male	1327 (43.0)	1193 (44.2)	134 (34.9)	769 (43.4)	124 (36.4)	596 (41.6)	69 (34.7)
Smoking status (%)							
Current smoker	439 (14.2)	389 (14.4)	50 (13.0)	224 (12.6)	36 (10.6)	162 (11.3)	25 (12.6)
Ex-smoker	1122 (36.4)	980 (36.3)	142 (37.0)	619 (34.9)	132 (38.7)	489 (34.1)	66 (33.2)
Non-smoker	1525 (49.4)	1333 (49.3)	192 (50.0)	929 (52.4)	173 (50.7)	782 (54.6)	108 (54.2)
Any pre-existing disease[a] (%)	812 (26.3)	701 (25.9)	111 (28.9)	423 (23.9)	93 (27.3)	276 (19.3)	59 (29.7)
Statin use	101 (3.3)	90 (3.3)	11 (2.9)	53 (3.0)	12 (3.5)	43 (3.0)	8 (4.0)
BP medication	994 (32.2)	812 (30.0)	182 (47.4)	508 (28.7)	137 (40.2)	372 (26.0)	77 (38.7)
Mean BMI (kg/m^2)(SD)	26.2 (4.4)	25.1 (3.4)	33.7 (3.3)	25.7 (4.4)	33.8 (3.6)	26.3 (4.2)	33.5 (3.5)
Low HDL (%)[b]	1012 (32.8)	849 (31.4)	163 (42.5)	372 (23.2)	160 (56.9)	324 (27.3)	123 (61.8)
High triglyceride (%)[c]	1283 (41.6)	989 (36.6)	294 (76.6)	557 (31.4)	235 (68.9)	202 (20.8)	110 (61.8)
High BP (%)[d]	2645 (85.7)	2271 (84.1)	374 (97.4)	1574 (89.7)	339 (99.4)	1081 (80.8)	191 (96.0)
Elevated FPG (%)[e]	547 (17.7)	400 (14.8)	147 (38.3)	300 (19.9)	157(40.0)	126 (8.8)	77 (38.7)

BMI=body mass index; BP=blood pressure; FPG=fasting plasma glucose; MetS=metabolic syndrome; SD=standard deviation.

[a]Any pre-existing disease at baseline (namely, cancer, angina, acute myocardial infarction, stroke and chronic lung disease) [b]serum HDL cholesterol <1.03 mmol/L in men and <1.29 mmol/L in women, or specific treatment for this lipid abnormality; [c] serum triglyceride level ≥ 1.7 mmol/L or specific treatment for this lipid abnormality; [d] systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥ 85 mmHg, or treatment of previously diagnosed hypertension; [e] fasting plasma glucose ≥5.6 mmol/L, or previous diagnosis or specific treatment for type 2 diabetes.

2.7 Descriptive profile of the study subjects

Table 2.2 presents the characteristics of study subjects based on MetS status at baseline, 5- and 10-year follow-up. The mean age of the 3086 subjects included in this thesis was 65.9 (standard deviation (SD) 9.5) years, and 43% were male. Apart from BMI, a mandatory component of the IDF criteria, a substantial proportion had high BP (85.7%), high TG (41.6%) and low HDL-cholesterol (32.8%) at baseline (Table 2.2). The prevalence of MetS increased slightly to 16.1% (95% confidence interval (CI) 14.6 – 17.8%) after 5 years follow-up from 12.4% (95% CI: 11.3 - 13.6%) at baseline, and was 12.2% (95% CI: 10.6 – 13.9%) at 10-year follow-up.

A comparison of demographic and clinical characteristics between participants and non-participants in the BMES study is listed in Table 2.3. Non-participants were less likely to wear glasses than participants. They were also significantly more likely to have seen an ophthalmologist. Symptomatic visual impairment was not significantly higher among participants, but the prevalence of chronic systemic diseases (hypertension and diabetes) was slightly more common among participants. There was no difference in gender distribution between participants and non-participants. The age profile showed an over-representation of those aged between 60-69 years; 35.8% for participants and 26.8% for non-participants. However, elderly aged ≥80 years were more likely to be non-participants (Attebo et al. 1996). The distributions of study characteristics of subjects included in the thesis were similar to that of the BMES participants (Table 2.3).

Table 2.3 Profile (%) of participants and non-participants in the BMES, as compared with thesis subjects

Characteristics		Participants (n=3654)	Nonparticipants (n=779)	Thesis subjects (n=3086)
Female		56.7	54.8	57.0
Male		43.3	45.2	43.0
Wears glasses **		97.2	55.1	97.6
Cannot read newspaper while wearing eye glasses		7.9	6.3	7.6
Cannot recognize friend across street		5.4	4.2	4.7
Age (years),	<60	27.9	30.3	27.8
	60-69*	35.8	26.8	37.4
	70-79	26.3	25.9	26.2
	≥80**	10.0	16.8	8.6
History of :				
Cataract		16.5	15.7	15.7
Glaucoma		6.0	4.9	5.6
AMD		2.4	3.8	2.5
Hypertension*		40.5	35.7	40.6
Diabetes		6.8	6.0	6.0
Ever seen ophthalmologist **		49.0	56.0	51.1

Note: In the non-participant group, information available in the following items were as follows: gender (n=754), wears glasses (n=544), cannot read newspaper while wearing eye glasses (n=539), cannot recognize friend across street (n=534), age 60-69 (n=641), history of cataract and glaucoma (n=553), AMD (n=549), hypertension (n=530), diabetes (n=531) and ever seen ophthalmologist (n=521). Comparison between participants and non-participants: *P <0.05; **P <0.01

Figure 2.2 shows the general pattern of 10-year changes in MetS and its components among, participants with complete information for the study factors at baseline (n = 3086), 5- (n = 2133) and 10-year (n = 1632) follow-up, respectively. Among the 5-MetS components, the prevalence of high TG increased from baseline to 5-year and then decreased by 10-year. However, the prevalence of low HDL cholesterol decreased from baseline to 5-year and then increased by 10-year (Figure 2.2).

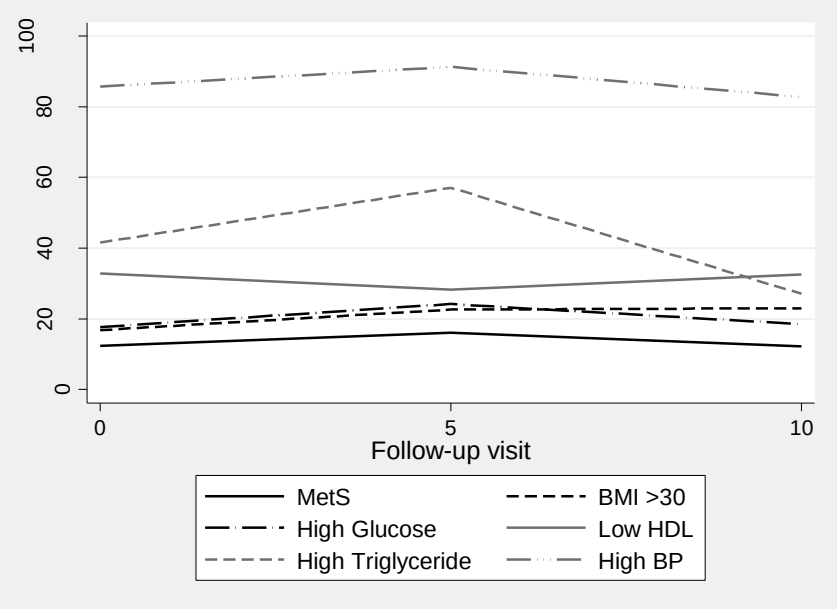


Figure 2.2 Changes in prevalence of MetS and its components over 10-year follow-up

Table 2.4 shows the ICC between MetS components at baseline, 5- and 10-year follow-up. An ICC tells us about the correlation of the respective MetS components within an individual (Snijders and Bosker 2012). If the correlation is shown to be relatively low, then one might choose to ignore the correlation and analyze the data in a standard way. For example, if the outcome is continuous, then multiple linear regression is used or if the outcome is binary, then multiple logistic regression model is applied. However, if the correlation is large enough, then it would be more appropriate to apply statistical models which account for the within subject correlation between repeated measures of MetS or its components. An ICC of 0.3 is considered quite large. (http://www.ats.ucla.edu/stat/stata/library/cpsu.htm). As shown in Table 2.3, MetS components were all highly correlated within an individual. For example,

an ICC of 0.843 for BMI means that, around 84% of the variance in BMI is due to differences within individuals (Bates and Pinheiro 1998; Rabe-Hesketh and Skrondal 2012). Therefore, it is important to take into account the within subject correlation in the relationship between predefined outcomes of interest and MetS components which were repeatedly measured at baseline and during the study follow-up at 5- and 10-year.

Table 2.4 Intra-class correlations between MetS components at baseline, 5- and 10-year follow-up

	ICC	95% CI
BMI	0.843	0.833-0.853
FPG	0.636	0.612-0.660
HDL	0.739	0.723-0.755
TG	0.623	0.599-0.646
Systolic BP	0.419	0.391-0.447
Diastolic BP	0.371	0.343-0.402

BP=blood pressure; BMI= body mass index; CI=confidence interval; FPG=fasting plasma glucose; HDL=high density lipoprotein; ICC=intra-class correlation; TG=triglycerides.

2.8 Strengths and limitations of the study

While this study has its strength such as a representative elderly Australian population, long-term follow-up, full utilisation of MetS information at each visit as well as high quality data collection involving standardised measures at each examination thus eliminating bias in self-reporting, its drawbacks must also be noted. The overall sample size of study might result in the lack of statistical power to detect the relationships with small effect sizes, especially when the number of events was low in outcomes such as PSC cataract and late AMD. In

addition, epidemiological studies tend to have some degree of bias which may not be avoided or removed. “Bias”, defined as “any systematic error in the design, conduct or analysis of a study that results in a mistaken estimate of an exposure’s effect on the risk of disease” (Rothman et al. 2008), is a major issue for any kind of epidemiological study. In the BMES study data on which this thesis is based, participants were more likely to wear glasses as compared with non-participants. This is a potential self-selection bias (Attebo et al. 1996) that might be a concern for eye-disease outcome, for example, age-related cataract and AMD (Pan et al. 2013a; Pan et al. 2013b; Pan et al. 2013c). It should be noted that although the selection of the two post codes for the BMES was not random, BMES participants covered 82.4% of all residents in that eligible age groups, or 87.9% of residents after excluding those who were found not to be eligible after further contact by the study coordinator.

CHAPTER 3— Metabolic Syndrome and Mortality in the Elderly: A Time-Dependent Association

SUMMARY

The metabolic syndrome (MetS) status of an individual may vary from time to time (i.e. at baseline, 5- and 10-year) and as such, MetS can be regarded as a time-dependent covariate. In this study, we aim to evaluate the association between MetS components with all-cause and cause-specific mortality, using the Cox proportional hazards and the competing risks models, considering MetS as a time-dependent covariate. In order to show whether further information of MetS at 5- and 10-year follow-up would provide more robust estimate in the relationships, we also examine the associations between baseline MetS and its components with all-cause and cause-specific mortality, and compare it with the time-dependent covariate models. The time-dependent receiver-operating-characteristic curve, integrated-discrimination-improvement and net-reclassification-improvement tests were further carried out to assess the predicting abilities of individual and combined MetS components. There was no association between baseline MetS with all-cause and cardiovascular mortality. However, baseline MetS was associated with an elevation in risk of cancer mortality. Utilising full information of MetS at follow-up, we found MetS to have a time-varying effect on all-cause and cause-specific mortality. The discrimination analyses showed that different MetS components were associated with different causes of death. The long-term effect of MetS on mortality in an older population was detected using time-dependent models while simulating the real scenarios of MetS changes over time.

3.1 Literature review on the relationship between MetS and its components with mortality

Table 3.1 provides a review on the association between MetS and mortality. Among the different MetS definitions, IDF and NCEP criteria have been used most frequently, and so we selected studies involving these two definitions of MetS in our review. Ten cohort studies were reviewed with follow-up duration of between 4.4 to 16 years. In prospective cohort studies in the USA, Italy and France, MetS was found to be positively associated with all-cause death in all subjects as well as by gender (Malik et al. 2004; Mozaffarian et al. 2008; Zambon et al. 2009; Akbaraly et al. 2010). A collaboration of 9 cohort studies in Europe, found a significant adverse effect of MetS on all-cause death among men, but not

women (DECODE Study Group and Qiao 2006). However, in two Finnish (Wang et al. 2007a; Salminen et al. 2010) and one Russian study (Sidorenkov et al. 2010), MetS had no effect on all-cause mortality regardless of gender. The Japan Public Health Centre-based Prospective Study showed that MetS was a predictor of all-cause death only among women (Satio et al. 2009a). The Investigations Préventives et Cliniques center (Paris, France) showed that, MetS was significantly associated with increased risk of all-cause death among subjects aged between 55-65 years, but not over 65 years (Thomas et al. 2011).

With regards to the relationship between MetS and cardiovascular death, Malik et al. (2004) and Wang et al. (2007a) found MetS to be positively associated with CVD death. However, Satio et al. (2009a), Sidorenkov et al. (2010) and Salminen et al. (2010) showed that MetS had no effect on CVD death regardless of gender or in the whole population.

While Satio et al. (2009a) found MetS to have no effect on cancer death, Akbaraly et al. (2010) found it to be associated with increased risk of cancer death, whereas Jaggers et al (2009) reported such an association in males only.

Table 3.1 Association between metabolic syndrome and mortality

Study, year	Place	N	Age	Follow-up (year)	MetS	HR (95%CI)		
All-cause						All	Female	Male
Malik, 2004	USA	6255	30-75	13.3	NCEP	1.40 (1.19-1.66)		
Qiao, 2006	Europe	10269	30-89	7-16	IDF		1.20 (0.97-1.49)	1.26 (1.06-1.49)
Wang, 2007a	Finland	1025	65-74	13	IDF		1.11 (0.84-1.46)	1.09 (0.83-1.43)
Mozafarian, 2008	USA	4258	≥65	15	IDF	1.17 (1.06-1.29)		
Saito, 2009a	Japan	34051	40-69	12.3	NCEP		1.22 (1.03-1.43)	1.06 (0.92-1.23)
Zambon, 2009	Italy	2910	≥65	4.4	NCEP	1.41 (1.16-1.72)	1.47 (1.13-1.91)	1.42 (1.06-1.89)
Sidorenkov, 2010	Russia	3555	≥18	9	IDF		1.13 (0.76-1.68)	0.76 (0.48-1.18)
Salminen, 2010	Finland	1260	≥64	9	IDF	0.90 (0.69-1.17)		
Akbaraly, 2010	France	7118	≥65	7	NCEP	1.54 (1.24-1.92)		
Thomas, 2011	France	20610	55-65	4.9	IDF	1.37 (1.12-1.68)		
		6210	>65			1.05 (0.84-1.32)		
Cardiovascular-death								
Malik, 2004	USA	6255	30-75	13.3	NCEP	1.82 (1.40-2.37)		
Wang, 2007a	Finland	1025	65-74	13	IDF	1.33 (1.03-1.72)		
Saito, 2009a	Japan	34051	40-69	12.3	NCEP		1.44 (0.98-2.11)	1.41 (0.99-2.02)
Sidorenkov, 2010	Russia	3555	≥18	9			1.08 (0.64-1.82)	1.09 (0.63-1.89)
Salminen, 2010	Finland	1260	≥64	9		1.07 (0.74-1.56)		
Cancer-death								
Saito, 2009a	Japan	34051	40-69	12.3	NCEP		1.17(0.92-1.49)	0.97(0.78-1.20)
Jaggers, 2009	USA	33230	20-88	14	NCEP			1.41 (1.19-1.66)
Akbaraly, 2010	France	7118	≥65	7	NCEP	1.49 (1.04-2.14)		

CI=confidence interval; HR=hazard ratio; IDF=international diabetes federation; MetS=metabolic syndrome; NCEP=national cholesterol education program.
Note: Jaggers, 2009 only included men in the studies.

Table 3.2 provides a review on the association between individual MetS components with mortality. Of the 5 MetS components, low HDL cholesterol (Wang et al. 2007a, Mozafarian et al. 2008, Zambon et al. 2009), hypertension (Mozafarian et al. 2008) and elevated glucose (Mozafarian et al. 2008, Zambon et al. 2009) were positively linked to increase risk of all-cause death. Further, Satio et al. (2009a) showed high BP and elevated glucose to be significant predictors of all-cause-death in both gender. However, Salminen et al. (2010) found elevated BP was associated with lower risk in all-cause mortality, while Thomas et al. (2011) showed that high BP and elevated glucose were the significant predictors of all-cause death only among those aged between 55-65 years.

As for cardiovascular death, Wang et al. (2007a) found high glucose and low HDL were linked to increase risk of CVD death. Satio et al. (2009a) reported that high BP and elevated glucose were significant predictors of CVD death in both gender. However, Salminen et al. (2010) found none of the MetS components to have any effect on the risk of CVD death.

As for cancer death, Satio et al. (2009a) showed that elevated glucose was a significant predictor of cancer death among women only, whereas Jaggers et al. (2009) found abdominal obesity, low-HDL cholesterol and elevated glucose to be associated with increased risk of cancer death in men (Jaggers et al. 2009).

Table 3.2 Association between metabolic syndrome components and mortality

Study	Place	N	Age	Follow-up (year)	MetS Component	HR (95%CI)		
All-cause						All	Female	Male
Wang, 2007	Finland	1025	65-74	13	Low-HDL	1.71 (1.17-2.49)		
Mozafarian, 2008	USA	4258	≥65	15	Low-HDL	1.11 (1.01-1.22)		
					High BP	1.31 (1.18-1.45)		
					High glucose	1.45 (1.32-1.59)		
Saito, 2009a	Japan	34051	40-69	12.3	High BP		1.24 (1.06-1.44)	1.19 (1.04-1.35)
					High glucose		1.70 (1.39-2.07)	1.22 (1.05-1.41)
Zambon, 2009	Italy	2910	≥65	4.4	High glucose	1.27 (1.02-1.59)	1.61 (1.16-2.24)	
					Low HDL		1.48 (1.08-2.02)	
Salminen, 2010	Finland	1260	≥64	9	High BP	0.65 (0.47-0.89)		
Thomas, 2011	France	20610	55-65	4.9	High BP	1.45 (1.15-1.83)		
					High glucose	1.43 (1.18-1.75)		
		6210	>65		No association			
Cardiovascular-death								
Wang, 2007	Finland	1025	65-74	13	High glucose	1.34 (1.02-1.77)		
					Low HDL	1.50 (1.12-2.01)		
Saito, 2009a	Japan	34051	40-69	12.3	High BP		1.55 (1.03-2.33)	1.52 (1.12-2.05)
					High glucose		1.64 (1.01-2.68)	1.51 (1.04-2.18)
Salminen, 2010	Finland	1260	≥64	9	5 MetS Components*			
Cancer-death								
Saito, 2009a	Japan	34051	40-69	12.3	High glucose		1.42 (1.03-1.94)	
Jaggers, 2009	USA	33230	20-88	14	Obesity			1.25 (1.06-1.47)
					Low HDL			1.25 (1.06-1.46)
					High glucose			1.22 (1.04-1.42)

BP=blood pressure; CI=confidence interval; HR=hazard ratio; MetS=metabolic syndrome; TG=triglyceride.
*P > 0.05, Note: Jaggers, 2009 only included men in the study.

3.2 Significance of study

MetS is a cluster of cardiometabolic abnormalities which is thought to predict the risk of developing CVD and diabetes (Alberti et al. 2006). Different MetS definitions, namely EGIR, NCEP ATP-3 and IDF have been proposed, but most of them include sets of cut-points for the same five components: abdominal obesity, hyperglycaemia, hypertriglyceridaemia, low HDL cholesterol and hypertension (Zimmet et. al 2005). Although MetS is an acknowledged predictor, although a weak one, on all-cause mortality in adult population, results from older population are conflicting (Lakka et al. 2002; Hu et al. 2004; Hunt et al. 2004). Clarifying this issue is important for researchers because the prevalence of MetS increases with increasing age.

The utility of MetS in predicting mortality among elderly is not clearly understood. First, underweight elderly populations may be predisposed to an increased risk of mortality (Flegal et al. 2005; Berrington de Gonzalez et al. 2010). Secondly, some MetS components, namely hypertriglyceridemia and diastolic BP, are not clearly related to poor health outcomes later in life (Fried et al. 1998; Burke et al. 2000). Furthermore, the cut-off point for individual MetS components may not be appropriate for predicting mortality in the elderly population, since these distributions were often characterized based on middle-age populations (Wilson et al. 1998). Some studies showed MetS to be a predictor of all-cause (Satio et al. 2009a; Zambon et al. 2009) and CVD mortality (Malik et al. 2004; Wang et al. 2007a). However, other studies demonstrated no effects of MetS on either deaths in the elderly (Satio et al. 2009a; Salminen et al. 2010;

Sidorenkov et al. 2010). Although MetS was found to predict cancer death in some studies (Jaggers et al. 2009; Akbaraly et al. 2010), this relationship was not evident in the study by Satio et al. (2009a).

While hypertension (Mozafarian et al. 2008), hyperglycemia (Maggi et al. 2006; Mozafarian et al. 2008; Zambon et al. 2009; Akbaraly et al. 2010), low HDL (Maggi et al. 2006; Zambon et al. 2009; Akbaraly et al. 2010) and high TG (Satio et al. 2009a) have been shown to predict all-cause and CVD-death, there is inconsistency with regards to which of these components better predict mortality. Moreover, it remains unclear whether MetS as a whole or its individual components provide a better prediction of all-cause and cause-specific mortality (Dekker et al. 2005; Franks and Olsson 2005). Finally, no studies have clarified whether the earlier or most updated status of MetS best predicts all-cause and cause-specific mortality.

As demonstrated in **Chapter 2**, the prevalent of MetS and its components varied from visit to visit over the 10-year study follow-up, and thus they can be regarded as a time-dependent covariate. As such, it is important to appropriately apply a time-dependent covariate model to unravel the effect of such changes on all-cause and cause-specific mortality in order to establish a more robust relationship between MetS and its components with mortality using quantities that vary over time (Giorgi and Gouvernet 2005). Therefore, in this study, we evaluate the effect of MetS and its components on subsequent all-cause and cause-specific mortality in an older Australian population by fully utilizing the information on

MetS collected at baseline, 5-year and 10-year visits. We further determine whether this association changes with time.

3.3 Methods

Study design and population

A detailed description of the study design and population of the BMES was provided in **Chapter 2**. In brief, this is a population-based cohort study of vision, common eye diseases and other health outcomes of a suburban population in the west of Sydney, Australia. Between 1992 and 1994, non-institutionalised permanent residents aged 49 years and older were invited to participate in this study, and requested to return for follow-up examinations at 5 (1997-1999) and 10 (2002-2004) years. We included 3086 participants at baseline who had complete information for the study factors including MetS and its components, age, sex, smoking status, pre-existing diseases at baseline (namely, cancer, angina, AMI and stroke) (Mitchell et al. 1998a).

Data collection

A detailed description of the data collection was provided in **Chapter 2**. Briefly, at each visit, trained interviewers completed a comprehensive questionnaire comprising demographic information, smoking status, eye and general medical history including hypertension, diabetes, and pre-existing diseases (namely, cancer, angina, AMI and stroke) as well as medication used (Mitchell et al. 1998a). Height, weight and seated BP (WHO 2003) were measured. Fasting blood tests, including serum total cholesterol, HDL cholesterol, TG (Cugati et al. 2003)

and fasting plasma glucose (FPG) (WHO 1999), were also measured within a month of each interview.

Definition of metabolic syndrome

In this thesis, we define MetS according to the IDF criteria (Zimmet et al. 2005). This includes obesity (ie. BMI units >30 kg/m^2) plus any two of the following four factors:

i. TG ≥1.7 mmol/L or specific treatment for this lipid abnormality;
ii. HDL cholesterol <1.03 mmol/L in men and <1.29 mmol/L in women, or specific treatment for this lipid abnormality;
iii. Systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg, or treatment of previously diagnosed hypertension; or
iv. FPG ≥5.6 mmol/L, or previous diagnosis or specific treatment for type 2 diabetes.

Study outcomes

All-cause and cause-specific mortality including cardiovascular-, cancer- and other causes of death were our study outcomes. Deaths occurring after baseline recruitment (1992–1994) until 31 December 2007 were confirmed by matching the demographic information of the participants with the Australian National Death Index (NDI) using probabilistic record linkage. Causes of death were provided by the NDI using the International Classification of Diseases (ICD) 9th revision and the International Statistical Classification of Diseases, 10th revision. Cardiovascular death included the following codes from ICD-9 (3949, 4029,

4109, 4119, 4140, 4148, 4149, 4151, 4240, 4241, 4254, 4269, 4273, 4274, 4275, 4278, 4280, 4281, 4289, 4290, 4291, 4410, 4411, 4413, 4414, 4415, and 4439) and ICD-10 (I059, I10, I132, I219, I249, I251, I255, I259, I269, I271, I350, I352, I358, I429, I469, I48, I500, I514, I515, I516, I709, and I711). Stroke death (thrombotic, haemorrhagic) included the following codes from ICD-9 (430.0–438.9) and ICD-10 (160.0–169.9). In addition, cancer death was defined as C00–C97 in ICD-9 and C140–C234 in ICD-10. Deaths and cause(s) of death were confirmed by medical certifiers, which include the physician in attendance, coroner or medical examiner, regardless of whether the death occurred in a hospital or in the community. The sensitivity and specificity of the Australian NDI were estimated at 93.7% and 100% for all-cause deaths, and 92.5% and 89.6%, respectively, for cardiovascular deaths. Validation of stroke- and cancer-death was, however, not possible (Wang et al. 2006).

Statistical analyses

In examining the associations between baseline MetS and its components with all-cause and cause-specific mortality, we used the Cox proportional hazards and competing risks model (Tai et al. 2011a; Tai et al. 2011b) respectively. Time-to-death from any cause (year) is the primary outcome variable for all-cause mortality, while time-to-specific cause of death (year) is the outcome variable for cause-specific mortality. As previously mentioned in **Chapter 1**, the elderly population is more likely to face with multiple causes of death such as cancer- and cardiovascular-deaths which are regarded as competing risks. In such situations, it is important to appropriately account for each competing risk in the analysis by

applying a competing risks model to yield a more accurate estimation of the exposure effect (Wolbers et al. 2009; Tai et al. 2011a, Tai et al. 2011b). Of note, in the competing risks model, the effect estimate is summarized by the subdistribution hazard ratio (SHR), where the subdistribution hazard is directly interpretable in terms of the cumulative incidence function (Beyersmann et al. 2007; Wolbers et al. 2009). This is in contrast to all-cause mortality where the effect estimate is quantified by the HR.

Since data were available with respect to how MetS (and its components) might have changed in each subject throughout the study duration, the Cox proportional hazards and competing risks regression models with time-dependent covariates (Collett 2003) were used to determine the relationship between MetS and its components with all-cause and cause-specific mortality (Tai et al. 2011), and whether the association changes with time. In these models, MetS and its individual components were regarded as time-dependent covariats (Collett 2003).

In the Cox model with MetS as the time-dependent covariate, the hazard function is modeled as:

$$h(t)= h_0(t)\exp(\beta_1*\text{MetS} + \beta_2*\text{MetSt})$$

where $h_0(t)$ is the baseline hazard function, and β_1 and β_2 are the regression coefficients (Collett 2003). The model contains MetS and a second term MetSt corresponding to an interaction between MetS and the survival time, *t*, which is defined as MetSt=MetS**t*. This model can be extended to include other fixed and time-dependent covariates. It allows MetS to be linearly dependent on the survival time, and so we were able to estimate the HR of MetS at *t*=2, 5 or 10 years.

We also explored possible interactions between MetS and its components with age, sex, and pre-existing disease. Additionally, the proportional hazards assumption underlying the Cox model was checked for individual covariates and globally.

Furthermore, to assess the prognostic value of a new marker, namely MetS components on the risk of all-cause and cause-specific mortality, we implemented the time-dependent ROC curve for censored survival model (Chambless and Diao 2006) and summarized the results of the area under the curve at time *t* (AUC(*t*)) using the Harrell's concordance index (Harrell et al. 1982; Harrell et al. 1984). Bootstrap method was used to compare the AUC. As the events of interest involving all-cause and cause-specific mortality are time-dependent, the time-dependent ROC curves are therefore more appropriate than the conventional ROC which was developed for assessing the performance of a variable based on a binary classification (Heagerty et al. 2000; Haibe-Kains et al. 2008).

Since the AUC may not be sensitive enough to express the improvement of discrimination performance, we also calculate two other performance measures to check the predictive value of MetS components for all-cause and cause-specific mortality, including net reclassification improvement (NRI) and integrated discrimination improvement (IDI), which provide new insight on model comparison and prediction (Pencina et al. 2008). Continuous NRI is the most objective and versatile measure of improvement in risk prediction. It defines upward and downward movement as any change in predicted probabilities. NRI is

a measure of discrimination for binary data and can be expressed in terms similar to the AUC. It offers immediate extension to survival data (Pencina et al. 2011):

$$\text{NRI}=\frac{\left(P(event \backslash up)-P(event)\right).P(up)+\left(Pevent)-P(event \backslash down)\right).P(down)}{P(event).(1-P(event))} \quad (3.1)$$

The IDI can be seen as similar to the continuous version of NRI, and is defined as a difference in discrimination slopes. Discrimination slope in the binary concept is defined as difference in mean predicted probabilities of events and non-events. The IDI was viewed as a difference between improvement in average sensitivity and any potential increase in average 'one minus specificity' (Schmid and Griffith, 1998), and the statistic was a difference in Yates discrimination slopes between the models with and without a new marker (Yates 1982; Schmid et al. 1998). The IDI can also be extended for survival analysis (Uno et al. 2009). The IDI and NRI tests therefore gauge whether a novel marker improves the level of discrimination between groups of individuals classified with and without the use of a new test. The time-dependent AUC, NRI and IDI were generated using R statistical package (www.r-project.org).

3.4 Results

The demographic and clinical characteristics of the 3086 study subjects were summarized in **Chapter 2**. Over a median follow-up duration of 14.6 years, 1170 (38%) deaths were reported. Of these, 483 (41.3%) were CVD-deaths and 342 (29.2%) were cancer-deaths.

Association between baseline MetS and its components with all-cause and cause-specific mortality

There was no effect of baseline MetS on all-cause mortality (HR 1.18, 95% CI: 0.99-1.40). However, among the 5-MetS components, elevated glucose (HR 1.30, 95% CI: 1.14-1.49) and high TG (HR 1.14, 95% CI: 1.01-1.28) at baseline were found to be associated with an increased risk of all-cause mortality, after adjusting for age, sex, smoking status and pre-existing disease at baseline (Table 3.3).

Table 3.3 Effects of baseline metabolic syndrome and its components on all-cause and cause-specific mortality

	All-cause (n=1170)		Cardiovascular-death (n=483)		Cancer- death (n=342)	
	No. of death	HR (95% CI)	No. of death	SHR(95% CI)	No. of death	SHR (95% CI)
MetS	152 (13.0)	1.18 (0.99-1.40)	53 (34.9)	0.96(0.71-1.30)	52 (34.2)	1.45(1.07-1.96)*
BMI >30	189 (16.1)	1.15(0.98-1.34)	70 (37.0)	1.03(0.79-1.34)	64 (33.9)	1.35(1.02-1.79)*
Elevated FPG [a]	272 (23.2)	1.30(1.14-1.49)**	113 (41.5)	1.13(0.90-1.43)	87 (32.0)	1.40(1.09-1.79)**
Low HDL[b]	334 (28.5)	0.88(0.77-1.01)	134 (40.1)	0.89(0.72-1.10)	88 (26.3)	1.04(1.03-1.05)**
High Triglyceride [c]	517 (44.2)	1.14(1.01-1.28)*	212 (41.0)	1.14(0.95-1.37)	161 (31.1)	1.27(1.02-1.57)
Hypertension [d]	1043 (89.1)	0.96(0.80-1.15)	444 (42.6)	1.39(0.99-1.96)	297 (28.5)	0.90(0.65-1.24)

BMI=body mass index; CI= confidence interval; FPG=fasting plasma glucose; HR=hazard ratio; MetS=metabolic syndrome; SHR=subdistribution hazard ratio. [a]fasting plasma glucose ≥ 5.6 mmol/L, or previous diagnosis or specific treatment for type 2 diabetes. [b]serum HDL cholesterol < 1.03 mmol/L in men and < 1.29 mmol/L in women, or specific treatment for this lipid abnormality; [c] serum triglyceride level ≥ 1.7 mmol/L or specific treatment for this lipid abnormality; [d] systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg, or treatment of previously diagnosed hypertension; Note : Models adjusted for age, gender, smoking status, pre-existing disease at baseline (namely, cancer, angina, acute myocardial infarction and stroke) *P<0.05 and **P<0.001

With respect to cause-specific mortality, there was no evidence of effect of baseline MetS and its components on CVD-death. However, baseline MetS (HR 1.45, 95% CI: 1.07-1.96) and four of its components, namely BMI >30 kg/m^2

(HR 1.35, 95% CI: 1.02-1.79), high glucose (HR 1.40, 95% CI: 1.09-1.79), low HDL (HR 1.04, 95% CI: 1.03-1.05) and high TG (HR 1.27, 95% CI: 1.02-1.57) were associated with an elevation in risk of cancer mortality (Table 3.3).

Table 3.4 Bivariate association between fixed and time-dependent risk factors with all-cause and cause-specific mortality

	All-cause (n=1170)	Cardiovascular (n=483)	Cancer (n=342)
	HR (95% CI)	SHR (95% CI)	SHR (95% CI)
Fixed covariate			
Sex (Male)	1.54 (1.37-1.72)**	1.63 (1.28-2.06)**	1.51 (1.22-1.87)*
Age	1.11 (1.10-1.12)**	1.10 (1.09-1.11)**	1.04 (1.03-1.06)*
Smoking status			
Non-smoker	Reference (1)	Reference (1)	Reference (1)
Ex-smoker	1.39 (1.22-1.57)**	1.11 (0.86-1.44)	1.46 (1.16-1.85)**
Current smoker	1.46 (1.24-1.73)**	1.13 (0.79-1.59)	1.62 (1.20-2.18)*
Any, pre-existing disease [a]	2.20 (1.95-2.46)**	2.72 (2.15-3.44)**	1.70 (1.37-2.12)**
Time-dependent Covariate			
MetS			
2-year	0.76 (0.55-1.04)	0.38 (0.21-0.71)*	1.42 (0.88-2.29)
5-year	0.85 (0.68-1.05)	0.56 (0.37-0.85)*	1.14 (0.82-1.57)
10-year	1.02 (0.84-1.25)	1.07 (0.79-1.44)	0.78 (0.49-1.24)
BMI > 30			
2-year	0.58 (0.43-0.78)**	0.36 (0.22-0.61)**	1.00 (0.63-1.58)
5-year	0.66 (0.54-0.80)**	0.51 (0.36-0.71)**	0.88 (0.65-1.19)
10-year	0.81 (0.67-0.96)*	0.87 (0.67-1.14)	0.71 (0.48-1.05)
Elevated glucose [b]			
2-year	1.17 (0.92-1.50)	1.07 (0.73-1.58)	1.16 (0.76-1.78)
5-year	1.21 (1.03-1.43)*	1.17 (0.90-1.51)	1.20 (0.90-1.60)
10-year	1.28 (1.08-1.52)*	1.34 (1.04-1.73)	1.27 (0.91-1.79)
Low HDL [c]			
2-year	0.97 (0.78-1.20)	1.07 (0.77-1.49)	0.93 (0.63-1.36)
5-year	0.94 (0.81-1.09)	0.98 (0.78-1.23)	0.88 (0.67-1.14)
10-year	0.89 (0.76-1.05)	0.84 (0.66-1.08)	0.79 (0.57-1.10)
High triglyceride [d]			
2-year	1.21 (0.99-1.48)	0.91 (0.66-1.24)	1.79 (1.25-2.57)*
5-year	1.15 (1.01-1.32)	0.99 (0.80-1.23)	1.42 (1.12-1.80)*
10-year	1.07 (0.92-1.24)	1.14 (0.91-1.44)	0.96 (0.70-1.31)
Hypertension [e]			
2-year	1.26 (0.90-1.74)	2.20 (1.21-4.01)*	1.02 (0.60-1.74)
5-year	1.39 (1.10-1.74)	2.21 (1.45-3.37)**	1.10 (0.76-1.58)
10-year	1.64 (1.28-2.09)**	2.23 (1.45-3.45)**	1.25 (0.79-1.95)

BMI=body mass index; CI=confidence interval; HR=hazard ratio; MetS=metabolic syndrome; SHR=subdistribution hazard ratio. [a] Any pre-existing disease (namely, cancer, angina, acute myocardial infarction and stroke) [b]fasting plasma glucose ≥ 5.6 mmol/L, or previous diagnosis or specific treatment for type 2 diabetes. [c]serum HDL cholesterol < 1.03 mmol/L in men and < 1.29 mmol/L in women, or specific treatment for this lipid abnormality; [d] serum triglyceride level ≥ 1.7 mmol/L or specific treatment for this lipid abnormality; [e] systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg, or treatment of previously diagnosed hypertension. *P<0.05 and **P<0.001

Time-dependent association between MetS and its components with all-cause mortality

Among the exposures of interest that were repeatedly measured at baseline, 5-year and 10-year follow-up visits, without any adjustment, BMI, elevated glucose, TG and hypertension showed a time-dependent association with all-cause mortality (Table 3.4). Of the fixed covariates considered in this study, gender, age, smoking and pre-existing disease were associated with all-cause mortality (Table 3.4).

Adjusting for these fixed covariates, the risk of all-cause-mortality increased gradually from 2-year to 10-year follow-up amongst those with MetS (2-year: HR 0.96 (95% CI: 0.69-1.34); 5-Year: HR 1.06 (95% CI: 0.84-1.32); 10-year: HR 1.23 (95% CI: 1.01-1.51). However, individually, none of the MetS components appeared to have a significant effect on all-cause mortality (Table 3.5).

Time-dependent association between MetS and its components with cause-specific mortality

In bivariate analysis, hypertension was associated with increased risk of cardiovascular-deaths at 2-, 5- and 10-year follow-up (Table 3.4). After adjusting for age, sex, smoking status and pre-existing disease status at baseline, the association between MetS and cardiovascular-death changed with time, with increased risk of cardiovascular-death at 10-year (SHR 1.38, 95% CI: 1.02-1.86), and reduced risk at 2-year (SHR 0.53, 95% CI: 0.30-0.95) and 5-year (SHR 0.76, 95% CI: 0.51-1.13). Of the five MetS components, BMI >30 kg/m^2 showed a

time-dependent association with cardiovascular-death with lower risk at 2-year and increased risk by 10-year (Table 3.5).

In contrast to cardiovascular-death, MetS was associated with a notably higher risk of cancer death at 2-year (SHR 1.62, 95% CI: 1.01-2.62), with diminished risk by 10-year (SHR 0.90, 95 % CI: 0.57-1.44). Among the 5 MetS components, high TG also exhibited a time-dependent association with cancer death, where the elevation in risk of cancer death at 2-year dissipated by the 10-year follow-up (Table 3.5).

Table 3.5 Time-dependent effects of MetS and its components on all-cause and cause-specific mortality

	2-year		5-year		10-year	
	No. of death	HR (95% CI)	No. of death	HR (95% CI)	No. of death	HR (95% CI)
All-cause (n=1170)						
MetS	152 (13.0)	0.96 (0.69-1.34)	75 (13.2)	1.06 (0.84-1.32)	21 (10.7)	1.23 (1.01-1.51)*
BMI > 30	189 (16.2)	0.83 (0.61-1.12)	103 (18.1)	0.90 (0.74-1.11)	36 (18.3)	1.05 (0.88-1.25)
Elevated FPG [a]	272 (23.3)	0.95 (0.74-1.22)	141 (29.2)	0.97 (0.82-1.14)	29 (25.2)	0.99 (0.83-1.18)
Low HDL[b]	334 (28.6)	1.06 (0.85-1.32)	147 (30.4)	1.00 (0.85-1.17)	59 (36.0)	0.91 (0.76-1.07)
High Triglyceride[c]	517 (44.2)	1.08 (0.89-1.32)	831 (71.0)	1.03 (0.90-1.19)	33 (27.3)	0.97 (0.83-1.13)
Hypertension[d]	1043 (89.2)	0.93 (0.66-1.30)	512 (91.3)	1.02 (0.82-1.30)	157 (80.1)	1.21 (0.94-1.55)
Cardiovascular-death (n=384)		SHR (95% CI)		SHR (95% CI)		SHR (95% CI)
MetS	53 (34.9)	0.51 (0.27-0.94)*	29 (38.7)	0.76 (0.51-1.13)	11 (52.4)	1.38 (1.02-1.86)*
BMI > 30	70 (37.0)	0.54 (0.32-0.91)*	43 (41.7)	0.74 (0.52-1.05)	15 (41.7)	1.23 (0.93-1.62)
Elevated FPG [a]	113 (41.5)	0.86 (0.58-1.27)	55 (39.0)	0.91 (0.70-1.19)	13 (44.8)	1.01 (0.77-1.33)
Low HDL[b]	134 (40.1)	1.14 (0.82-1.58)	61 (41.5)	1.05 (0.84-1.32)	19 (32.2)	0.92 (0.71-1.19)
High Triglyceride[c]	212 (41.0)	0.82 (0.60-1.13)	354 (42.6)	0.90 (0.72-1.12)	16 (48.5)	1.04 (0.83-1.32)
Hypertension[d]	444 (42.6)	1.69 (0.92-3.10)	203 (39.6)	1.69 (1.10-2.60)*	56 (35.7)	1.69 (1.08-2.66)*
Cancer-death (n=342)						
MetS	52 (34.2)	1.62 (1.01-2.62)*	19 (25.3)	1.30 (0.94-1.81)	4 (19.1)	0.90 (0.57-1.44)
BMI > 30	64 (33.9)	1.21 (0.77-1.92)	26 (25.2)	1.08 (0.79-1.47)	11 (30.6)	0.88 (0.60-1.30)
Elevated FPG [a]	87 (32.0)	0.98 (0.64-1.50)	38 (26.9)	1.02 (0.76-1.35)	5 (17.2)	1.08 (0.77-1.51)
Low HDL[b]	88 (26.3)	0.98 (0.67-1.43)	41 (27.9)	0.91 (0.70-1.19)	12 (20.3)	0.81 (0.58-1.13)
High Triglyceride [c]	161(31.1)	1.70 (1.19-2.43)*	239 (28.8)	1.34 (1.05-1.72)*	8 (24.2)	0.91 (0.66-1.25)
Hypertension [d]	297 (28.5)	0.83 (0.48-1.43)	141 (27.5)	0.89 (0.62-1.29)	40 (25.5)	1.00 (0.63-1.57)

BMI=body mass index; CI= confidence interval; FPG=fasting plasma glucose; HR=hazard ratio; MetS=metabolic syndrome; SHR=subdistribution hazard ratio [a]fasting plasma glucose ≥ 5.6 mmol/L, or previous diagnosis or specific treatment for type 2 diabetes. [b]serum HDL cholesterol <1.03 mmol/L in men and <1.29 mmol/L in women, or specific treatment for this lipid abnormality; [c] serum triglyceride level ≥1.7 mmol/L or specific treatment for this lipid abnormality;[d]systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg, or treatment of previously diagnosed hypertension. Note : Models adjusted for age, gender, smoking status, pre-existing disease at baseline (namely, cancer, angina, acute myocardial infarction and stroke)*P<0.05

Time-dependent ROC

We further sought to identify the individual and specific combinations of MetS components that best predicted all-cause and cause-specific mortality (Table 3.6). Among the five individual MetS components, TG was the best single predictor of all-cause and cancer mortality, while high glucose was the best predictor for CVD death (Table 3.6). For all-cause mortality, the best model comprised three components and included triglyceride, HDL-cholesterol and glucose. In the case of cause-specific mortality, the best model consisted of the following four components for cancer-death: triglyceride, HDL-cholesterol, glucose and BMI. For CVD-death, the best model included only two- components: high glucose and high BP. In the evaluation of all-cause and cause-specific mortality, there was significant improvement to the model fit as each new component was added to the more parsimonious preceding model (all $P < 0.05$), with no further improvement thereafter. For example, the model for all-cause death significantly improved the AUC when three MetS components, namely TG, HDL-cholesterol and glucose were included into the model, with no further improvement when the fourth and fifth MetS components was added into the preceding model. Similarly for cardiovascular and cancer death, the results indicated that when the MetS components were combined, the AUC improved significantly (Model 1, Table 3.6). However, after adjusting for age, sex, smoking status and pre-existing disease status at baseline, none of these models were statistically enhanced as compared with the preceding model (Model 2, Table 3.6).

Integrated discrimination improvement (IDI) and net reclassification improvement (NRI)

Improvement in all-cause mortality risk reclassification was numerically better in the 4-component model. The components included TG, HDL-cholesterol, glucose and BP. The addition of BP to TG, HDL-cholesterol and glucose increased the difference in mean predicted probability between subjects who died and survived with an IDI of 0.002. The improvement in discrimination by NRI when BP was added to TG, HDL-cholesterol, glucose between subjects who had died and survived was 0.048. For cancer-death, the improvement in discrimination persisted in the 5-component model, while for CVD-death the improvement in discrimination stopped in the 2-component model (Model 1, Table 3.6). Generally, the results of IDI and NRI suggested that combined MetS-components improved the discrimination of the model significantly (Model 1) ($P < 0.05$) in the prediction of all-cause and cause-specific mortality risk among the Australian elderly population. However, there was no improvement in the discrimination of death after including age, sex, pre-existing disease and smoking status (Model 2, Table 3.6).

Table 3.6 Time-dependent ROC curve, integrated discrimination improvement and net reclassification improvement for prediction of all-cause and cause-specific mortality

		Model 1			Model 2		
	MetS Component(s)	Integral AUC(t) (Harrell's c)	IDI	NRI	Integral AUC(t) (Harrell's c)	IDI	NRI
All-cause							
Best single component of MetS	T	0.5281	-	-	0.8207	-	-
Best 2 components of Mets	T+H	0.5399[b]	0.001	0.045	0.8210	< 0.001	< 0.001
Best 3 components of Mets	T+H+G	0.5458[b]	0.001	0.046	0.8215	< 0.001	< 0.001
Best 4 components of Mets	T+H+G+BP	0.5501	0.002[c]	0.048[c]	0.8217	< 0.001	< 0.001
5 components of Mets	T+H+G+BP+BMI	0.5531	0.000	0.000	0.8218	< 0.001	< 0.001
Cardiovascular-death							
Best single component of MetS	G	0.5452	-	-	0.8640	-	-
Best 2 components of Mets	G+BP	0.5750[b]	0.008[c]	0.090[c]	0.8642	< 0.001	< 0.001
Best 3 components of Mets	G+BP+T	0.5757	0.009	0.093	0.8649	< 0.001	< 0.001
Best 4 components of Mets	G+BP+T+BMI	0.5760	0.009	0.099	0.8653	< 0.001	< 0.001
5 components of Mets	G+BP+T+BMI+H	0.5764	0.012	0.103	0.8653	< 0.001	< 0.001
Cancer-death							
Best single component of MetS	T	0.5300	-	-	0.8096	-	-
Best 2 components of Mets	T+H	0.5418[b]	0.001	0.010	0.8103	< 0.001	< 0.001
Best 3 components of Mets	T+H+G	0.5474[b]	0.004	0.052	0.8111	< 0.001	< 0.001
Best 4 components of Mets	T+H+G+BMI	0.6050[a]	0.006[c]	0.098[c]	0.8111	< 0.001	< 0.001
5 components of Mets	T+H+G+BMI+BP	0.6322	0.006[c]	0.105[c]	0.8111	< 0.001	< 0.001

AUC(t)= time-dependent area under curve; IDI = integrated discrimination improvement; NRI = net reclassification improvement; BMI=body mass index; BP=blood pressure; G=glucose;H=HDL-cholesterol; MetS=metabolic syndrome; T=triglyceride. Note: Model 1 without including age, sex, smoking status, pre-existing disease at baseline (namely, cancer, angina, acute myocardial infarction, stroke and chronic lung disease) and Model 2 included above covariates [a] $P < 0.05$ and [b] $P < 0.001$, for comparison of AUC(t) with the model immediately preceding. [c] confidence interval for IDI and NDI estimate was significant ($P < 0.05$).

3.5 Discussion

In this prospective cohort study of an Australian white population participating in the BMES, we found the following: First, MetS, exhibited a time-dependent association with all-cause, CVD and cancer deaths. Secondly, the AUC(t), IDI and NRI analyses showed that different MetS components were associated with different causes of death. Finally, the inclusion of age improved the model fitting substantially as compared to any single or combined MetS components.

In studies where the exposure of interest, such as MetS and its components vary over the study follow-up, these covariates may be regarded as time-dependent. In such situations, it is important to take into account the changing effect of the covariates during the model building. To our knowledge, this is the first study to have fully utilised the information of MetS recorded at baseline and all-follow-up visits to determine whether its relationship with mortality changes with time. Longitudinal studies that do not account for changes in exposure over time will not be able to distinguish between short and long term effects, and hence may result in less sensitive estimates of the exposure effect on outcomes (Collett 2003).

In this study, we found that, the risk of all-cause- and CVD-mortality increased gradually from 2-year to 10-year follow-up amongst those with MetS. Previous studies with follow-up duration ranging between 4.4 and 12.3 years, examining the relationship between baseline MetS and all-cause or CVD mortality, have reported inconsistencies in the relationship (Fried et al. 1998; Hu et al. 2004; Satio et al. 2009a; Zambon et al. 2009; Akbaraly et al. 2010;

Berrington de Gonzalez 2010; Salminen et al. 2010; Sidorenkovet al. 2010). In studying whether mortality is associated with MetS, it is important to take into account the duration of follow-up and changes in the status of MetS over time.

In contrast to all-cause and CVD death, MetS was more likely to be associated with a greater risk of early cancer death after 2 years, but this increased risk was attenuated over time. This argument is plausible, since people with cancer are more likely to lose their weight over time and as BMI is a mandatory component of MetS by definition, they would not be categorized as having MetS. However, the induction period between MetS components and the incidence of cancer which had been started years before cancer-death would be another main concern. Previous prospective studies adopting different definitions of MetS at baseline with follow-up duration ranging between 7 and 14 years (Jaggers et al. 2009; Akbaraly et al. 2010) have also found it to predict cancer death. Moreover, uncontrolled confounding such as chronic inflammation may be present. MetS is a multifactorial condition and the mechanisms behind its associated increase in cancer mortality are not completely understood (Jaggers et al. 2009). However, excess glucose has been shown to promote the formation of reactive oxygen species, which can promote cancer development (Jaggers et al. 2009).

When we considered only the information about MetS at baseline, without taking into account changes in MetS status at follow-up, we did not detect any positive effects of MetS on all-cause and CVD mortality even after adjustment for age, sex, smoking and pre-existing disease status. Therefore, the time-varying effects of MetS on all-cause and CVD mortality would not have been detected if

we had only utilized its baseline information. The results of this study underscore that the presence of MetS at longer term follow-up (eg. 10-year) is more likely to confer a better prediction of all-cause death.

Interestingly, consistent with the increase in AUC(t), the result of IDI and NRI tests showed MetS and its components improved the prediction of mortality. TG was the best single predictor of all-cause and cancer mortality in the elderly Australian population, while high glucose was the best single predictor of CVD death. BMI, a mandatory MetS component based on the IDF criteria, on its own was not as good a predictor. Based on IDI and NRI tests, an additional MetS component, namely BP for both all-cause and cancer-death was detected in the model in comparison with AUC(t) test. This may be because the IDI and NRI are more sensitive discrimination tools than AUC (Pencina et al. 2008). The findings that these risk factors clustered, thus leading to an increase in mortality risk may be useful to physicians for risk assessment (Wilken 2005).

Another key finding of this study was that the model fit improved significantly after adjusting for age and lethal diseases, with more than a 1.5-fold increase in AUC(t). This implied that age and lethal diseases, more than any of the MetS components, were important predictors of death in the elderly. As they had profound effect on mortality which was not seen with MetS and its components, they should thus be appropriately accounted for in the analysis. On the other hand, the effects of MetS were close to chance alone with Harrell's *c* ranging between 0.52 to 0.55.

While this study has its specific strength such as low likelihood of misclassification error due to high specificity and sensitivity of death registration, its drawbacks must also be noted. In this study, the IDF criteria for defining MetS was used. As mentioned in **Chapter 2**, the prevalence of MetS was low, and so this may result in inadequate statistical power. Thus, it might be better to compare the results obtained using IDF definition with other MetS criteria such as ATP 3.

In conclusion, the time-dependent association found between MetS with all-cause, cardiovascular- and cancer deaths underscores the importance of fully accounting for the information about MetS collected at each follow-up in order to better predict all-cause and major causes of death among the elderly. Hence, time-dependent models may be clinically more relevant, as they depict the clinical scenarios where MetS and its components may change over time. This allows the physicians to better evaluate and manage the elderly.

CHAPTER 4— The Prognostic Role of Body Mass Index on Mortality amongst the Middle-Aged and Elderly: A Competing Risk Analysis

SUMMARY

Studies that have examined the association between obesity and cause-specific mortality have failed to take into account "competing risks" from other causes of death. This study aims to determine the relationship between body mass index (BMI) including its 5-year changes, with mortality using the Cox and competing risks models and compare the results thus obtained. We examined the pattern of relationship between baseline BMI and all-cause mortality using cubic spline, and found it to be dependent on age. Based on the competing risks model, obesity at baseline was associated with increased risk of cardiovascular death and a reduction in BMI at 5-year was linked to an increase risk of cancer death amongst those aged ≤ 70 years. The cause-specific Cox model showed that reduction in BMI at 5-year was associated with cancer-death regardless of age, and with cardiovascular deaths among subjects aged ≤ 70 years. The Cox regression model showed a larger magnitude of effect with wider confidence interval as compared with the competing risks model. Conditions associated with obesity are more likely to affect mortality among subjects aged ≤70 years, but not those aged over 70 years. BMI reduction, a marker of disease severity, was associated with cancer-death and cardiovascular-death only among those aged ≤ 70 years. In the presence of multiple causes of death, the competing risks model allows for a more accurate estimate of the effect as compared with cause-specific Cox regression.

4.1 Literature review

Baseline body mass index and all-cause / cause-specific mortality

Table 4.1 shows the pattern of association between baseline BMI and all-cause mortality. Different studies have exhibited different patterns of relationship. For example, a study in U.S. found no association (Tayback et al. 1990), whereas two large scale cohort studies found a linear relationship between BMI and mortality (Lindsted and Singh 1997; Ajani et al. 2004). Yet again, a large scale cohort study found a U-shaped relationship between baseline BMI and mortality (Adams et al. 2006). In contrast, a study in Denmark showed the U-shaped relationship between baseline BMI and mortality levelled off with advancing age in females and that higher BMI had no association with mortality in elderly males (Thinggaard et al. 2008). However, Tsai and Hsiao (2012) showed an L-shaped relationship between BMI and mortality among elderly over 65 years in Taiwan.

Table 4.1 Pattern of association between BMI and all-cause mortality

Study, year	Place	N	Age	Pattern
Tayback, 1990	USA	4710	55-74	No association
Lindsted and Singh 1997	USA	12576	55-74	Linear
Ajani, 2004	USA	85078	40-84	Linear
Adams, 2006	USA	527265	50-71	U-shaped
Thinggaard, 2008	Denmark	4253	70-95	Female: U shaped Male: No association
Tsai and Hsiao, 2011	Taiwan	2892	≥ 65	L shaped

Table 4.2 shows the magnitude of association between baseline BMI with all-cause and cause-specific mortality. The relationship between baseline BMI and mortality may be different in older adults as compared with the middle-aged (Corrada et al. 2006). The Framingham Heart Study found high extreme of BMI ($\geq$ 28.7 kg/m^2) to be associated with an increased risk of death only among women (Harris et al. 1988). A prospective cohort study in the Netherlands showed a significant association between BMI $\geq$27.77 kg/m^2 and increased risk of all-cause mortality (Maru et al. 2004). However, the National Health and Nutritional Examination Survey (Flegal et al. 2005) as well as Tsai and Hsiao (2012) found that being underweight was a positive risk factor for all-cause death. Kuk and Ardern (2009) showed that being underweight had no effect on mortality, while obesity had an adverse effect on mortality among men and women aged 18-64 years. A study on three cohorts showed that higher BMI was associated with lower mortality amongst the elderly aged 70 to 88 years (Stessman et al. 2009), whereas a collaborative cohort study showed that being underweight was associated with increased risk of all-cause death among subjects aged 60-69 years. However, obesity was a significant risk factor in the 50 – 69 age groups (Berrington et al. 2010).

Table 4.2 Association between baseline BMI with all-cause and cause-specific mortality

Study, year	Place	N	Age			HR (95% CI)		HR (95% CI)
				Reference group BMI kg/m^2	BMI level for underweight	Underweight	BMI level for obesity	Obesity
All-cause								
Harris, 1988	USA	1723	> 30	23.0-25.2		-	≥28.7 ≥28.5	F:1.6 (1.1-2.3) M: 1.4 (0.9-2.2)
Maru, 2004	Netherland	8100	50-66	≤23.3		-	≥27.8	1.4 (1.2-1.6)
Flegal, 2005	USA	14985	≥ 70	18.5-24.9	< 18.5	1.69 (1.38-2.07)	≥30	1.17 (0.94-1.47)
Kuk, 2009	USA	33994	18-64	15.1-24.0	≤15.0	M:3.39 (0.77-14.9) F:1.13 (0.38-3.30)	≥32.9	M:2.85 (1.28-6.34) F: 4.26 (2.10-8.63)
			65-75			M:2.41 (0.64-9.12) F:2.41 (0.64-9.12)		M:0.96 (0.25-3.64) F:1.23 (0.56-2.67)
Stessman, 2009	Jerusalem	2403	70-88	18.0-24.9		-	≥30	F:0.93 (0.87-0.99) M:0.93 (0.88-0.98)
Berrington, 2010	USA	900000	50-59	22.5-24.9	15.0-18.4	1.15 (0.90-1.46)	30.0-34.9	1.56 (1.46-1.68)
			60-69			1.49 (1.30-1.71)		1.34 (1.28-1.41)
Tsai, 2012	Taiwan	4442	≥ 53	21.0-27.0	<21.0	2.29 (1.11-4.75)	>27.0	0.60 (0.27-1.31)
Cardiovascular-death								
Maru, 2004	Netherland	8100	50-66	≤23.3		-	≥27.8	1.8 (1.3-2.3)
Funada, 2008	Japan	43916	40-79	22.5-24.9	<18.5	1.62 (1.19-2.19)	≥30	1.88 (1.23-2.87)
Cancer-death								
Baade, 2011	Australia	1825	> 20	18.5-24.9	<18.5	1.74 (1.01-3.04)	≥30	0.78 (0.59-1.03)
Parr, 2011	Asia-Pacific	401215	≥ 20	18.5-24.9	<18.5	1.12 (0.96-1.31)	≥30	1.21 (1.09-1.36)

HR= Hazard ratio; CI=confidence interval. Maru (2004) is a study involving female only. BMI units ≤23.30 kg/m^2 was regarded as reference group. "F" refers to female and "M" refers to male.

Regarding the relationship between baseline BMI and cardiovascular death, Maru et al. (2004) showed an increased risk of CVD mortality amongst the obese. Among Japanese middle-aged adults, being underweight and being obese were positively associated with CVD-death (Funada et al. 2008).

A prospective study in Australia showed that being underweight was positively linked to cancer-specific death (Baade et al. 2011), whereas the Asia-Pacific Cohort Studies Collaboration showed that obesity was positively associated with cancer-death (Parr et al. 2011).

BMI changes and all-cause/cause-specific mortality

Table 4.3 shows the literature review on the association between changes in BMI and mortality. A cohort study in UK showed no effect of changes in BMI on all-cause death (Wannamethee et al. 2001). Two prospective cohort studies in the USA and Norway showed that BMI loss but not BMI gain was positively associated with all-cause death (Newman et al. 2001; Droyvold et al. 2005). Moreover, in London, a prospective cohort study showed that, both BMI loss and gain were positively associated with all-cause death (Breez et al. 2006). A large prospective study showed that weight loss was associated with increased risk of all-cause death, while weight gain was a protective factor for all-cause death (Satio et al. 2009b). The Health and Retirement Study found that weight loss was associated with excess mortality for initial BMI levels below 32 kg/m^2, while large weight gains were associated with excess mortality at high BMIs. (Myrskylä and Chang 2009).

As for cardiovascular mortality, Maru et al. (2004) showed a significant association between BMI loss and increased risk of CVD mortality in females. However, Droyvold et al. (2005) found that BMI loss was associated with increased risk of CVD death in both genders.

With respect to cancer-death, a large prospective study showed that weight loss but not weight gain was positively associated with cancer-death (Satio et al. 2009b).

Table 4.3 Association between BMI changes with all-cause and cause-specific mortality

Study, year	Place	N	Age	Change (year)	HR (95% CI)	
All-cause					Loss	Gain
Wannamethee, 2001	UK	7735	40-59	5	1.15 (0.84-1.58)	1.79 (0.89-3.61)
Newman, 2001	USA	4255	≥ 65	3	1.67 (1.29-2.15)	0.94 (0.65-1.46)
Droyvold, 2005	Norway	M:20542 F:23712	≥ 20	11	1.6 (1.4-1.8) 1.7 (1.5-2.0)	1.0 (0.9-1.1) 0.9 (0.8-1.0)
Breez, 2006	UK	4862	40-69	5	1.26 (1.1-1.5)	1.36 (1.1-1.7)
Satio, 2009b	Japan	88419	40-69	-	1.44 (1.32-1.56)	0.89(0.82-0.97)
Myrskylä and Chang, 2009	USA	13104	50-70	2	1.61 (1.31-1.98)	1.33 (1.00-1.77)
Cardiovascular-death						
Maru, 2004	Netherland	F: 8100	50-66	1	1.5 (1.1-2.1)	0.9 (0.6-1.3)
Droyvold, 2005	Norway	M:20542 F:23712	≥ 20	11	1.5 (1.2-1.9) 1.7 (1.3-2.1)	1.0 (0.9-1.2) 1.0 (0.8-1.3)
Cancer-death						
Satio, 2009b	Japan	88419	40-69	-	1.27 (1.12-1.44)	0.90 (0.80-1.02)

HR= Hazard ratio; CI=confidence interval. "F" refers to female and "M" refers to male

4.2 Significance of study

The prevalence of obesity in younger adults and elderly will increase in most countries (Haslam and James 2005; Prospective Studies Collaboration et al. 2009). A high incidence of obesity in the population has huge consequences for health care, now and in the future. An increased proportion of overweight and obese subjects will lead to poor health outcomes such as hypertension, diabetes,

CVD and disability, which place an immense strain on health and social services (Haslam and James 2005).

The specific pattern of the relationship between BMI and all-cause mortality, especially in the overweight and obese range, is still a matter of debate. While some studies exhibited a U-shaped (Adams et al. 2006) or L-shaped (Tsai and Hsiao 2012) relationship between BMI and mortality among the middle-aged and elderly, others have shown a linear (Lindsted and Singh 1997; Ajani et al. 2004) or no association (Tayback et al. 1990; Thinggaard et al. 2008). Previous prospective cohort studies have tried to describe the impact of obesity on all-cause and cause-specific mortality, however, conflicting results remain amongst the middle-aged and elderly, with a lack of evidence to prove the strength of association between obesity and mortality (Tayback et al. 1990; Lindsted and Singh 1997; Flegal et al. 2005; Adams et al. 2006; Corrada et al. 2006; Kuk and Ardern 2009; Berrington de Gonzalez et al. 2010; Teucher et al. 2010; Thinggaard et al. 2010; Tsai and Hsiao 2012). Variation in age of participants in different studies may contribute to the conflicting findings in these studies, with some studies suggesting that overweight and obesity may not be a risk factor for mortality in the elderly (Flegal et al. 2005; Kuk and Ardern 2009). Moreover, the impact of changing BMI over a period of time on mortality remains uncertain (Yun et al. 2010). Some studies reported that an increase or decrease in BMI over time predicts a greater risk of CVD, cancer or all-cause mortality among middle-aged or elderly (Breeze et al. 2006; Bamia et al. 2007; Myrskylä and Chang

2009), while others have not noted this association (Corrada et al. 2006; Saito et al. 2009b).

Although obesity is associated with an increase in risk of mortality from multiple causes, studies that have examined the association between obesity and cause-specific mortality have failed to take into account "competing risks" from other causes of death. As mentioned in **Chapter 1**, when competing risks are not rare especially among the elderly population, the Cox-regression model may overestimate the relationship between exposure of interest such as BMI and multiple failure endpoints such as cardiovascular- and cancer-death (Koller et al. 2008). Therefore, for analysis of different causes of death, competing risks analysis provides a more robust estimate of exposure on different causes of death, by accounting for each competing risks in the analysis (Wolbers et al. 2009; Tai et al. 2010; Tai et al. 2011a; Tai et al. 2011b).

To our best knowledge, competing risk models have not been used to evaluate the relationship between BMI and its changes with cause-specific mortality. Therefore, in this study, we first sought to exhibit the pattern of the relationship between BMI and mortality. We then determine the association between baseline BMI and the 5-year change in BMI with all-cause and cause-specific mortality in the BMES, and compare the results obtained using standard survival models such as the Kaplan-Meier method and Cox regression with the competing risks model.

4.3 Methods

Study design and population

A detailed description of the study design and population of the BMES was provided in **Chapter 2**. In brief, the BMES is a prospective cohort study of vision and other health outcomes in white Australians. Two adjoining urban postcode areas in the Blue Mountains area, west of Sydney, in New South Wales, Australia, were selected as target population (Mitchell et al. 1998a).

In this study, we included 2216 subjects with complete information on age, sex, smoking status, physical activity and pre-existing diseases, as well as BMI from both the baseline (1992-1994) and 5-year (1997-1999) examinations. Participants who died shortly after the study baseline visit were excluded from the analysis as in a previous study (Corrada et al. 2006), to control for the relation between reduced BMI, morbidity and early death (Wannamethee et al. 2001).

Data collection

A detailed description of the data collection was provided in **Chapter 2**. Briefly, at each visit, a comprehensive questionnaire comprising demographic information, smoking status (current, former and never smoker), alcohol intake (gram per week) and a detailed history of diseases, including hypertension, diabetes, angina, AMI, stroke and cancer as well as medication was recorded at face-to-face interviews conducted by trained interviewers using a standardised questionnaire (Mitchell et al. 1998a). We define pre-existing disease(s) as a binary variable based on past history or medication for at least one of the above mentioned diseases. In addition, self-reported physical activity based on time

spent on activities per week using the International Physical Activity Questionnaire (Craig et al. 2003) was collected. Similar to previous studies (Breeze et al. 2006; Saito et al. 2009b; Berrington de Gonzalez et al. 2010; Thinggaard et al. 2010), we define middle-aged and elderly using age ≤ 70 and > 70 years respectively.

Study factor

Participants had their weight (after removal of shoes and heavy clothing) measured by standing on an automated scale, to which a vertical height measure was attached (Younan et al. 2003). The BMI was calculated as weight (kg)/height (m^2). Baseline BMI was re-categorized using the classification of the World Health Organization Expert Committee on Physical Status (1995): underweight: <18.5 kg/m^2, normal weight: 18.5 to <25 kg/m^2, overweight: 25 to <30 kg/m^2, and obese: ≥30 kg/m^2. Normal weight was considered as the reference group in all analyses.

Five-year change in BMI from baseline was categorized as follows: stable: <1 BMI unit change, gain: ≥1 BMI unit gain, reduction: ≥1 BMI unit loss (Myrskylä and Chang 2009). Stable BMI was regarded as the reference group in all analyses involving changes in BMI from the baseline to 5-year visit.

Study outcome

A detailed description of the study outcome was provided in **Chapter 3**. Briefly, all-cause and cause-specific mortality including cardiovascular-, cancer- and other causes of death were our study outcomes in this study. Chapter 3 focused on the association between all-cause and cause-specific mortality assuming MetS and its

components were time-dependent. In this study, we focus first on the pattern of association between baseline BMI and all-cause death. We then evaluate the relationship between change in BMI over 5-year since baseline with all-cause and cause-specific mortality and compare the estimates obtained using Cox regression and Kaplan-Meier (KM) method with competing risks analysis. As mentioned in **Chapter 3**, deaths occurring after baseline recruitment (1992–1994) until 31 December 2007 were confirmed by matching the demographic information of the participants with the Australian NDI, using probabilistic record linkage. Causes of death were provided by the NDI using the ICD 9^{th} revision and 10^{th} revision (Wang et al. 2006).

Statistical analyses

We first explored the relationship between baseline BMI (continuous) and the risk of death via non-parametric regression model based on cubic spline (Harrell 2001) with four internal knots at the 5^{th}, 15^{th}, 75^{th} and 90^{th} percentiles of the BMI distribution. In the graphical display, we selected the upper bound of the reference group (normal weight) at 23.5 kg/m^2 as reference.

In examining the associations between BMI and all-cause mortality, we used the Cox proportional hazards model. Time-to-death (year) is the primary outcome variable for all-cause mortality. We implemented the competing risks model (Tai et al. 2011a; Tai et al. 2011b) to study the associations between BMI (baseline and 5-year change) with cause-specific mortality. In the analysis of cause-specific mortality, the time-to-specific cause of death (year) was the outcome variable. We further compared the results of the competing risks

methods based on cumulative incidence (Tai et al. 2001; Wolbers et al. 2009; Tai et al. 2010; Tai et al. 2011a, Tai et al. 2011b) and competing risks regression (Beyersmann et al. 2007; Tai et al. 2011b) with the KM estimates and cause-specific Cox models respectively. As explained in **Chapter 1**, competing risks models are well-suited for outcomes involving multiple failure types (such as cancer- and cardiovascular-deaths), as it appropriately account for each competing risk in the analysis, yielding a more accurate estimation of exposure such as the effect of BMI on different causes of death (Wolbers et al. 2009; Tai et al. 2011a; Tai et al. 2011b).

Sex, smoking status and pre-existing disease(s) at baseline were considered as potential confounders in the multivariable analyses. We further explored effect modification of age, sex and pre-existing disease(s) on BMI. The effect estimate and its 95% CI were presented according to age groups as the interaction between age and BMI was significant ($P < 0.05$). The proportional hazards assumption was checked for individual covariates and globally. We also considered the possibility that our findings might have been confounded by the presence of pre-existing diseases at baseline and adjustment for it might not totally account for its effect as pre-existing disease might result in weight loss and consequently caused premature mortality. Therefore, in a supplementary analysis, we excluded people with pre-existing diseases at baseline and further explored the relationship between BMI and its changes with all-cause and cause-specific mortality using Cox regression and competing risks models in this subgroup of

subjects. The non-parametric plot of cubic spline was generated using R statistical package (www.r-project.org).

4.4 Results

Demographic profile of subjects

Table 4.4 provides a description of the baseline characteristics of the 2216 participants. Generally, underweight persons were more likely to be younger (65%) and predominantly female (74%). Moreover, obese persons were more likely to be younger (78%) or have a history of pre-existing disease(s) (58%) at baseline. There were 599 (27%) deaths reported until December 2007. Of these, 234 (39%) were cardiovascular-deaths and 167 (28%) were cancer-deaths. During a median follow-up duration of 14.7 years, 12 (39%) underweight and 109 (29%) obese subjects had died.

Table 4.4 Baseline characteristics of 2216 study subjects according to BMI categories

Variable	Total (n = 2216) %	Under weight (n = 31) %	Normal weight (n = 902) %	Overweight (n = 907) %	Obese (n = 376) %	P-value
Age (year) ≤70	75.4	64.5	71.9	78.3	77.7	0.005
>70	24.6	35.5	28.1	21.7	22.3	
Gender						
Female	57.6	74.2	60.0	50.2	68.4	<0.001
Male	42.4	25.8	40.0	49.7	31.6	
Smoking status						
Current smoker	12.7	22.6	14.9	10.9	11.2	0.068
Ex-smoker	35.6	29.0	33.4	37.8	35.9	
Non-smoker	51.7	48.4	51.8	51.3	52.9	
Diabetes	6.5	3.2	4.1	6.6	12.2	<0.001
Hypertension	30.7	12.9	25.5	31.6	42.3	<0.001
History of stroke	3.4	3.2	3.6	3.2	3.5	0.980
History of angina	11.3	6.5	9.1	13.2	12.6	0.031
History of AMI	8.0	6.5	6.7	8.9	9.1	0.257
History of cancer	7.7	8.8	6.4	6.5	8.0	0.332
Pre-existing disease(s)	46.2	41.3	29.0	46.6	58.5	<0.001

Abbreviations: AMI = acute myocardial infarction; BMI = body mass index.
Note: Figures in parentheses denote percentages.

Of the obese subjects who died during the study follow-up, the prevalence of pre-existing disease at baseline were higher amongst those aged ≤ 70 years than older subjects (history of diabetes 44% vs 27%, hypertension 26% vs 17%, stroke 13% vs 11%, angina 28% vs 9%, AMI 29% vs 12% and cancer 24% vs 15%) (Table 4.5).

Table 4.5 Prevalence of disease at baseline amongst subjects who died during study follow-up according to weight status and age group

Disease at baseline	Underweight	Normal weight	Over weight	Obese	P-value
Age ≤ 70 year					
Diabetes (n=23)	7 (30.4)	0 (0.0)	6 (26.1)	10 (43.5)	0.098
Hypertension (n=90)	25 (27.8)	0 (0.0)	42 (46.7)	23 (25.6)	0.119
History of stroke (n=15)	5 (33.3)	0 (0.0)	8 (53.3)	2 (13.3)	0.757
History of angina (n=54)	15 (27.8)	0 (0.0)	24 (44.4)	15 (27.8)	0.407
History of AMI (n=45))	12 (26.7)	0 90.0)	20 (44.4)	13 (28.9)	0.442
History of cancer (n=33)	9 (27.3)	0 (0.0)	16 (48.5)	8 (24.2)	0.723
Pre-existing disease(s) (n=152)	47 (30.9)	0 (0.0)	66 (43.4)	39 (25.7)	0.017
Age > 70 year					
Diabetes (n=30)	7 (23.3)	0 (0.0)	15 (50.0)	8 (26.7)	0.013
Hypertension (n=131)	60 (45.8)	0 (0.0)	49 (37.4)	22 (16.8)	0.151
History of stroke (n=19)	8 (42.1)	0 (0.0)	9 (47.4)	2 (10.5)	
History of angina (n=68)	28 (41.2)	0 (0.0)	34 (50.0)	6 (8.8)	0.057
History of AMI (n=42)	16 (38.1)	1 (2.4)	20 (47.6)	5 (11.9)	0.409
History of cancer (n=27)	14 (51.8)	1 (3.7)	8 (29.6)	4 (14.8)	0.583
Pre-existing disease(s) (n=198)	86 (43.4)	2 (1.0)	80 (40.4)	30 (15.1)	0.150

Abbreviation: AMI=acute myocardial infarction. Note: Figures in parentheses denote percentages.

Relationship between baseline BMI with all-cause and cause-specific mortality

Interaction effect was noted between age and baseline BMI for all-cause (P=0.049) and cardiovascular- (P=0.044) death. As such, we have reported the results of our analysis according to age. Figure 4.1 shows the risk of all cause-death was U shaped with the highest mortality rates at the two extreme ranges of BMI for all subjects as well as for those aged ≤ 70 years. However, for persons aged over 70 years at baseline, the L-shaped relationship suggests a higher risk of death amongst the underweight, with no elevation in the mortality risk for the overweight or obese, as compared with the normal weight.

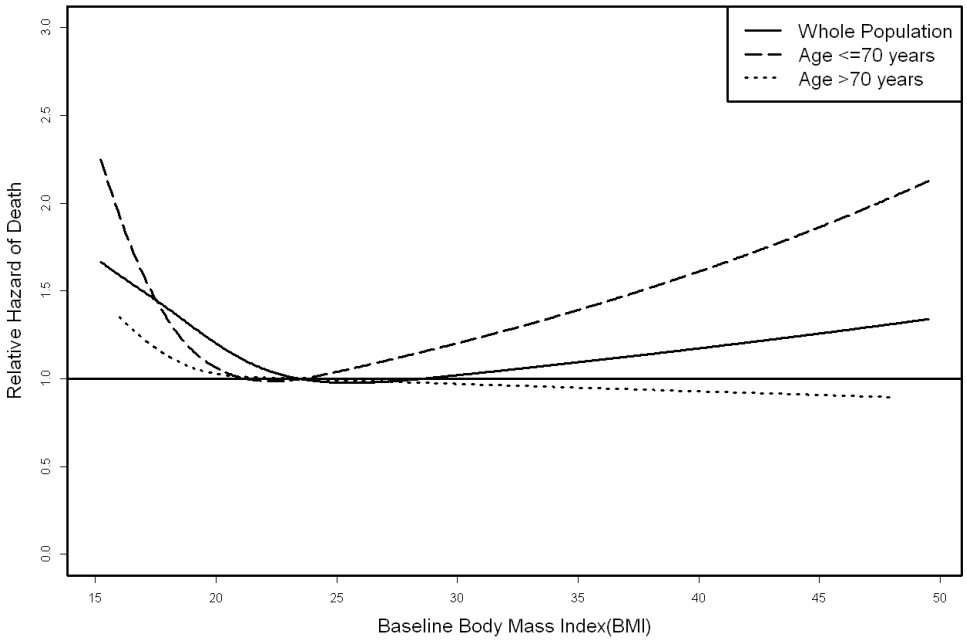


Figure 4.1 Cubic splines describing the nonlinear relationship between body mass index (kg/m^2) and the relative hazard of death

Table 4.6 Age-specific associations between baseline BMI and its 5-year changes with all-cause and cause-specific mortality according to competing risks and cause-specific Cox regression models

	All-cause (*n*=599)		Cancer (*n* = 167)		Cardiovascular (*n*=234)		Cancer	Cardiovascular
	Cox-regression model		**Competing risks model**				**Cause-specific Cox regression**	
Baseline BMI (kg/m^2)	No. died	HR (95% CI)	No. died	SHR (95% CI)	No. died	SHR (95% CI)	HR (95% CI)	HR (95% CI)
Age ≤ 70								
Underweight (n=20)	6	1.82 (0.80-4.15)	2	0.95 (0.14-6.53)	2	1.34 (0.18-7.25)	0.96 (0.13-6.81)	1.73 (0.17-7.50)
Overweight (n=710)	118	1.07 (0.82-1.41)	37	0.97 (0.61-1.54)	37	1.43 (0.84-2.42)	0.99 (0.62-1.59)	1.43 (0.85-2.41)
Obese (n=292)	64	1.44 (1.05-1.98)	23	1.51 (0.88-2.59)	22	2.06 (1.14-3.70)	1.58 (0.98-2.68)	2.07 (1.15-3.72)
Age > 70								
Underweight (n=11)	6	1.20 (0.53-2.72)	2	0.68 (0.09-4.94)	4	1.73 (0.55-5.40)	0.90 (0.12-6.64)	1.95 (0.60-5.45)
Overweight (n=197)	116	0.98 (0.77-1.25)	27	1.01 (0.60-1.69)	53	0.85 (0.60-1.22)	1.02 (0.61-1.69)	0.87 (0.61-1.24)
Obese (n=84)	45	0.94 (0.67-1.32)	11	1.07 (0.54-2.15)	20	0.78 (0.47-1.31)	1.12 (0.56-2.25)	0.81 (0.49-1.33)
Change in BMI(kg/m^2)								
Age ≤ 70 years								
Reduction (*n* =169)	55	2.22 (1.60-3.09)	23	3.03 (1.76-5.23)	14	1.55 (0.83-2.89)	3.20 (1.86-5.50)	1.85 (1.02-3.46)
Gain (*n* = 875)	124	0.88 (0.68-1.14)	41	1.01 (0.63-1.60)	34	0.74 (0.46-1.18)	1.01 (0.63-1.60)	0.78 (0.49-1.25)
Age > 70 years								
Reduction (*n* = 109)	81	1.76 (1.32-2.35)	19	1.42 (0.78-2.60)	35	1.07 (0.69-1.65)	1.89 (1.04-3.43)	1.40 (0.92-2.14)
Gain (*n* = 223)	113	0.86 (0.66-1.11)	25	0.92 (0.53-1.58)	54	0.81 (0.56-1.17)	0.92 (0.52-1.58)	0.82 (0.55-1.19)

Abbreviations: BMI = body mass index; CI = confidence interval; HR = hazard ratio; SHR=subdistribution hazard ratio. Note: Model is adjusted for sex, smoking status and pre-existing disease(s) at baseline. For baseline BMI, normal weight and for BMI changes, stable BMI regarded as reference group. Stable BMI: < ±1 unit BMI change, BMI gain/reduction: ± ≥ 1 unit BMI change.

Consistent with Figure 4.1, Table 4.6 shows that for persons aged ≤ 70 years at baseline, there was an increased risk of all-cause mortality amongst the obese (HR 1.44, 95% CI: 1.05-1.98). There was also suggestion that being underweight may increase the risk of all-cause death. Similarly, obesity was associated with a greater risk of cardiovascular mortality in this age group based on competing risk (SHR 2.06, 95% CI: 1.14-3.70) and Cox regression (HR 2.07, 95% CI: 1.15-3.72) analyses (Table 4.6). Amongst persons aged over 70 years, there was no evidence of association between baseline BMI and all-cause or cause-specific mortality (Table 4.6). Although the conclusions drawn based on the two methods were largely similar, the magnitude of effect was larger, and with wider CI based on the cause-specific Cox model as compared with the competing risk regression in most instances (Table 4.6).

Changes in BMI and all-cause or cause-specific mortality

Over the 5-year period, reduction in BMI was observed in 278 (13%) subjects, while 1098 (50%) of them experienced an increase in BMI. Generally, persons with reduced or increased BMI tended to be younger (61% and 80%, respectively). A higher proportion with pre-existing disease(s) at baseline was noted amongst those with a decrease in BMI in subsequent 5 years, as compared with the other groups (Table 4.7).

Table 4.7 Baseline characteristics of 2216 study subjects according to 5-year changes in BMI

	Total (n = 2216)	Stable BMI (n = 840)	Reduction (n = 278)	Gain (n = 1098)	P-value
Age (year) ≤70		627 (74.6)	169 (60.8)	875 (79.7)	< 0.001
>70		213 (25.4)	109 (39.2)	223 (20.3)	
Sex (%)					
Female	1277 (57.6)	421 (50.1)	181 (65.1)	675 (61.5)	< 0.001
Male	939 (42.4)	419 (49.9)	97 (34.9)	423 (38.5)	
Smoking status (%)					
Current smoker	282 (12.7)	99 (11.8)	46 (16.5)	137 (12.5)	0.025
Ex-smoker	788 (35.6)	329 (39.2)	91 (32.7)	368 (33.5)	
Non-smoker	1146 (51.7)	412 (49.0)	141 (50.7)	593 (54.0)	
Diabetes (%)	142 (6.5)	54 (6.5)	32 (11.9)	56 (5.1)	< 0.001
Hypertension (%)	680 (30.7)	260 (30.9)	108 (38.8)	312 (28.4)	0.003
History of stroke (%)	75 (3.4)	34 (4.1)	15 (5.4)	26 (2.4)	0.018
History of angina (%)	250 (11.3)	91 (10.9)	42 (15.2)	117 (10.7)	0.095
History of AMI (%)	177 (8.0)	58 (6.9)	29 (10.5)	90 (8.2)	0.162
History of cancer (%)	170 (7.7)	66 (7.9)	25 (9.0)	79 (7.2)	0.584
Pre-existing disease(s) (%)	1025 (46.2)	392 (46.7)	156 (56.1)	477 (43.4)	0.001

Abbreviations: AMI = acute myocardial infarction; BMI = body mass index.
Note: Stable BMI: < ±1 unit BMI change, BMI gain/reduction: ± ≥ 1 unit BMI change.

The overall mortality rate was the highest amongst those with a BMI decrease (49%) and the lowest amongst those with a BMI increase (22%). The magnitude of 5-year changes in BMI according to age group is shown in Table 4.8. In particular, the proportion with BMI reductions among elderly subjects (<-5 [1.5%], -5 to -3 [3.7%], <-3 to -1 [11.1%]) were higher as compared to younger subjects (< -5 [0.6%], -5 to -3 [1.7%], <-3 to -1 [6.4%]).

Table 4.8 Magnitude of 5-year BMI changes according to age group

Unit BMI change	≤ 70 years	> 70 year
< -5	7 (0.6)	17 (1.5)
-5 to -3	19 (1.7)	41 (3.7)
< -3 to -1	72 (6.4)	122 (11.1)
< ±1 (Stable BMI)	411 (36.7)	429 (39.1)
1 to < 3	404 (36.1)	374 (34.1)
3 to 5	165 (14.7)	89 (8.1)
>5	41 (3.7)	25 (2.3)

Note: The figures presented above denote frequency and percentage.

Moreover, a higher proportion of those who were obese at baseline experienced BMI reduction (16.8%) while, a lower proportion of those who were underweight at baseline experienced BMI reduction (5.0%) among those aged ≤ 70 years. Among the elderly subjects, the proportions with BMI reduction in the obese and underweight groups were 30.9% and 9.1% respectively (Table 4.9).

Table 4.9 Five-year changes in BMI according to baseline BMI categories and age group

Baseline BMI categories	Age ≤ 70			Age > 70		
	BMI reduction	Stable BMI	BMI increase	BMI reduction	Stable BMI	BMI increase
Underweight	1 (5.0)	7 (35.0)	12 (60.0)	1 (9.1)	7 (63.6)	3 (27.3)
Normal weight	35 (5.4)	247 (38.1)	367 (56.5)	34 (13.4)	107 (42.3)	112 (44.3)
Overweight	84 (11.8)	276 (38.9)	350 (49.3)	48 (24.4)	75 (38.1)	74 (37.6)
Obese	49 (16.8)	97 (33.2)	146 (50.0)	26 (30.9)	24 (28.6)	34 (40.5)

Note: The figures presented above denote frequency and percentage.

Figure 4.2 shows the KM cumulative incidence curve for cancer- and cardiovascular-deaths according to changing BMI status. The estimates were larger than those obtained using the competing risks method for all BMI groups under consideration.

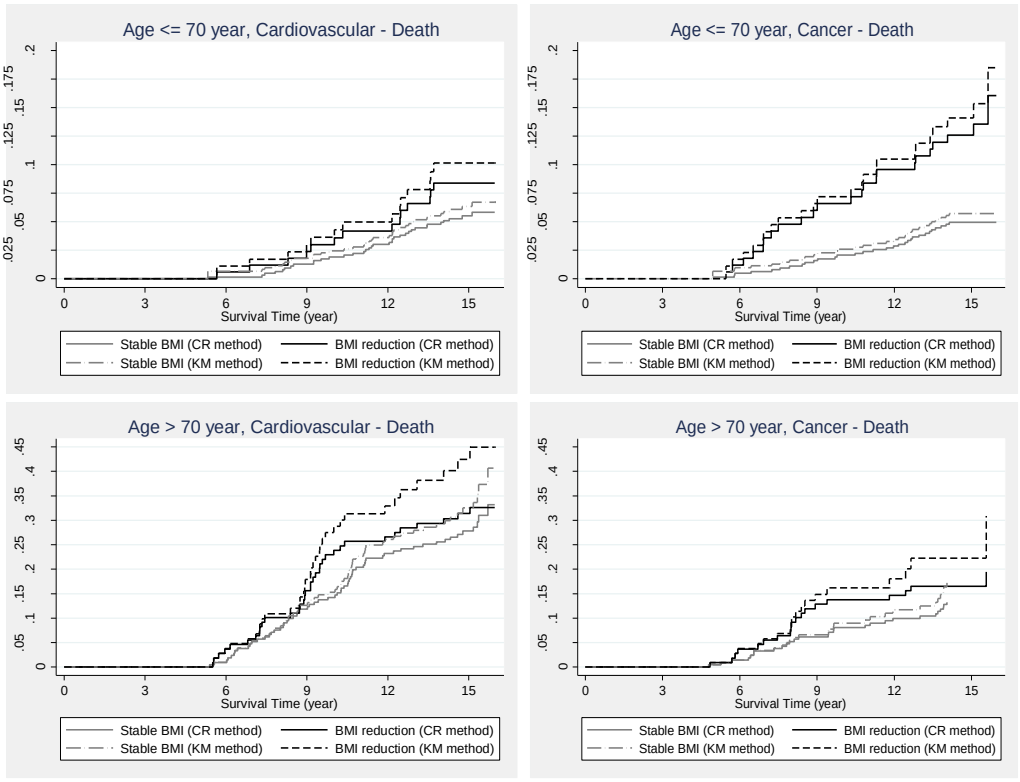


Figure 4.2 Comparison of cumulative incidence of cardiovascular and cancer mortality according to 5-year BMI changes: Competing risks (CR) versus Kaplan-Meier (KM) methods

Reduced BMI was associated with a higher risk of all-cause mortality regardless of age (≤70 years: HR 2.22, 95% CI: 1.60-3.09; >70 years: HR 1.76, 95% CI: 1.32-2.35) (Table 4.6). Amongst subjects aged ≤ 70 years, reduction in BMI was significantly associated with cardiovascular death (HR 1.85, 95% CI: 1.02–3.46) and cancer-death (HR 3.20, 95% CI: 1.86–5.50) in the cause-specific Cox model, although this association was not confirmed by the competing risks model for cardiovascular-death (SHR 1.55, 95% CI: 0.83–2.89) (Table 4.6). Similarly, subjects aged >70 years with reduced BMI were also found to have an elevated risk of cancer death (HR 1.89, 95% CI: 1.04–3.43) in the cause-specific Cox model only (Table 4.6).

Table 4.10 Age-specific associations between BMI changes with all-cause and cause-specific mortality in overweight/obese group according to competing risks and cause-specific Cox regression models

	All-cause (*n*=343)		Cancer (*n* = 98)		Cardiovascular (*n*=132)		Cancer (*n* = 98)	Cardiovascular (n=132)
	Cox-regression model				**Competing risks model**		**Cause-specific Cox regression**	
	No. died	HR (95% CI)	No. died	SHR (95% CI)	No. died	SHR (95% CI)	HR (95% CI)	HR (95% CI)
Change in BMI(kg/m^2)								
Age ≤ 70 years								
Reduction (*n* =181)	79	2.04 (1.38-3.01)	26	2.33 (1.21-4.48)	29	1.38 (0.67-2.78)	2.52 (1.31-4.85)	1.49 (0.73-3.03)
Gain (*n* = 570)	111	0.89 (0.64-1.23)	34	0.92 (0.32-2.64)	35	0.76 (0.43-1.34)	0.88 (0.49-1.59)	0.77 (0.43-1.36)
Age > 70 years								
Reduction (*n* = 158)	78	2.52 (1.70-3.73)	24	3.87 (1.69-8.90)	31	1.21 (0.68-2.17)	4.32 (1.85-10.10)	1.89 (1.08-3.32)
Gain (*n* = 458)	103	1.21 (0.82-1.79)	28	0.69 (0.09-5.10)	34	0.83 (0.48-1.46)	1.59 (0.66-3.84)	0.90 (0.51-1.59)

Abbreviations: BMI = body mass index; CI = confidence interval; HR = hazard ratio; SHR=subdistribution hazard ratio.

Note: Model is adjusted for sex and smoking status and pre-existing disease(s) at baseline. Stable BMI regarded as reference group.

Stable BMI: $< \pm 1$ unit BMI change, BMI gain/reduction: $\pm \geq 1$ unit BMI change.

Supplementary analysis amongst the subgroup of overweight/obese subjects showed BMI reduction to be significantly associated with all-cause (≤ 70 years: HR 2.04, 95% CI: 1.38-3.01; > 70 years: HR 2.52, 95% CI: 1.70-3.73) and cancer- (≤ 70 years: SHR 2.33, 95% CI: 1.21-4.48; >70 years: SHR 3.87, 95% CI: 1.69-8.90) death among both age groups. Cox-specific regression model additionally showed that BMI reduction in the overweight/obese group was positively linked to an increase in cardiovascular mortality (HR 1.89, 95% CI: 1.08-3.32) among elderly subjects (Table 4.10).

The associations between baseline BMI and its 5-year changes with all-cause and cause-specific mortality amongst subjects without baseline pre-existing diseases

Of the 2216 study subjects, 1191 (54%) had no history of pre-existing disease at baseline. Being underweight at baseline was associated with all-cause death in both age groups (≤70 years: HR 3.29, 95% CI: 1.40-7.69; >70 years: HR 2.82, 95% CI: 1.01-7.89), while obesity was linked to increase risk of cancer-death amongst younger subjects (SHR 2.26, 95% CI: 1.07-4.78) (Table 4.11). As before, the magnitude of effect was larger, and with wider CIs based on the cause-specific Cox model as compared with the competing risk regression in most instances.

Table 4.11 Age-specific associations between baseline BMI and its 5-year changes with all-cause and cause-specific mortality according to competing risks and cause-specific Cox regression models amongst subjects without pre-existing disease(s) at baseline

	All-cause (*n*=249)		Cancer (*n* = 76)		Cardiovascular (*n*=83)		Cancer	Cardiovascular
	Cox-regression model			**Competing risks model**			**Cause-specific Cox regression**	
Baseline BMI (kg/m^2)	No. died	HR (95% CI)	No. died	SHR (95% CI)	No died	SHR (95% CI)	HR (95% CI)	HR (95% CI)
Age ≤ 70								
Underweight (n=16)	6	3.29 (1.40-7.69)	1	1.49 (0.23-9.88)	1	3.25 (0.42-25.00)	1.55 (0.21-11.74)	3.43 (0.43-27.50)
Overweight (n=409)	52	1.02 (0.69-1.51)	15	0.85 (0.43-1.68)	14	1.76 (0.73-4.28)	0.85 (0.43-1.69)	1.79 (0.70-4.33)
Obese (n=127)	25	1.84 (1.14-2.98)	11	2.26 (1.07-4.78)	6	2.59 (0.90-7.46)	2.30 (1.08-4.87)	2.69 (0.93-7.76)
Age > 70								
Underweight (n=6)	4	2.82 (1.01-7.89)	1	1.41 (0.19-10.69)	2	1.76 (0.32-9.72)	3.31 (0.42-25.92)	2.21 (0.51-9.51)
Overweight (n=75)	36	0.93 (0.62-1.41)	11	1.20 (0.55-2.65)	18	1.02 (0.56-1.83)	1.27 (0.54-2.84)	1.02 (0.55-1.86)
Obese (n=29)	15	1.23 (0.69-2.18)	4	1.30 (0.43-3.91)	7	1.01 (0.43-2.36)	1.42 (0.46-4.35)	1.07 (0.46-2.50)
Change in BMI(kg/m^2)								
Age ≤ 70 years								
Reduction (*n* =87)	26	2.91 (1.78-4.75)	11	4.05 (1.78-9.22)	4	1.28 (0.41-3.96)	4.25 (1.87-9.67)	1.42 (0.47-4.36)
Gain (*n* = 523)	66	1.13 (0.77-1.67)	22	1.33 (0.66-2.66)	12	0.63 (0.29-1.37)	1.34 (0.66-2.70)	0.64 (0.29-1.41)
Age > 70 years								
Reduction (*n* = 35)	23	1.74 (1.05-2.88)	4	0.80 (0.25-2.52)	11	1.38 (0.64-3.00)	1.07 (0.35-3.32)	1.71 (0.82-3.55)
Gain (*n* = 98)	44	0.81 (0.54-1.23)	14	1.06 (0.49-2.30)	20	0.81 (0.44-1.48)	1.06 (0.49-2.31)	0.88 (0.46-1.58)

Abbreviations: BMI = body mass index; CI = confidence interval; HR = hazard ratio; SHR=subdistribution hazard ratio.Model is adjusted for sex and smoking status. For baseline BMI, normal weight and for BMI changes, stable BMI regarded as reference group. Stable BMI: < ±1 unit BMI change, BMI gain/reduction: ± ≥ 1 unit BMI change.

With regard to BMI changes over 5-year follow-up since baseline, BMI reduction was associated with an increase risk in all-cause death in both age groups (≤70 years: HR 2.91, 95% CI: 1.78-4.75; >70 years: HR 1.74, 95% CI: 1.05-2.88), and cancer-death amongst those aged ≤70 years (Table 4.11). For the latter, the Cox regression model again showed a higher magnitude of effect as compared with the competing risk model.

4.5 Discussion

In this population-based prospective cohort study of the Australian middle-aged and elderly population, we found the following: First, amongst the younger subjects, the relationship between baseline BMI and all-cause mortality was U-shaped, with both the underweight and obese groups predisposed to have a greater risk of death; obesity was also associated with increased risk of cardiovascular death in this age group. Amongst elderly persons, an L-shaped relationship was seen: only low but not excessive BMI was found to be associated with increased risk of all-cause death. Second, a reduction in BMI between baseline and the 5-year follow-up visit was associated with all-cause mortality in both age groups and cancer deaths among those aged ≤ 70 years. Finally, the cause-specific Cox regression model showed larger magnitude of effect of between 1-33%, as compared with the competing risks model, especially among the elderly subjects.

All-cause mortality risk

Our study has shown that the pattern of relationship between BMI and mortality is dependent on age. The U-shaped relationship between BMI and mortality in

subjects aged ≤ 70 years at baseline is consistent with the findings of Berrington et al. (2010) and Adams et al. (2006) However, this pattern of relationship was not noted amongst the elderly who were aged above 70 years. In particular, there was no elevation in risk of death amongst those who were overweight or obese in this age group. This observation is consistent with that reported by Tsai and Hsiao (2012), who found a similar L-shaped relationship between BMI and all-cause death among Taiwanese over 65 years old. The L-shaped association between baseline BMI and mortality in those > 70 years suggests that overweight/obesity does not predispose the elderly subjects to be at a greater risk of mortality. Although, it is unclear why excess weight protects older adults, we consider three possibilities. Firstly, the advantage of being overweight could be that fat mass stores energy that can be used during negative energy balance (Dahl et al. 2013). For example, extra weight could give older people reserves to recover from stresses such as surgery or pneumonia. Secondly, even though obesity is associated with higher rates of chronic disease such as diabetes, the impact of these conditions on mortality may be reduced when they occur in elderly individuals. For example, Tan et al. (2004) showed that diabetes mellitus that was diagnosed after age of 65 was not associated with increased mortality in Scotland, whereas it was associated with increased mortality when diagnosed below this age. In the Asia Pacific Cohort Studies Collaboration, Woodward et al. (2003) also showed that the effect of diabetes on the risk of CVD and death decreased with increasing age at risk. Thirdly, we also considered the possibility that our findings could have been confounded by the presence of pre-existing diseases at

baseline that could have resulted in weight loss and caused premature mortality. However, we analyzed the data excluding subjects with these underlying conditions and again found overweight/obesity to have no association with death.

Cause-specific mortality risk

In our study, obesity was associated with increased risk of cardiovascular mortality in subjects aged ≤ 70 years. This was consistent with a study in the USA that showed obesity to be associated with coronary heart disease mortality among subjects aged 35-74 years (Mann et al. 2006). Obesity is associated with multiple cardiovascular risk factors including diabetes, hypertension and dyslipidemia (Sowers 2003). As BMI reduction even in obese is a risk factor for death among both middle-aged and elderly subjects and obesity is associated with all-cause and cardiovascular death amongst subjects aged ≤ 70 years, it may be important to control weight and modify lifestyle years before the ageing process sets in. However, our data does not necessarily suggest that weight loss may be detrimental in some instances in older individuals because inference of causality between BMI reduction and mortality cannot be fully established.

A unique aspect of our study is the ability to demonstrate changes in BMI over time. BMI changes in fact occurred in about 60% of the study population over the 5-year period since baseline. As in previous studies (Newmann et al. 2001; Myrskylä and Chang 2009; Bamia et al. 2010), we also found that a reduction in BMI was associated with an increased risk in all-cause mortality amongst both the middle-aged and the elderly. Further, BMI reduction was a

predictor for cancer related mortality amongst those ≤70 years. In general, a decrease in BMI prior to death in the elderly is more likely to be related to the underlying health status (Wannamethee et al. 2001). We therefore excluded participants who died shortly after the study baseline visits in the analysis, as did a previous study (Corrada et al. 2006), and included only subjects who were alive at the 5-year follow-up visit with a minimum follow-up duration of 4 years. We also consider possible effect modification of disease status as well as medication used on BMI but found no evidence of their interactions with either baseline pre-existing disease status (no disease, prevalent disease) or status of pre-existing disease over 5-year follow-up (no disease, prevalent disease, incident disease). These analyses do not exclude the possibility that other disease could have developed during follow up that could have resulted in both weight loss and increased mortality. Considering only subjects who were free of pre-existing disease at baseline, obesity was found to be associated with cancer death only among the subgroup of healthy subjects aged ≤ 70 years.

It is postulated that BMI and its changes may be associated with different causes of death such as cardiovascular- and cancer-deaths which are regarded as competing risks. Therefore, in such situations, it is important to apply an appropriate statistical technique such as the competing risks methods, to appropriately account for each competing risk in the analysis, to yield a more accurate estimate of the association between BMI the and different causes of death.

Importantly, consistent with previous studies (Tai et al. 2001; Wolbers et al. 2009; Tai et al. 2010; Tai et al. 2011a; Tai et al. 2011b), when we analyzed the relationship between baseline BMI and its 5-year changes using cause-specific Cox regression model, the effect estimates were larger than those of the competing risks model by as much as 1-33%. The differences were appreciable especially in the older age group for cancer- (31%) and cardiovascular-death (33%). This finding suggests that as population ages, the presence of competing risks would be more common especially among the frail population. Hence, we encourage the use competing risks models as a standard tool for developing predictive models involving competing risks endpoints especially among elderly population, to provide a more accurate estimate of exposure (Wolbers et al. 2009).

The specific limitations of this study need to be considered. First, there was limited number of underweight subjects resulting in low statistical power. Thus, the findings relating to the underweight should be interpreted with caution. In addition, the possibility of Type II error may exist especially when we analyzed the data amongst the subgroup of healthy subjects. Further, when the *P*-value reported in our study is less than 0.05, we may make Type I error due to chance as several endpoints and subgroups were evaluated. Second, the results could have been biased by residual confounding factors, such as varying levels of body composition, visceral adiposity or physical fitness (Flegal et al. 2005), which were not measured in this study. Third, we had no information about whether BMI loss was achieved intentionally or unintentionally. Fourth, as mentioned in **Chapter 3**, the cause of mortality which was determined by the NDI and the death certificates

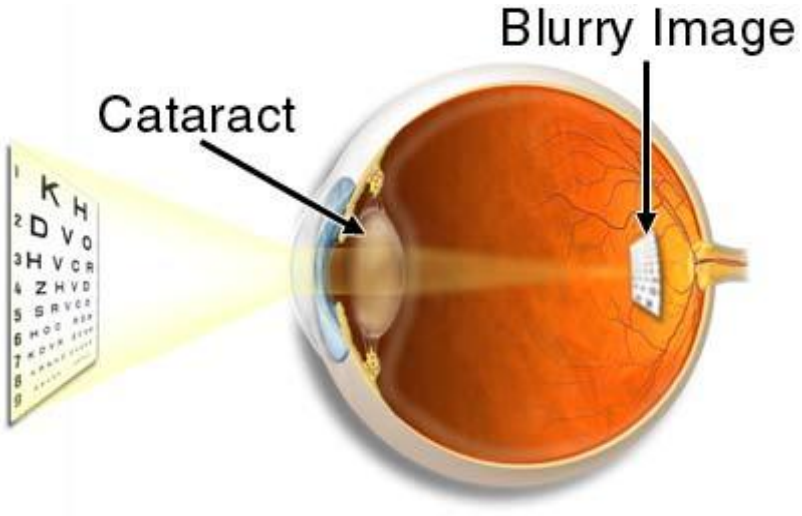
may be biased by the choices of the physicians who filled them out. The strengths of this study are as discussed in **Chapters 2 and 3**.

In conclusion, we have shown that the pattern and association between BMI and mortality are modified by age. Amongst the younger subjects, the relationship between baseline BMI and all-cause mortality was U-shaped, with both the underweight and obese groups predisposed to have a greater risk of death. Amongst elderly persons, an L-shaped relationship was seen: only low but not excessive BMI was found to be associated with increased risk of all-cause death. Moreover, obesity was associated with greater risk of all-cause and cardiovascular-specific mortality amongst subjects ≤70 years old. With respect to changes in BMI over 5 years, BMI reduction, a marker of greater severity of mortality-related diseases, was associated with increased risk of all-cause mortality regardless of age, and cancer-related mortality amongst subjects aged ≤70 years. Competing risk model appears to provide more accurate and precise estimates for the association between BMI and cause-specific mortality.

CHAPTER 5— Metabolic Syndrome and Risk of Age-related Cataract over Time: An Analysis of Interval-Censored Data using Random Effects Model

SUMMARY

This study aims to investigate whether the effect of MetS and its components on the incidence of different cataract sub-types (cortical, nuclear and posterior subcapsular cataract [PSC]) change with time. In this study, the occurrence of cataract is said to be interval-censored since the event was only known to occur between two assessment periods, that is, between baseline and 5-year or between 5- and 10-year follow-up. To deal with interval-censoring, the random effects complementary log log model was implemented. In order to evaluate whether accounting for further follow-up information of MetS and its components would provide a more accurate and efficient estimate of their relationships with age-related cataract, the logistic regression was performed to evaluate the association between baseline MetS and its components with the 10-year cumulative incidence of age-related cataract. It showed that baseline MetS was linked to an increased risk of 10-year cumulative incidence of cortical and PSC cataract. The complementary log-log model showed that changes in MetS were associated with the 5-year incidence of cortical and PSC cataract. Different MetS components were associated with the incidence of different cataract sub-types at varying time-intervals. This underscores the importance of fully accounting for covariate information collected at each follow-up visit in order for physicians to better predict the risk of different cataract sub-types in older persons at varying time-intervals.



5.1 Types of cataract

A cataract is a clouding of the natural intraocular crystalline lens that focuses the light entering the eye onto the retina. This cloudiness can cause a decrease in vision and may lead to eventual blindness if left untreated. Cataracts often develop slowly and painlessly, so vision and lifestyle can be affected without a person realizing it. There are three principal cataract sub-types:

1. Nuclear cataract or nuclear sclerosis is the most common type of cataract that occurs in age-related cataract and in patients with diabetic mellitus. It occurs in the centre of the lens.
2. Cortical cataract is the second most common cataract and from its name it occurs in the cortex or the outer part of the lens.
3. PSC cataract occurs in the posterior part of the lens and it occurs mostly with corticosteroid. However, it can occur also in diabetic patients.

Sometimes more than one of the above described varieties of cataract may occur together in a lens. In general, a cataract will start as one type but eventually become mixed as the other lens regions become involved in the degenerative process (http://www.online-eye-info.com/cataract-definition.html).

5.2 Literature review on the relationship between metabolic syndrome and its components with age-related cataract

Table 5.1 summarizes the literature review on the association between MetS and age-related cataract. A survey in Lithunia showed a significant and positive association between any cataract and MetS in women aged 45-64 years (Paunksnis et al. 2007). The BMES, using the WHO criteria for defining MetS, reported baseline MetS to be associated with increased risk of all three types of cataract namely, cortical, nuclear and PSC cataract (Tan et al. 2008d). A cross-sectional study amongst Malay in Singapore found that MetS was positively associated with prevalent cortical cataract (Sabanayagam et al. 2011).

Table 5.1 Association between metabolic syndrome and age-related cataract

Study, year	Place	N	Age (years)	MetS	Odds ratio (95%CI)		
					Cortical	Nuclear	PSC
Paunksnis, 2007	Lithuania	573 709	M:55-64 F:45-64	NCEP	Any cataract: 1.59 (0.77-3.26) Any cataract: 1.60 (1.03-2.49)		
Tan, 2008d	Australia	1920	≥ 49	WHO	1.73(1.12-2.68)	1.71(1.07-2.73)	1.94(1.07-3.54)
Sabanayagam, 2011	Singapore	2794	40-80	NCEP	1.48(1.23-1.79)	0.83(0.66-1.05)	1.12(0.90-1.40)

CI=confidence interval; F=female; M=male; Mets=metabolic syndrome; PSC=posterior subcapsular cataract; WHO=World Health Organization; NCEP=National Cholesterol Education Program.

Table 5.2 shows the literature review on the association between MetS components and age-related cataract. Paunksnis et al. (2007) showed that cataract was significantly associated with central obesity for men aged 55-64 years, and with central obesity, higher arterial pressure and elevated level of serum triglycerides in women aged 45-64 years. The BMES also showed baseline impaired fasting glucose (IFG) and diabetes to predict cortical and nuclear cataract respectively. Each SD increase in glucose and BMI were also positively associated with cortical and PSC cataract respectively (Tan et al. 2008d). Moreover, Sabanayagam et al. (2011) found high BP was positively associated with all three cataract types; diabetes was associated with cortical and PSC cataract; and low HDL and BMI $\geq$ 25 kg/m^2 were associated with cortical cataract. However, BMI $\geq$ 25 kg/m^2 was a protective factor for nuclear cataract.

Table 5.2 Association between metabolic syndrome components and age-related cataract

Study, year	Place	N	Age (year)	Mets components	Cortical Odds ratio (95% CI)	Nuclear Odds ratio (95% CI)	PSC Odds ratio (95% CI)
Paunksnis, 2007	Lithuania					*Any-cataract*	
		573	M:55-64	Obesity		1.80 (1.01-3.20)	
		709	F:45-64	Obesity		1.54 (1.01-2.35)	
		709	F:45-64	TG		1.86 (1.20-2.90)	
		709	F:45-64	Arterial pressure		1.98 (1.21-3.25)	
Tan, 2008d	Australia	1920	≥49	IFG	2.01 (1.20-3.36)		
				Glucose per unit increase	1.13 (1.01-1.27)		
				Diabetes		1.64 (1.02-2.64)	
				BMI per unit increase			1.20 (1.03-1.41)
Sabanayagam, 2011	Singapore	2794	40-80	BP	1.46 (1.18-1.81)	1.37 (1.04-1.80)	1.57 (1.19-2.06)
				Diabetes	2.28 (1.83-2.83)		1.39 (1.09-1.77)
				BMI ≥25	1.22 (1.01-1.48)	0.65 (0.52-0.81)	
				HDL	1.34 (1.09-1.65)		

BP=blood pressure; F=female; M=male; Mets=metabolic syndrome; PSC=posterior subcapsular cataract; TG=triglyceride; IFG=impaired fasting glucose; SD=standard deviation.

5.3 Significance of study

Age-related cataract is a leading cause of blindness and poor vision and a major public health concern globally (Attebo et al. 1996). Worldwide, cataract is the number one cause of preventable blindness. There is no medical treatment to prevent the development or progression of cataract. Several studies have found associations between age-related cataract and increased risk in mortality (Hennis et al. 2001). This suggests that cataract may share similar pathogenesis with systemic diseases associated with ageing and reduced survival, particularly CVD (Tan et al. 2008d).

So far, a few studies have investigated the association between cataract and MetS, and whether some individual components are more important risk factors than others for specific cataract sub-types. While Tan et al. (2008d) found MetS was a significant risk factor for all three subtypes of cataract, Sabanayagam et al. (2011) found MetS to be a risk factor for cortical cataract only. Further, both studies have reported that baseline BMI, high BP, diabetes or low HDL to be associated with age-related cataract, while Paunksnis et al. (2007) suggested elevated serum TG was a predictor of cataract among women.

However, there are a number of unanswered questions. First, previous studies used different definitions for MetS, namely, WHO and NCEP ATP-3, and it has been reported that these definitions were not as successful in predicting diabetes, cardiovascular disease and other health outcomes (Balkau and Charles 1999; WHO 1999; NCEP 2001; Stern et al. 2004**).** Thus in this study, we define MetS based on the IDF criteria (Alberti et al. 2006). Second, previous studies,

including earlier report of BMES (Tan et al. 2008d) used only MetS data at baseline in the evaluation of its relationship with cataract. However, experimental studies in rats and human have shown that the effect of glucose and lipid abnormalities on cataract formation may change over time (Jacob and Mason 2005; Kyselová et al. 2005). This therefore underscores the importance of collecting further information on glucose and lipid abnormalities beyond baseline measurements to better detect cataract formation.

In order to evaluate whether accounting for further follow-up information of MetS and its components in addition to baseline information would provide a more accurate and efficient estimate of their relationships with age-related cataract, the logistic regression was firstly performed to examine the association between baseline MetS and its components with the 10-year cumulative incidence of age-related cataract. In this study, repeated measures of MetS and its components have been shown to be highly correlated. As such, it is natural to apply statistical technique which appropriately accounts for intra-subject correlation, to yield a more robust estimate of the effect of MetS and its components on subtypes of cataract. Further, since the outcome, different cataract sub-types, was measured in discrete time interval, we implement the random effects complementary log-log regression as it would be more appropriate for detecting stronger and more robust relationships (Neuhaus 1992; Rabe-Hesketh and Skrondal 2008) between individual MetS components than the logistic regression as used in previous studies. Thus to evaluate the effect of MetS and its components on the incidence of different age-related cataract sub-types (namely

cortical, nuclear and PSC) more precisely, and to determine whether these associations differed at varying time intervals (i.e. 0-5 years or 5-10 years), we utilized full information that was collected at each follow-up and implemented appropriate statistical models to better describe the relationships.

5.4 Methods

Study design and population

A detailed description of the study design and population of the BMES has been provided in **Chapter 2**. In brief, the BMES is a population-based prospective cohort study of vision, common eye diseases and other health outcomes in a suburban Australian population west of Sydney (Mitchell et al. 1998a). Between 1992 and 1994, non-institutionalized permanent residents aged 49 years and older were invited to participate, and were requested to return for follow-up examinations after 5 (1997-1999) and 10 years (2002-2004). A total of 2564 participants were examined for eye examination at least once after baseline (Tan et al. 2008d). Of these, 1997 subjects with complete information for the study factors namely, MetS and its components, age, sex, smoking status, pre-existing cardiovascular diseases, patient's history of eye diseases and family history of eye disease, family history of blindness, eye iris color and skin sun-tanning characteristics at baseline contributed to the analysis of age-related cataract. Specifically, 1820 individuals contributed information for the analysis of cortical cataract, 1357 for nuclear cataract and 1962 for PSC cataract.

Data collection

A detailed description of the data collection has been provided in **Chapter 2**. Briefly, at each visit, trained interviewers completed a comprehensive questionnaire comprising demographic information, eye and general medical history including hypertension, diabetes, and cardiovascular pre-existing diseases (namely, angina, acute AMI and stroke) as well as medication used. Height, weight and seated BP (WHO 2003) were measured. Fasting pathology tests, including HDL cholesterol, TG (Cugati et al. 2007) and FPG (WHO 1999) were also measured within two months of each interview. In addition, information on smoking (never, former and current smoker) and alcohol intake were collected. Moreover, history of eye diseases including cataract, AMD, myopia and glaucoma as well as family history of eye disease or blindness were obtained and recorded (Tan et al. 2008d). Eye iris color and skin sun-tanning characteristics were also estimated on a 4-point scale (Always burn, never tan; Usually burn, tan with difficulty; Burn and tan above average; Rarely burn, tan above average) (Mitchell et al. 1998b).

As mentioned in **Chapter 2**, we define MetS according to the IDF criteria (Zimmet et al. 2005) as obesity (ie. BMI units >30 kg/m^2) plus any two of the following four factors:

v. TG ≥1.7 mmol/L or specific treatment for this lipid abnormality;

vi. HDL cholesterol <1.03 mmol/L in men and <1.29 mmol/L in women, or specific treatment for this lipid abnormality;

vii. Systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg, or treatment of previously diagnosed hypertension; or

viii. FPG ≥5.6 mmol/L, or previous diagnosis or specific treatment for type 2 diabetes.

Cataract grading

All participants examined underwent a detailed eye examination, which included subjective refraction using a LogMar chart. The type and extent of the three major types of cataract (nuclear, cortical and PSC) were assessed by graders from two types of lens photographs taken during the study using Ektachrome 200 color film (Kodak, Rochester, New York). The protocol developed from the Beaver Dam Eye Study (Klein et al. 1990a) was followed closely. Slit-lamp photographs of the lens katen using the Topcon SL-7E photograph slit-lamp camera (Topcon Optical Co., Tokyo, Japan) were used to assess nuclear cataract. Retroillumination lens photographs, taken using the Neitz CT-R cataract camera (Neitz Instruments Co., Tokyo, Japan) were used to assess cortical and posterior subcapsular opacities. Both cameras had fixation target modifications provided courtesy of Michael Neider, University of Wisconsin Madison (Magli et al. 1990).

The population at risk for cataract comprised participants who had at least one follow-up visit, but whose lens photographs were retrospectively shown not to show signs of cataract at baseline. They also had complete information to define MetS at baseline. Different sub-types of cataract were determined using standard photographic grading at each of the three examinations. The Wisconsin Cataract Grading System was used to perform masked grading of the lens

photographs. Two masked graders used a five-point scale to assess the presence and severity of nuclear cataract by comparing participant photographs of each eye with the set of four Wisconsin standards (Klein et al. 1990b). A decimalized system of nuclear grading was also employed, (Bailey et al. 1991) in which the grader estimated the score on a continuous scale between each standard (e.g., 3.8). Nuclear cataract was defined as nuclear opacity worse than standard 3. The presence and severity of cortical lens opacities were graded from Neitz photographs using a circular circle. Graders estimated the percentage of area in each of the nine segments involved by cortical opacities. The presence and severity of PSC cataract were also recorded if any definite typical PSC cataract was present on the Neitz photographs. Both the nuclear standards and the grid for assessing cortical and PSC opacities were provided by Dr. Barbara E. K. Klein, University of Wisconsin-Madison. Cortical opacity involving at least 5% of the total lens area or the presence of any PSC opacity was used to define the presence of the respective cataract sub-types (Tan et al. 2008d). Thus, distinct types of cataract were categorized and analyzed independently.

Reproducibility

Intergrader and intragrader reproducibilities of lens grading were assessed by the BMES group using quadratic weighted kappa (*K*) statistics (Kanthan et al. 2008). Of note, Quadratic Weighting is formulated as follow:

$$\text{Quadratic weight} = 1 - \left(\frac{i-j}{k-1}\right)^2$$

where *i-j* is the difference between the row category on the scale and the column category on the scale (the number of categories of disagreement), for the cell concerned, and *k* is the number of points on the scale (Sim and Wright 2005).

A single grader assessed baseline cortical cataract and PSC, with adjudication provided by a senior ophthalmologist. Two graders performed nuclear cataract grading of both the baseline and 5-year follow-up lens photographs. Weighted *K* for intragrader and intergrader reliability were above 0.70 for all cataracts. The 10-year follow-up photographs were graded by one examiner for all 3 types of cataract, with all positive cortical cataract cases also graded by another senior grader and nuclear cataract and PSC cases also graded by a senior researcher. The same examiner graded a random sample of baseline photographs to compare intergrader reproducibilities. This gave weighted *K* values above 0.70 for cortical and PSC cataract and 0.52 for nuclear cataract (Kanthan et al. 2008).

Statistical analyses

The logistic regression was performed to evaluate the association between baseline MetS and its components with the 10-year cumulative incidence of age-related cataract. As mentioned in **Chapter 1**, an individual's MetS and cataract status were prospectively evaluated at pre-defined time intervals (ie. baseline, 5- and 10-year). Hence, the exact time that cataract developed was not known. Such information was interval-censored, and thus the effect of 10-year changes in MetS and its components on the incidence of each cataract sub-type was modeled using a random effects complementary log-log regression model (Neuhaus 1992; Rabe-

Hesketh and Skrondal 2008). This statistical technique is readily available for survival analysis with discrete time, and is one of the most frequently used discrete-time hazard functions (Singer and Willett 2003). In this study, the outcomes of interest, time-to-development of different cataract sub-types, were included in the model based on discrete-time intervals (i.e. 0-5 years or 5-10 years), in accordance to the follow-up schedule. This approach includes indicator variables for the examination time-interval (0-5, 5-10 years) as covariates (Allison 1982; Neuhaus 1992; Lecaire et al. 2006; Rabe-Hesketh and Skrondal 2008). The random effects model accounts for possible intra-subject correlation in the assessment of MetS and its components which were repeatedly measured at baseline, 5- and 10-year.

In the simplest form the random-effects complementary log-log regression model for cataract can be modelled as follow:

$$\log[-\log\{1 - P_{ij}(t)\}] = \beta_0^{*} + \beta_{MetS} MetS_{ij} + \eta_{ij}$$

where $P_{ij}(t)$ is probability of developing cataract at time t for an individual i at the j^{th} visit. This model is fitted assuming a random intercept, β_0^{*}, and the slope parameter, β_{MetS}, is considered as a fixed effect. The component, η_{ij}, estimates the SD of the random intercept and the residual variation. It can be extended to allow the slope to assume a random effect as well as to adjust for other covariates (Collett 2003).

Of note, when the dichotomous outcome is rare, the complementary log-log regression is more appropriate. However, Nelder (2001), Hardin and Hilbe

(2007) have suggested that when a binary outcome is common, the complementary log-log regression model may also fit the data well.

Age, sex, smoking, pre-existing disease (namely angina, AMI and stroke), family history of eye disease (namely; cataract, AMD, myopia, glaucoma and blindness), history of eye disease (namely AMD, myopia and glaucoma), eye iris color and skin sun-tanning characteristics, were considered as possible confounders in the model building. Furthermore, we included interactions between MetS (as well as its components) and the time-interval in order to evaluate whether its relationship with the different cataract sub-types varied according to the 5- and 10-year time-intervals (Allison 1982; Lecaire et al. 2006). We further explored possible interaction between age and sex with MetS and its components. It should be noted that for each cataract sub-type, the control group included participants without the same cataract sub-type.

5.5 Results

Description of study population

Table 5.3 presents the baseline characteristics of the study subjects according to the cumulative incidence of cataract at 10 years. Over the 10-year follow-up, 857 (42.9%) persons developed incident cataract. Of these, 455 (25.0%) were cortical cataract, 436 (32.1%) were nuclear cataract and 135 (6.9%) were PSC cataract.

Of the 455 persons with incident cortical cataract, 242 (53.2%) had more than 5% and less than 10% severity and 213 (46.8%) had 10% or more severity in the worse eye. Of the 135 persons with incident PSC cataract, 104 (77.0%) had less

than 5% severity and 31 (23.0%) had 5% or more severity in the worse eye. The mean age of participants was 63.9 (SD 8.3) years with a female predominance (57.7%).

Table 5.3 Baseline characteristics of study population according to 10-year cumulative incidence of age-related cataract

	Total (n=1997)	No cataract (n=1140)	Cataract (n=857)	*P*-value
Baseline mean age (SD)	63.9 (8.3)	62.3 (8.3)	65.9 (7.8)	< 0.001
Sex (%), Male	844 (42.3)	517 (45.3)	327 (38.2)	0.001
Female	1153 (57.7)	623 (54.7)	530 (61.8)	
Family history of blindness (%)	83 (4.2)	39 (3.4)	44 (5.1)	0.058
Family history of any eye disease (%)[a]	643 (32.2)	366 (32.1)	277 (32.3)	0.918
History of any eye disease at baseline (%)[b]	400 (20.0)	221 (19.4)	179 (20.9)	0.407
Pre-existing disease (%)[c]	308 (15.4)	161 (14.1)	147 (17.2)	0.064
Smoking status (%), Non-smoker	1046 (52.4)	601 (52.7)	445 (51.9)	0.416
Ex-smoker	698 (34.9)	387 (33.9)	311 (36.3)	
Current smoker	253 (12.7)	152 (13.3)	101 (11.8)	
Eye iris color (%), Blue	978 (49.0)	565 (49.5)	413 (48.2)	0.897
Hazel/Green	572 (28.6)	323 (28.3)	249 (29.0)	
Tan/Brown	251 (12.6)	144 (12.6)	107 (12.5)	
Dark brown	196 (9.8)	108 (9.5)	88 (10.3)	
Sun skin-burned (%)				
Always burn, never tan	271 (13.6)	152 (13.3)	119 (13.9)	0.927
Usually burn, tan with difficulty	496 (24.8)	288 (25.3)	208 (24.2)	
Burn and tan above average	784 (39.3)	448 (39.4)	336 (39.2)	
Rarely burn, tan above average	446 (22.3)	251 (22.0)	194 (22.7)	
MetS (%)	246 (12.3)	119 (10.4)	127 (14.8)	0.004
BMI >30 (%)	346 (17.3)	173 (15.2)	173 (20.2)	0.004
High glucose (%)[d]	306 (15.3)	149 (13.1)	157 (18.3)	0.001
Low-HDL (%)[e]	591 (29.6)	318 (27.9)	273 (31.9)	0.055
High triglyceride (%)[f]	815 (40.8)	461 (40.4)	354 (41.3)	0.713
High BP (%)[g]	1689 (84.6)	941 (82.5)	748 (87.3)	0.004

BMI=body mass index; BP=blood pressure; MetS=metabolic syndrome.
[a]Includes family history of cataract, glaucoma, macular and blindness, [b]Includes history of age-related macular degeneration, myopia and glaucoma at baseline, [c]Includes history of angina, stroke and acute myocardial infarction at baseline, [d]fasting plasma glucose ≥5.6 mmol/L, or previous diagnosis or specific treatment for type 2 diabetes; [e]serum HDL cholesterol <1.03 mmol/L in men and <1.29 mmol/L in women, or specific treatment for this lipid abnormality; [f]serum triglyceride level ≥1.7 mmol/L or specific treatment for this lipid abnormality; [g]systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, or treatment of previously diagnosed hypertension.

Figure 5.1 shows the changes in MetS and its components at baseline, 5- and 10-year follow-up among individuals with different cataract sub-types.

Generally, a lower proportion of individuals with nuclear cataract had MetS or its components as compared with cortical or PSC cataract. MetS increased from baseline to 5-year follow-up and decreased by 10-year follow-up for all 3 subtypes of cataract. This may be due to people with MetS dying after 5-year follow-up and decreased prevalent MetS at 10-year follow-up.

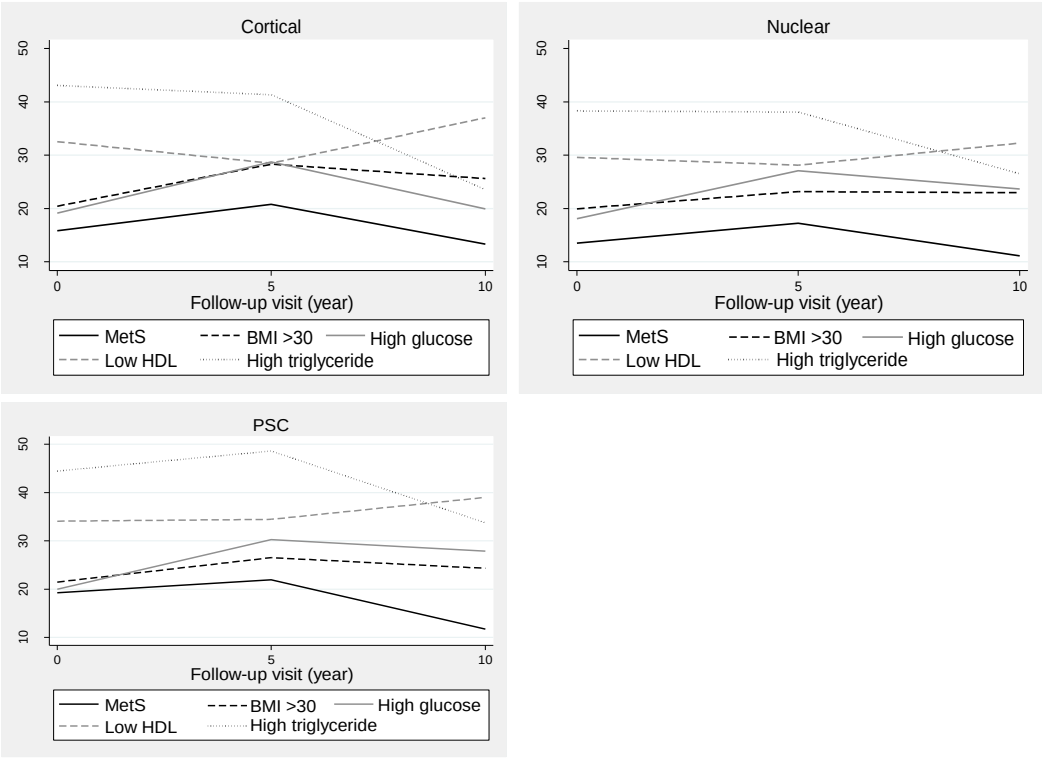


Figure 5.1 Changes in prevalent metabolic syndrome and its components among individuals with cortical, nuclear and PSC cataract at baseline, 5- and 10-year follow-up

Baseline MetS and its components and 10-year cumulative incidence of age-related cataract

After controlling for age, sex, eye disease at baseline, pre-existing disease at baseline and family history of blindness, baseline MetS (HR 1.44, 95% CI: 1.06-1.96) and high glucose (HR 1.52, 95% CI: 1.15-2.03) were linked to an increased risk of the 10-year cumulative incidence of cortical cataract (Table 5.4). There was no evidence of association between baseline MetS and any of its components with the 10-year cumulative incidence of nuclear cataract. However, MetS was found to be associated with the 10-year cumulative incidence of PSC cataract (HR 1.76, 95% CI: 1.11-2.78) (Table 5.4).

Table 5.4 Effects of baseline MetS and its components on the 10-year cumulative incidence of age-related cataract

	Cortical	Nuclear	PSC
	HR (95% CI)[a]	HR (95% CI) [a]	HR (95% CI) [a]
MetS	1.44 (1.06-1.96)*	1.25 (0.86-1.81)	1.76 (1.11-2.78)*
BMI >30	1.26 (0.96-1.66)	1.30 (0.95-1.79)	1.32 (0.85-2.03)
Elevated glucose[b]	1.52 (1.15-2.03)**	1.14 (0.81-1.60)	1.41 (0.90-2.21)
Low-HDL[c]	1.23 (0.97-1.56)	1.00 (0.75-1.30)	1.40 (0.96-2.05)
Hyper TG[d]	1.15 (0.93-1.44)	0.89 (0.69-1.15)	1.21 (0.85-1.73)
High BP[e]	0.94 (0.70-1.28)	1.41 (0.95-2.07)	1.04 (0.61-1.76)

BP=blood pressure; BMI=body mass index; CI=confidence interval; HR=hazard ratio; MetS=metabolic syndrome; PSC=posterior subcapsular cataract; TG=triglycerides.

[a]Adjusted for age, sex, eye disease at baseline (namely: myopia, macular and glaucoma), pre-existing disease at baseline (namely: acute myocardial infarction, angina and stroke) and family history of blindness.

[b]fasting plasma glucose ≥5.6 mmol/L, or previous diagnosis or specific treatment for type 2 diabetes; [c]serum HDL cholesterol <1.03 mmol/L in men and <1.29 mmol/L in women, or specific treatment for this lipid abnormality; [d]serum triglyceride level ≥1.7 mmol/L or specific treatment for this lipid abnormality; [e]systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, or treatment of previously diagnosed hypertension. Note: * $P < 0.05$, ** $P < 0.01$

MetS and its components and the incidence of age-related cataract at varying time-interval

We found MetS (HR 1.48, 95% CI: 1.05-2.09), BMI >30 kg/m^2 (HR 1.59, 95% CI: 1.16-2.17) and elevated glucose (HR 1.60, 95% CI: 1.15-2.23) to be associated with increased 5-year incidence of cortical cataract, while, low-HDL cholesterol (HR 1.57, 95% CI: 1.10-2.24) was associated with an excess in incidence of cortical cataract at 10-year (Table 5.5).

Table 5.5 Effect of MetS and its components on the incidence of age-related cataract at varying time-interval

	Cortical	Nuclear	PSC
	HR (95% CI)[a]	HR (95% CI) [a]	HR (95% CI) [a]
Incidence at 5-year			
MetS	1.48 (1.05-2.09)*	1.01 (0.75-1.36)	1.75 (1.01-3.04)*
BMI >30	1.59 (1.16-2.17)**	0.84 (0.64-1.10)	1.30 (0.76-2.20)
Elevated glucose[b]	1.60 (1.15-2.23)**	1.13 (0.87-1.56)	1.59 (0.93-2.72)
Low-HDL[c]	1.14 (0.82-1.58)	0.94 (0.73-1.22)	1.43 (0.84-2.45)
Hyper TG[d]	1.09 (0.82-1.44)	0.98 (0.78-1.23)	1.44 (0.90-2.32)
High BP[e]	1.12 (0.67-1.89)	1.08 (0.70-1.68)	1.10 (0.44-2.74)
Incidence at 10-year			
MetS	1.40 (0.88-2.20)	0.93 (0.54-1.61)	1.39 (0.70-2.76)
BMI >30	1.44 (1.00-2.09)	1.24 (0.84-1.86)	1.52 (0.89-2.60)
Elevated glucose[b]	1.24 (0.79-1.97)	1.30 (0.81-2.08)	1.90 (1.01-3.61)*
Low-HDL[c]	1.57 (1.10-2.24)*	1.03 (0.69-1.54)	1.45 (0.85-2.46)
Hyper TG[d]	0.76 (0.49-1.16)	0.97 (0.63-1.51)	1.50 (0.81-2.76)
High BP[e]	0.96 (0.63-1.47)	1.27 (0.75-2.15)	1.11 (0.56-2.19)

BP=blood pressure; BMI=body mass index; CI=confidence interval; HR=hazard ratio; MetS=metabolic syndrome; PSC=posterior subcapsular cataract; TG=triglycerides.

[a]Adjusted for age, sex, eye disease at baseline (namely: myopia, macular and glaucoma), pre-existing disease at baseline (namely: acute myocardial infarction, angina and stroke) and family history of blindness.

[b]fasting plasma glucose ≥5.6 mmol/L, or previous diagnosis or specific treatment for type 2 diabetes; [c]serum HDL cholesterol <1.03 mmol/L in men and <1.29 mmol/L in women, or specific treatment for this lipid abnormality; [d]serum triglyceride level ≥1.7 mmol/L or specific treatment for this lipid abnormality; [e]systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, or treatment of previously diagnosed hypertension. Note: * $P < 0.05$, ** $P < 0.01$

However, there was no association between MetS or any of its components with the incidence of nuclear cataract at either 5 or 10 years, even after accounting for information of MetS and its components at baseline and subsequent follow-up visits as well as controlling for confounders.

Similarly, MetS was associated with an increase in 5-year incidence of PSC cataract (HR 1.75, 95% CI: 1.01-3.04), whereas elevated glucose was associated with an increase in 10-year incidence of PSC cataract (HR 1.90, 95% CI: 1.01-3.61) (Table 5.5).

5.6 DISCUSSION

In this prospective cohort study of an Australian white population participating in the BMES, we found the following: First, after accounting for baseline and further follow-up information on MetS and its components as defined by the IDF criteria, MetS, elevated glucose and BMI >30 kg/m^2 contributed to an increase in 5-year incidence of cortical cataract, while low-HDL cholesterol was linked to an increase in 10-year incidence of cortical cataract. Second, MetS and elevated glucose were positively associated with the incidence of PSC cataract at 5-year and 10-year, respectively.

The association between elevated glucose and the incidence of cortical and PSC cataract at different time-intervals, suggests that glucose was associated with late incidence of PSC cataract, and early incidence of cortical cataract. Mechanisms connecting hyperglycemia with cataract include advanced glycation of lens proteins (Stitt 2001), hyperosmotic effects of sorbitol on lens fibers via the

aldose reductase pathway (Kador and Kinoshita 1984) with induction of apoptosis in lens epithelial cells leading to the development of cataract (Pollreisz and Schmidt-Erfurth 2010).

Additionally, our study demonstrated that BMI >30 kg/m^2 was associated with the 5-year incidence of cortical cataract, suggesting that the contribution of obesity to cortical cataract formation may reduce over time. In the Singapore Malay Eye Study (Sabanayagam et al. 2011) and the study by Lim et al. (2009), baseline BMI have been shown to contribute to a higher risk of cortical cataract and PSC cataract (Lim et al. 2009). The underlying mechanism behind the relationship between obesity and cataract is unclear (Cheung and Wong 2007). To-date, there has not been any study that examined how changes in BMI over time would affect cataract formation. However, it has been suggested that obesity was related to cataract by its associated complications such as diabetes, glucose intolerance, insulin resistance, hyperlipidemia, inflammation and hormonal differences (Cheung and Wong 2007). Moreover, it has been shown that the relationship between glucose and cholesterol with cataract formation changed over time (Jacob and Mason 2005; Kyselová et al. 2005). Therefore, this may partly explain why the relationship between obesity and incidence of cataract may also change with time.

Studies have suggested that inflammation and oxidative stress resulting from low-HDL cholesterol levels might contribute to cataract formation (Varma et al. 1984; Klimov et al. 1993; von Eckardstein et al. 2005). Our finding has shown an association between low-HDL cholesterol and an excess in 10-year

incidence of cortical cataract, suggesting that it takes a longer observation time for low-HDL cholesterol to be confirmed as a predictor of cortical cataract. Previous BMES report which considered only baseline information using logistic regression (Tan et al. 2008d) failed to detect such a relationship. This finding thus suggests the importance of full utilization of baseline and follow-up data, to better describe the discrete time-to-development of cataract using random-effects complementary log-log model.

Finally, as a specific entity, our finding demonstrated a positive association between MetS and 5-year incidence of cortical and PSC cataract. In particular, MetS as a whole rather than its individual components, best predicted PSC cataract at 5 years. Interestingly, when we considered only the effect of Mets components at baseline without accounting for its changing status at follow-up, we did not detect any effects of BMI or low-HDL cholesterol on cortical cataract even after adjusting for age, sex, eye-diseases and pre-existing disease status. Therefore, the effects of MetS and its components on the incidence of cortical cataract at different time-intervals would not have been detected if we had only utilized the baseline data.

However, based on previous report of BMES (Tan et al. 2008d), MetS as defined by the WHO criteria, was a predictor of nuclear cataract, although our study did not confirm this association. We further analyzed the data by defining MetS based on the WHO criteria in accordance with previous report of BMES. Using the random-effects complementary log-log regression model, regardless of whether the IDF and WHO criteria was used, similar results were reported for

nuclear cataract. There was no association between MetS or any of its components with the incidence of nuclear cataract at either 5 or 10 years, even after accounting for information on MetS and its components at baseline and subsequent follow-up visits, despite adjustment for confounders (result not shown). Therefore, this difference between our study and the study by Tan et al. (2008d) may be due to differences in technique and sample size. Moreover, BMI has been shown to have different relationships with nuclear cataract, with lower BMI being an independent risk factor for nuclear cataract (Cheung and Wong 2007). This suggests the possibility of distinct etiological pathways for different cataract sub-types (Cheung and Wong 2007). Since obesity was a mandatory component in defining MetS in our study, this may partially explain why there was no effect of MetS on nuclear cataract.

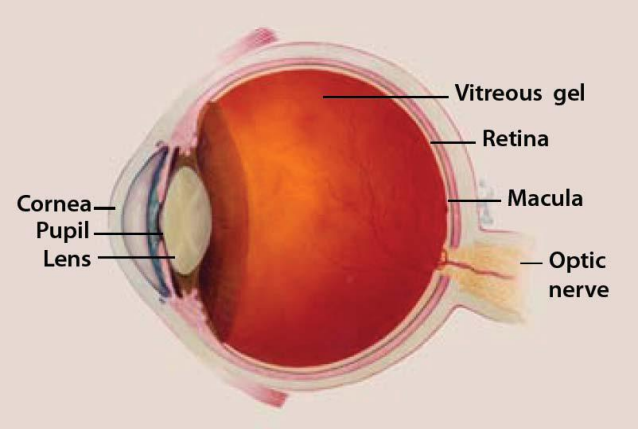
The specific strengths of this study include (1) applying random effects complementary log-log regression model which can detect stronger and more robust relationships (Neuhaus 1992; Rabe-Hesketh and Skrondal 2008) between individual MetS components and cataract sub-types where occurrences are measured in discrete time interval, and (2) cataract diagnosis based on standardized lens photographic grading, which have been shown to have high reproducibility (Panchapakesan et al. 1997; Kanthan et al. 2008). However, some specific drawbacks should also be noted. Statistical significance was not achieved for the relationship between MetS components and PSC cataract, mainly because of the lack of statistical power due to the limited number of PSC cases. This warrants further investigation in studies with more PSC cases.

In conclusion, changes in MetS were associated with the 5-year incidence of cortical and PSC cataract. Different MetS components were associated with the incidence of different cataract sub-types at varying time-intervals. This underscores the importance of fully accounting for the data on MetS components collected at each follow-up visit in order for physicians to better predict the risk of different cataract sub-types in older persons at varying time-intervals.

CHAPTER 6- Metabolic Syndrome and Risk of Age-related Macular Degeneration

SUMMARY

This study aims to investigate the relationship between metabolic syndrome (MetS) and its components with the risk of early and late stage age-related macular degeneration (AMD). Individuals aged ≥ 49 years were followed up over a period of 10 years in the Blue Mountains Eye Study. The outcomes and main exposure of interest, namely early or late stage AMD as well as MetS and its components respectively, were measured at baseline, 5- and 10-year follow-up. Conventional logistic regression was used to evaluate the relation between baseline MetS with 10-year cumulative incidence of early or late AMD. To explore the relationship between MetS with subsequent development of early or late AMD during 10-year follow-up, the mixed-effects logistic regression was implemented to account for intra-subject correlation which arose with repeated measurement. The logistic regression model found only baseline glucose to be associated with 10-year cumulative incidence of late AMD amongst those aged ≤70 years. The mixed-effects logistic model showed that amongst subjects aged ≤70 years, MetS, obesity, high glucose and high TG were associated with increased incidence of late AMD during the 10-year follow-up. Full utilization of follow-up data via the mixed model provides a more robust and stronger relationship between MetS (and its components) with late AMD in comparison with the conventional logistic regression model. These data also provide additional insights into the pathogenesis of AMD.



6.1 Forms of age-related macular degeneration

AMD is a disease affecting the elderly that gradually destroys the macula resulting in loss of sharp, central vision. The retina is the light-sensitive tissue at the back of the eye, similar to that of a film in a camera. It is made up of many cells, called photoreceptors. Images are captured by these photoreceptors on the retina or 'film'. They are converted to nerve signals and sent to the brain to be viewed as pictures. The centre of the retina is called the macula. It enables us to see fine detail and differentiate colour. It also enables us in our daily detailed activities like reading, writing and driving (Alfaro 2006).

There are two forms of AMD: Dry and Wet (Alfaro 2006):

- **Dry or non-exudative AMD** is the more common form, affecting majority of patients with AMD, and has three stages — early, intermediate, and advanced. The pathogenesis of macular degeneration has always been a confounding aspect of the disease. However, recently, other processes of macular degeneration have been hypothesized. These include: oxidative damage, abnormal lipid metabolism, apoptosis, structural abnormalities of photoreceptor outer segments, dysfunction of ion

channels in the retinal pigment epithelium, choroidal neovascularization, abnormalities of the extracellular matrix and variation in the immune system (Stone 2007). As a person gets older, these photoreceptors slowly fail to function properly. This results in abnormal deposits or debris called drusen, and is one of the most common early signs of dry AMD to accumulate under the retina. Fortunately, these deposits rarely cause visual loss or blindness. However, in some patients, the photoreceptors slowly degenerate with time, resulting in an advanced form of dry AMD called geographical atrophy (GA). In a small group of patients, drusen can progress to develop to wet AMD. The GA is the advanced (late) form of dry AMD.

- **Wet or exudative AMD** accounts for 10 to 15% of cases of late AMD. This is due to growth of abnormal blood vessels under the retina called choroidal neovascularization. These new blood vessels are very fragile and may leak fluid or blood. This results in scarring that causes rapid and severe visual loss. Neovascular or exudative AMD is the "wet" form of advanced (late) AMD.

Both advanced form of dry AMD and wet AMD can cause visual loss.

6.2 Literature review on the relationship between cardiovascular disease risk factors and age-related macular disease

Table 6.1 summarizes the relationship between CVD risk factors and AMD. A cross-sectional study of the BMES showed that obesity was the only factor which

was significantly and positively associated with prevalent early AMD (Smith et al. 1998). The BMES also showed that only prevalent GA, a subtype of late AMD, was significantly and positively associated with diabetes (Mitchell and Wang 1999). Yet again, the BMES indicated that increasing HDL cholesterol was inversely related to incident late AMD per SD increase. Elevated total/HDL cholesterol ratio was associated with late AMD and GA, while diabetes was associated with incident GA, but not neovascular AMD, a subtype of late AMD (Tan et al. 2007).

Moreover, in a population based study of residents of Séte (South of France), obese subjects were found to have increased risk of late AMD in comparison with lean subjects. The risk of soft drusen, a subtype of early AMD was increased with elevated levels of HDL-cholesterol (Delcourt et al. 2001). Additionally, after pooling the data of BMES (Attebo et al. 1996), Beaver Dam Eye Study (Klein et al. 1997) and Rotterdam Study (Hofman et al. 1991), total serum cholesterol was shown to be associated directly with incident GA, a subtype of late AMD (Tomany et al. 2004). Further, in the Age-related Eye Disease Study, obesity was significantly and positively associated with GA, a subtype of late AMD (Clemons et al. 2005). A population-based cohort study, among African participants, also reported a direct and significant association between elevated systolic BP and diabetes history with late AMD (Leske et al. 2006). The Women's Health Initiative Sight Examination suggested that self-reported history of diabetes and obesity were risk factors for late AMD in women, whereas systolic BP was a protective factor for late AMD (Klein et al. 2007).

Table 6.1 Literature review on the relationship between cardiovascular risk factors and age-related macular degeneration

Author, year	Place	N	Age	CVD risk factor	Early AMD OR (95%CI)	Late AMD OR (95%CI)
Smith W, 1998	Australia	3654	≥49	Obesity	1.78 (1.19-2.68)	
Mitchell and Wang, 1999	Australia	3654	≥49	Diabetes		4.0 (1.6-10.3)**
Delcourt, 2001	France	2584	60-95	High HDL	1.52 (1.14-2.02)*	
				Obesity		2.29 (1.00-5.23)**
Tomany, 2004	Australia Netherland USA	9523	43-95	Total cholesterol		1.08(1.00-1.15)**
Clemons, 2005	USA	2506	55-80	Obesity		1.93(1.25-2.65)
Leske, 2006	Africa	2793	>40	Systolic BP		2.8 (1.1–7.4)
				History of diabetes		3.2 (1.2–8.7)
Klein, 2007	USA	4288	≥63	Obesity		1.05 (1.001- 1.10)
				History of diabetes		2.00 (1.01-3.96)
				Systolic BP		0.84 (0.71-0.995)
Tan, 2007	Australia	2014	≥49	High HDL		0.74(0.56-0.99)
				Total/HDL ratio		1.35 (1.07-1.70)
				Diabetes		3.89 (1.36-11.08)**

AMD=age related macular degeneration; BP=blood pressure; CI=confidence interval; CVD=cardiovascular disease; GA=geographic atrophy; OR=odds ratio. * Soft drusen ** Geographic atrophy Note; Klein et al. 2007 studied only among women.

6.3 Significance of study

AMD is the leading cause of blindness and poor vision amongst elderly Caucasians in the United States (McCarty et al. 2008), Australia (Shankar et al. 2007a) and other western nations, with a significant impact on the quality of life of those afflicted (Brown et al. 2003). Despite the magnitude of this problem, the pathogenesis of AMD remains poorly understood. Atherosclerosis has long been postulated to be associated with late stage AMD. This association may relate to atherosclerosis which may cause CVD (Friedman 2000). There is also a growing body of evidence that among risk factors that promote atherosclerosis, MetS is a powerful and prevalent predictor of cardiovascular events (Mathieu et al. 2006). However, there have been conflicting results on the relationship between CVD risks factors such as BP and lipid abnormalities and AMD. So far, no studies have looked at the relationship between MetS (as a whole) and AMD.

There are contradictory reports about the independent associations of CVD risk factors such as diabetes, BP or serum lipid and the risk of AMD. For example, Smith et al. (1998) found obesity to be associated with the prevalence of early AMD, while Tan et al. (2007) showed total and HDL serum cholesterol to be associated with incident late AMD. Tomany et al. (2004) reported total serum cholesterol was inversely associated with incident neovascular AMD but positively associated with incident GA. To date, epidemiological data have not been consistent regarding the association between diabetes and AMD (Klein et al. 1992; Klein et al. 1997; Michell and Wang 1999; Clemons et al. 2005; Leske et al. 2006; Chiang et al. 2013). Furthermore, previous studies on AMD analyzed its

association with individual MetS risk factors, usually measured at baseline, and in isolation (Smith et al. 1998; Tan et al. 2007). Thus, there is uncertainty with regards to the relationship between MetS as defined based on a combination of risk factors, and AMD.

In order to evaluate whether accounting for further follow-up information of MetS and its components would provide a more powerful and precise estimate of their relationships with early or late AMD, the conventional logistic regression was first performed to evaluate the association between baseline MetS and its components with the 10-year cumulative incidence of early or late AMD. As shown in **Chapter 2**, MetS (and its components) at baseline, 5- and 10-year follow-up were highly correlated. As such, it is important to apply statistical technique which appropriately account for intra-subject correlation which arose with repeated measurements, to yield a more robust estimate of MetS on AMD (Brown and Prescott 2006; Li et al. 2011).

Therefore, the aim of this study is to examine the relationship between MetS as defined according to the IDF criteria and the risk of AMD. We further explore the age-specific (≤70 versus >70 years) relationship between MetS and its components, which were repeatedly measured at baseline, 5- and 10-year follow-up with the subsequent development of early or late AMD via the mixed-model, thus accounting for intra-subject correlation to yield a more precise estimate of the relationships.

6.4 Methods

Study design and participants

A detailed description of the study design and population was provided in **Chapter 2**. Briefly, the BMES is a population-based cohort study of vision, common eye diseases and other health outcomes of a suburban Australian population in the west of Sydney. Between 1992 and 1994, non-institutionalized permanent residents aged 49 years and older were recruited into the study. The survivors were asked to return for follow-up examinations at 5 (1997-1999) and 10 (2002-2004) years (Mitchell et al. 1998a). Participants, who did not return for the 5-year follow-up, were also invited to attend the 10-year follow-up examination and had color retinal photographs for the assessment of AMD lesions (Tan et al. 2007). A total of 2564 participants had eye examination at least once after baseline (Tan et al. 2008d). Overall, 2218 subjects with complete information for the study factors at baseline including Mets and its components, age, sex, smoking status, pre-existing cardiovascular disease (angina, AMI and stroke), family history of eye disease (cataract, AMD, myopia, glaucoma and blindness), patient's history of eye disease (cataract, myopia and glaucoma), eye iris color, and skin sun-tanning characteristics contributed to the analysis of 10-year cumulative incidence of AMD in this study. Specifically, 2114 participants contributed to the analysis of early-stage AMD and 2218 to late-stage AMD.

Data collection

A detailed description of the data collection was provided in **Chapter 2**. Briefly, at each visit, trained interviewers filled out a comprehensive questionnaire comprising demographic information, eye and general medical history as well as medications used (Mitchell et al. 1998a). Height, weight and seated BP (WHO 2003) were measured. Fasting pathology tests, including total cholesterol (mmo/L), HDL cholesterol (mmo/L), TG (mmo/L) (Cugati et al. 2007) and FPG (mmo/L) (WHO 1999), were measured within a month of each interview and delivered by courier within the same day to Westmead Hospital Sydney for hematology and clinical biochemistry assessment (Shankar et al. 2007b). In addition, information on smoking, alcohol consumption (gram / week), history of eye diseases including cataract, AMD, myopia and glaucoma as well as family history of these eye diseases and blindness were obtained and recorded (Tan et al. 2007). Eye iris color (blue, hazel/ green, tan/ brown, dark brown) and skin sun-tanning characteristics were also estimated on a 4-point scale (always burn, never tan; usually burn, tan with difficulty; burn and tan above average; rarely burn, tan above average) (Mitchell et al. 1998b).

Definition of metabolic syndrome

As mentioned in **Chapter 2**, we define MetS according to the IDF criteria (Zimmet et al. 2005) as obesity (ie. BMI >30 kg/m^2) plus any two of the following four factors:

ix. TG ≥1.7 mmol/L or specific treatment for this lipid abnormality;

x. HDL cholesterol <1.03 mmol/L in men and <1.29 mmol/L in women, or specific treatment for this lipid abnormality;

xi. Systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg, or treatment of previously diagnosed hypertension; or

xii. FPG ≥5.6 mmol/L, or previous diagnosis or specific treatment for type 2 diabetes.

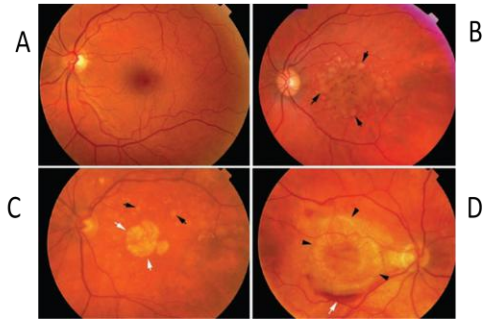
Age-related macular degeneration grading

Population at risk for AMD comprised participants who had at least one follow-up visit, and whose retinal photographs were retrospectively shown not to contain AMD at baseline. At each visit, 30° stereoscopic retinal photographs of the macula and other retinal fields of both eyes were taken, using an FF3 fundus camera (Carl Zeiss, Oberkochen, Germany). Photographs were obtained for both eyes in 98%, or at least one eye in 99%, of the baseline and 5-year examination participants, and for both eyes in 85% (1649/1952), or at least one eye in 87% (1689/1952), of the 10-year examination participants (Wang et al. 2007b). The photographic grading for AMD lesions closely followed that of the Wisconsin age-related maculopathy grading system (Klein et al. 1991; Mitchell et al. 1995) (Table 6.2). All photographs taken from each examination were graded initially in a masked manner. Side-by-side grading of the baseline and 5-year photographs (Mitchell et al. 2002) and of the baseline and 10-year photographs (Wang et al. 2007b) was performed for participants with lesions identified after each follow-up examination. Assessments of inter-grader and intra-grader reliability showed good

agreement for AMD grading (Mitchell et al. 1995). Late-stage AMD was defined to include neovascular AMD and GA, the 2 late-stage lesions described in the International AMD classification (Bird et al. 1995). All late AMD cases detected from each examination were adjudicated and confirmed by a retinal specialist. Early-stage AMD was defined as the absence of late-stage AMD and presence of either (1) large (_125 _m diameter) indistinct soft or reticular drusen or (2) both large distinct soft drusen and retinal pigmentary abnormalities (hyperpigmentation or hypopigmentation) (Bird et al. 1995; Mitchell et al. 1995), within the macular area (Klein et al. 1991). Incident late AMD was defined by the appearance at either follow-up examination of neovascular AMD or GA in either eye of persons in whom no late AMD lesions were present in either eye at baseline. Incident early AMD was defined by the appearance at the follow-up examinations of either indistinct soft or reticular drusen or the co-presence of both distinct soft drusen and retinal pigmentary abnormalities, in either eye of persons in whom no late or early AMD was present in either eye at baseline. Patients with only distinct soft drusen or retinal pigmentary abnormalities, but not both lesions, at baseline who went on to develop complementary lesions that together comprised a diagnosis of early AMD were included as incident early AMD cases (Wang et al. 2007b).

Table 6.2 Wisconsin Age-Related Maculopathy Grading System

Grade	Diagnosis	Fundus criteria
0	No AMD	Absence of any of the features of grades 1–4
1	Early AMD	Presence of soft distinct drusen only or pigmentary abnormalities only
2	Early AMD	Soft indistinct or reticular drusen only or soft distinct drusen with pigmentary abnormalities
3	Early AMD	Soft indistinct or reticular drusen with pigmentary abnormalities
4	Late AMD	Neovascular AMD or geographic atrophy



A. Normal macula
B. Soft drusen
C. Geographic atrophy (GA)
D. Neovascular AMD

Statistical analysis

As mentioned in **Chapter 2**, the χ^2 test was used to determine the bivariate relationship between categorical covariates included in this study and the 10-year cumulative incidence of both early and late stage AMD. The association between baseline Mets and its components with 10-year cumulative incidence of early or late AMD was quantified using the odds ratio (OR) estimate via the conventional logistic regression model (fixed-effects model). Ten-year cumulative incidence of

early or late AMD was the primary outcome in the conventional logistic regression model.

Mixed-effects logistic regression model (Agresti 2013) with repeated measurements of MetS (or its components) at baseline, 5- and 10-year follow-up visits, was later used to explore the relationship between Mets and its components with the subsequent development of early or late AMD over 10-year follow-up. Early or late AMD which was measured repeatedly at baseline, 5- and 10-year follow-up, was the outcome for mixed-effects logistic regression model. As mentioned in **Chapter 1**, the mixed-effects model comprises both the fixed and random effects. The random effects are estimated when the data structure consists of repeated measures over time within each individual, in this case, MetS and its components at baseline, 5- and 10-year. Age, sex, smoking, pre-existing cardiovascular disease (angina, AMI and stroke), family history of eye disease (cataract, AMD, myopia, glaucoma and blindness), patient's history of eye disease (cataract, myopia and glaucoma), eye iris color, and skin sun-tanning characteristics were regarded as fixed covariates in the model. The regression coefficients in the fixed-effects model may be interpreted as a population average measure of the cumulative effects of MetS (and its components) on AMD, while those in the mixed-effects model may be interpreted as the subject-specific estimate of its effect on AMD. The random-effects model adjust for possible intra-subject correlation to achieve a more robust and stronger results (Brown and Prescott 2006; Agresti 2013).

In the simplest form the mixed-effects logistic regression for AMD can be modelled as follow:

$$\text{logit}\,(AMD_{ij}) = \beta_0^{*} + \beta_{MetS}\, MetS_{ij} + \eta_{ij}$$

where AMD_{ij} is a binary variable taking values 0 or 1 for an individual i at the j^{th} visit. This model is fitted assuming a random intercept, β_0^{*}, and the slope parameter, β_{MetS}, is considered as a fixed effect. The component, η_{ij}, estimates the SD of the random intercept and the residual variation. It can be extended to allow the slope to assume a random effect as well as to adjust for other covariates (Tai and Machin 2014).

However, among the fixed effects covariates mentioned, only age, sex and pre-existing cardiovascular disease were statistically significant in the bivariate model. We further explored possible interaction between age and sex with MetS or its components in these logistic regression models.

6.5 Results

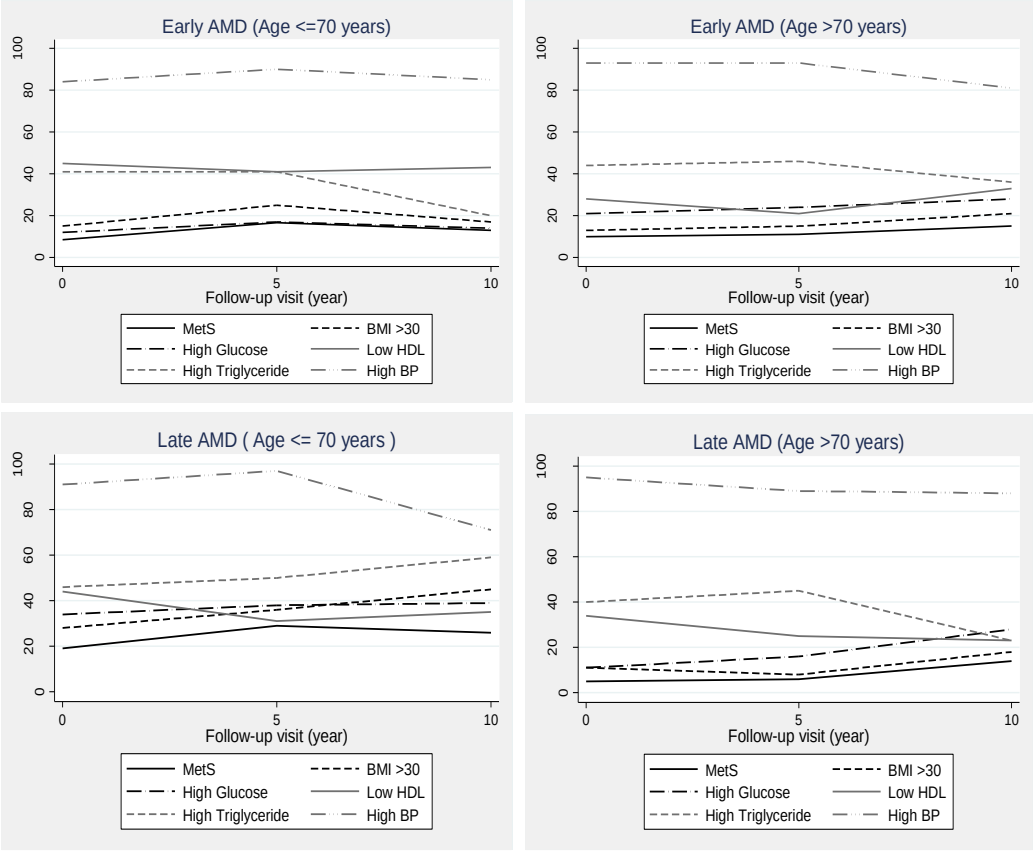
Over the 10-year follow-up, 262 (12.4%) cases of early AMD and 70 (3.2%) cases of late AMD were detected. Of the participants included in the present study, 76.5% were aged ≤70 years at baseline and 58% were females. Age, sex and pre-existing cardiovascular disease were associated with both early and late AMD (Table 6.3).

Table 6.3 Baseline characteristics of study subjects according to 10-year cumulative incidence of age-related macular degeneration

	Total (n=2218)	Early AMD (n=2114)			Late AMD (n=2218)		
		No (n=1852)	Yes (n=262)	*P*-value	No (n=2148)	Yes (n=70)	*P*-value
Age (year) (%), ≤ 70	1697 (76.5)	1546 (79.0)	151 (57.6)	< 0.001	1668 (77.6)	32 (45.7)	< 0.001
> 70	521 (23.5)	410 (21.0)	111 (42.4)		480 (22.4)	38 (54.3)	
Sex (%), Male	935 (42.2)	804 (43.4)	92 (35.1)	0.011	914 (42.5)	21 (30.0)	0.036
Female	1283 (57.8)	1048 (56.6)	170 (64.9)		1234 (57.4)	49 (70.0)	
Smoking status (%), Never	1159 (52.3)	964 (52.0)	141 (53.8)	0.492	1128 (52.5)	32 (45.6)	0.105
Former	781(35.2)	654 (35.4)	95 (36.2)		758 (35.3)	24 (33.8)	
Current	278 (12.5)	234 (12.6)	26 (10.0)		262 (12.2)	14 (20.6)	
Pre-existing cardiovascular disease (%)[a]	359 (16.2)	268 (14.5)	65 (24.8)	< 0.001	342 (15.9)	17 (24.3)	0.062
Sun skin-burned (%)							
Always burn, never tan	308 (13.9)	245 (13.2)	45 (17.2)	0.203	290 (13.5)	17 (23.9)	0.010
Usually burn, tab with difficulty	543 (24.5)	456 (24.6)	71 (27.1)		535 (24.9)	7 (10.4)	
Burn and tab above average	874 (39.4)	733 (39.6)	93 (35.5)		849 (39.5)	27 (38.8)	
Rarely burn, tab above average	493 (22.2)	418 (22.6)	53 (20.2)		474 (22.1)	19 (26.9)	
Eye iris color (%)							
Blue	1074 (48.4)	880 (47.5)	141 (53.8)	0.153	1038 (48.4)	37 (52.2)	0.056
Hazel/Green	633 (28.5)	544 (29.4)	67 (25.6)		619 (28.8)	14 (20.3)	
Tan\Brown	277 (12.5)	241 (13.0)	25 (9.5)		271 (12.6)	6 (8.7)	
Dark brown	234 (10.6)	187 (10.1)	29 (11.1)		220 (10.2)	13 (18.8)	
Family history of any eye disease (%)[b]	695 (31.3)	582 (31.4)	81 (30.9)	0.868	667 (31.0)	28 (40.0)	0.112
History of any eye disease at baseline (%)[c]	914 (41.2)	737 (39.8)	119 (45.4)	0.083	879 (40.9)	35 (50.0)	0.129
MetS (%)	271 (12.2)	236 (12.7)	24 (9.2)	0.098	263 (12.2)	8 (11.4)	0.838
BMI > 30 (%)	386 (17.4)	329 (17.8)	38 (14.5)	0.192	373 (17.4)	13 (18.6)	0.793
High glucose (%)[d]	345 (15.5)	291 (15.7)	40 (15.3)	0.853	330 (15.4)	15 (21.4)	0.168
Low-HDL (%)[e]	664 (29.9)	564 (30.4)	72 (27.5)	0.326	637 (29.7)	27 (38.6)	0.109
High triglyceride (%)[f]	916 (41.3)	765 (41.3)	110 (42.0)	0.835	882 (41.1)	34 (48.6)	0.209
High BP (%)[g]	1890 (85.2)	1565 (84.5)	229 (87.4)	0.220	1825 (85.0)	65 (92.9)	0.067

AMD= age-related macular degeneration; BMI=body mass index; MetS=metabolic syndrome; HDL=high density lipoprotein; BP=blood pressure; [a] Includes history of angina, stroke and AMI; [b]Includes family history of cataract, glaucoma, macular and blindness; [c] Includes history of cataract, myopia and glaucoma ; [d] fasting plasma glucose ≥ 5.6 mmol/L, or previous diagnosis or specific treatment for type 2 diabetes; [e] serum HDL cholesterol < 1.03 mmol/L in men and < 1.29 mmol/L in women, or specific treatment for this lipid abnormality; [f] serum triglyceride level ≥ 1.7 mmol/L or specific treatment for this lipid abnormality; [g] systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg, or treatment of previously diagnosed hypertension.

Amongst those who developed late AMD and were aged ≤70 years (n=32), there were notably higher proportions with MetS, increased BMI, high glucose and high TG over time. However, amongst those who developed early AMD and were aged ≤ 70 years, the changing status of MetS and its components was not appreciable. The observation was similar for those who developed early AMD and were aged >70 years, although declines in some Mets components were noted over time for early AMD (Figure 6.1).



AMD=age-related macular degeneration; BMI=body mass index; BP=blood pressure; MetS=metabolic syndrome; HDL=high density lipoprotein.

Figure 6.1 Prevalence of metabolic syndrome and its components at baseline, 5- and 10-year follow-up among individuals with early and late stage AMD according to age group

Baseline MetS and its components and early or late AMD

Generally, amongst both age groups, there was no evidence of relationship between baseline MetS and its components with early stage AMD (Table 6.4). However, the interaction between glucose and age group in the relationship with late stage AMD was significant ($P < 0.05$). After adjustment for sex, pre-existing cardiovascular diseases, baseline glucose was found to be significantly associated with 10-year cumulative incidence of late AMD amongst those aged ≤ 70 years (OR 2.29, 95% CI: 1.09-4.80) (Table 6.4).

Table 6.4 Age-specific associations between baseline metabolic syndrome and its components with 10-year cumulative incidence of early and late AMD

	Age ≤ 70 years		Age > 70 years	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Early AMD				
MetS	0.58 (0.33-1.02)	0.056	0.98 (0.46-2.07)	0.952
BMI > 30	0.74 (0.47-1.16)	0.187	0.84 (0.43-1.63)	0.608
High glucose [a]	0.75 (0.46-1.23)	0.253	1.51 (0.85-2.70)	0.162
Low-HDL [b]	0.82 (0.57-1.18)	0.284	0.91 (0.54-1.52)	0.727
High triglyceride [c]	0.91 (0.66-1.27)	0.593	1.28 (0.80-2.03)	0.298
High BP [d]	1.07 (0.69-1.66)	0.764	0.75 (0.30-1.87)	0.537
Late AMD				
MetS	1.50 (0.61-3.70)	0.375	0.43 (0.10-1.86)	0.258
BMI > 30	1.67 (0.76-3.66)	0.198	0.61 (0.21-1.79)	0.367
High glucose [a]	2.29 (1.09-4.80)	0.029	0.61 (0.21-1.79)	0.368
Low-HDL [b]	1.84 (0.91-3.75)	0.091	1.35 (0.66-2.77)	0.410
High triglyceride [c]	1.22 (0.60-2.49)	0.589	1.01 (0.50-2.00)	0.994
High BP [d]	1.96 (0.59-6.48)	0.270	1.07 (0.24-4.76)	0.931

AMD= age-related macular degeneration; BMI=body mass index; BP=blood pressure; HDL=high density lipoprotein; CI=confidence interval; OR=odds ratio. [a] fasting plasma glucose ≥ 5.6 mmol/L, or previous diagnosis or specific treatment for type 2 diabetes; [b] serum HDL cholesterol < 1.03 mmol/L in men and < 1.29 mmol/L in women, or specific treatment for this lipid abnormality; [c] serum triglyceride level ≥ 1.7 mmol/L or specific treatment for this lipid abnormality; [d] systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg, or treatment of previously diagnosed hypertension. Adjusted for sex, pre-existing cardiovascular disease (namely, angina, acute myocardial infarction and stroke) and including interaction between age group and MetS (or its components)

Longitudinal information of MetS and its components and early or late AMD

There was no evidence of any relationship between MetS and its components with early AMD in the mixed model (Table 6.5). However, there was an evidence of interaction effect between MetS, obesity and high glucose with age group in their relationship with late AMD (all $P < 0.05$). After adjusting for sex, pre-existing cardiovascular diseases, we found MetS to be significantly associated with late AMD only amongst those aged ≤70 years (OR 2.16, 95% CI: 1.01-4.65) (Table 6.5). Furthermore, amongst the five MetS components, after adjusting for sex, pre-existing cardiovascular diseases, we found BMI >30 kg/m^2 (OR 2.22, 95% CI: 1.09-4.49); high glucose (OR 3.12, 95% CI: 1.48-6.56) and high TG (OR 2.06, 95% CI: 1.01-4.22) were positively linked to the incidence of late AMD amongst those aged ≤ 70 years during the 10-year follow-up period (Table 6.5).

Table 6.5 Age-specific associations between metabolic syndrome and its components on incidence of early and late AMD over 10-year follow-up according to age

	Age ≤ 70 years		Age > 70 years	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Early AMD				
MetS	0.93 (0.59-1.45)	0.733	0.91 (0.44-1.90)	0.806
BMI > 30	0.88 (0.60-1.30)	0.521	0.95 (0.51-1.79)	0.879
High glucose [a]	0.77 (0.49-1.22)	0.271	1.05 (0.61-1.83)	0.855
Low-HDL [b]	0.84 (0.59-1.19)	0.324	0.66 (0.38-1.14)	0.141
High triglyceride [c]	0.60 (0.41-0.88)	0.009	1.37 (0.85-2.20)	0.202
High BP [d]	1.18 (0.74-1.87)	0.496	0.56 (0.27-1.13)	0.107
Late AMD				
MetS	2.16 (1.01-4.65)	0.049	0.42 (0.09-1.91)	0.260
BMI > 30	2.22 (1.09-4.49)	0.027	0.24 (0.05-1.11)	0.068
High glucose [a]	3.12 (1.48-6.56)	0.003	1.03 (0.38-2.76)	0.956
Low-HDL [b]	1.78 (0.89-3.57)	0.103	0.61 (0.25-1.49)	0.275
High triglyceride [c]	2.06 (1.01-4.22)	0.047	1.03 (0.47-2.25)	0.943
High BP [d]	0.84 (0.34-2.06)	0.696	0.56 (0.19-1.61)	0.278

AMD= age-related macular degeneration; BMI=body mass index; BP=blood pressure; HDL=high density lipoprotein; CI=confidence interval; OR=odds ratio. [a]fasting plasma glucose ≥5.6 mmol/L, or previous diagnosis or specific treatment for type 2 diabetes; [b]serum HDL cholesterol <1.03 mmol/L in men and <1.29 mmol/L in women, or specific treatment for this lipid abnormality; [c] serum triglyceride level ≥1.7 mmol/L or specific treatment for this lipid abnormality; [d] systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, or treatment of previously diagnosed hypertension. Adjusted for sex, pre-existing cardiovascular disease (namely, angina, acute myocardial infarction and stroke) and including interaction between age group and MetS (or its components)

6.6 Discussion

Our study investigated the relationship between MetS and the subsequent development of AMD over a 10-year period in a cohort of Australian white persons. We found that age modified the relationship between MetS, obesity and high glucose with late stage AMD. Amongst younger participants aged ≤ 70 years, MetS was associated with an increase in incidence of late AMD during the 10-year follow-up. Amongst the MetS components, obesity (i.e. BMI >30 kg/m^2), high glucose and high TG were found to be significant predictors of incidence of late AMD in the younger age group. No relationship was seen for MetS and early AMD.

The finding that the associations between MetS and its components with late AMD emerged during the 10-year follow-up, and that, this was observed only in those aged ≤ 70 years at baseline add the importance of the age modification in the relationship between MetS, obesity and high glucose with late stage AMD to the existing literature. While Delcourt et al. (2001) and Clemons et al. (2005) have shown a significant association between obesity and late AMD, others have not confirmed this association (Smith et al. 1998; Klein et al. 2001). The mechanism connecting obesity and AMD formation may be possibly explained by an increase in oxidative damage and inflammation in obese persons (Klein et al. 2007). Obesity is also associated with an increase in C-reactive protein, a marker for systemic inflammation which in turn is also significantly associated with AMD (Seddon et al. 2004).

We also observed an association between high glucose and late AMD in this age group. The Beaver Dam Eye Study (Klein et al. 1992; Klein et al. 1997) and the Barbados Eye Study (Leske et al. 2006) have also demonstrated an association between prevalent diabetes mellitus and any AMD. The mechanism behind the association between diabetes and AMD has been shown in eyes of long-term diabetic persons through the thickening of basement membrane of the choriocapillaris walls, luminal narrowing, dropout of the choriocapillaris, and thickening of Bruch's membrane which has been attributed to hyperglycemia (Hidayat and Fine 1985; Fryczkowski et al. 1988).

We further observed a positive association between high TG and increased incidence of late AMD during the 10-year follow-up among those aged ≤70 years. The observed relationship may be explained by the vascular model which suggests that AMD is the result of the accumulation of lipid in the sclera and the Bruch membrane, thus progressively increasing the stiffness of these tissues (Friedman et al. 2000).

Importantly, our study utilized full follow-up information and thus possible changes in MetS over time in contrast to previous studies which used only baseline information of MetS components (Smith et al. 1998; Delcourt et al. 2001; Tomany et al. 2004; Clemons et al. 2005; Leske et al. 2006; Klein et al. 2007; Tan et al. 2007). When we analyzed baseline data using the conventional logistic regression model, only high glucose was significantly associated with 10-year cumulative incidence of late AMD amongst those aged ≤ 70 years. This was in contrast to the mixed model which detected significant interaction not only

between high glucose and age, but also between MetS and obesity with age, with the OR for MetS, obesity, high glucose and high TG reaching statistical significance amongst those aged ≤ 70 years. Hence, our current analysis which considered all available information of Mets components at baseline and subsequent follow-up visits, provided a more comprehensive understanding of the risks of AMD and its association with MetS and its components.

The specific strengths of this study include (1) exploring the relationship between MetS and its components with early or late stage AMD, where its occurrence as well as those of the study main exposure, were repeatedly measured during the study follow-up at baseline, 5- and 10-year through applying the mixed-effects logistic regression. This model accounts for intra-subject correlation to yield a more robust and stronger estimate of the relationships (Brown and Prescott 2006; Agresti 2012), and; (2) use of standard method for assessing AMD incidence, including photographic grading by the same personnel at all examinations, and a detailed side-by-side comparison of baseline and follow-up examination photographs to ensure negligible misclassification for AMD diagnosis (Tan et al. 2007).

However, the drawbacks of this study should be noted. As mentioned in **Chapter 2**, the overall sample size of study which included limited number of subjects with MetS may limit our ability to detect the relationship between MetS and early AMD. In addition, the possibility of chance finding exists, especially when we analyzed the data related to late AMD in age group ≤ 70 years which involved small number of cases. Further, the possibility of residual confounding

effect cannot be ruled out, and the observed associations might have been due to other confounding factors such as genetic factors (Wei et al. 2013) or diet (Montgomery et al. 2010), not the MetS or its components per se.

Our study demonstrated that MetS and three of its components, namely BMI >30 kg/m^2, high glucose and high TG were predictors of progression to late-stage AMD amongst younger Australian white population aged ≤ 70 years. The findings also demonstrate the efficiency of mixed-effects model and the use of multiple measurements in statistical models to detect associations with the risk of disease.

CHAPTER 7- Conclusion

SUMMARY

Many longitudinal studies have been conducted to evaluate the relationship between various exposures and different morbidities and mortality. However, very often, only the baseline information was accounted for in the analysis due to the simplicity of statistical methods for evaluating data at a single time point. Such studies did not fully utilize the information of exposure that had been collected longitudinally at different time points, and hence limited the inferences that could be drawn from changes in exposure effect over time. The results of this thesis clearly demonstrated that accounting for baseline and further follow-up information of the exposure of interest such as metabolic syndrome (MetS) and its components, allowed for a more precise estimation of its effect on the respective outcomes. We thus encourage researchers to fully account for information involving multiple time points in longitudinal data analysis. Moreover, in the presence of multiple failure endpoints such as cause-specific mortality, we recommend the use of competing risks model especially among the elderly and frail population, to obtain a precise estimate of exposure effect as compared with the Cox regression model.

7.1 Overview

In the past decade, longitudinal studies commonly used only the baseline information in the evaluation of the association between exposures and health related outcomes, due to simplicity of statistical methods used for such data (Lewis et al. 2008; Dworetzky et al. 2010; Saczynski et al. 2010). Such studies did not fully utilize the information of exposure such as depression syndrome, BP or caffeine that had been collected longitudinally at different time points in their association with respective outcomes such as dementia, CVD or epilepsy. This limited the inferences that could have been drawn from changes in exposure effect over time.

To our best knowledge, this is the first study to fully utilize the information on MetS and its components including BMI, collected at baseline, 5- and 10-year visits to unravel their relationship with outcomes involving all-cause and cause-specific mortality, age-related cataract as well as AMD among the white Australian population.

First, we explored the effect of MetS and its components on subsequent all-cause and cause-specific mortality, and determined whether these associations change with time. When we analyzed only the information of MetS at baseline, without taking into account changes in MetS status at follow-up using the conventional Cox or competing risks regression models, we did not detect any effect of MetS on all-cause and CVD mortality. Accounting for further information of MetS at 5- and 10-year follow-up in addition to baseline information, by regarding it as a time-dependent covariate, the effects of MetS on

all-cause, cardiovascular- as well as cancer death was found to change over the study period. For example, the risk of all-cause-mortality increased gradually from 2-year to 10-year follow-up amongst those with MetS. The association between MetS and cardiovascular-death also changed with time, with increased risk of cardiovascular-death at 10-year and reduced risk at 2-year and 5-year. In contrast to cardiovascular-death, MetS was associated with a notably higher risk of cancer death at 2-year, with diminished risk by 10-year. This underscores that full utilization of MetS information at all assessments allows the detection of changing effect of MetS on all-cause and cause-specific mortality which would otherwise be impossible to detect if only baseline information were accounted for in the analysis. Therefore, the time-dependent models may also be clinically more relevant, as they reflect the actual clinical scenarios where MetS are likely to change over time, thus allowing the physicians to better evaluate and manage the elderly.

We also evaluated the age-specific association between baseline BMI (1992–1994) and 5-year changes in BMI (1997–1999) on the one hand, and overall and cause-specific mortality on the other, among the white Australian population. The results obtained using conventional Cox survival model were compared with those of the competing risks model. The association between BMI and mortality was found to be modified by age, with obesity being associated with greater risk of all-cause and cardiovascular-specific mortality amongst middle aged subjects ≤70 years, but not >70 years. With respect to changes in BMI over 5 years since baseline, BMI loss, a marker of greater severity of mortality-related

diseases, was associated with increased risk of all-cause mortality regardless of age, and cancer and cardiovascular-related mortality amongst subjects aged ≤ 70 years. Importantly, when we analyzed the relationship between baseline BMI and its 5-year changes using the cause-specific Cox regression model, the effect estimates were larger than those of the competing risks model. The differences were appreciable especially in the older age group for cancer- and cardiovascular-death.

In the third study, we evaluated the effect of MetS and its components on the incidence of different age-related cataract sub-types, namely cortical, nuclear and PSC cataract. In order to determine whether estimation of the effects differed at varying time interval, we utilized full information of the exposure that was collected at each follow-up and implemented the random-effects complementary log-log regression model to better describe the relationships. When we considered only the effect of MetS components at baseline without accounting for further follow-up information using the conventional logistic regression model, we did not detect any effects of obesity or HDL cholesterol on cortical cataract. However, after accounting for further information of MetS components at 5- and 10-year follow-up, the results showed that MetS was associated with the 5-year incidence of cortical and PSC cataract, and different MetS components were associated with the incidence of different cataract sub-types at varying time-intervals. Hence, full utilization of data provides a more robust estimate of the effect of MetS on age-related cataract, than baseline information only.

In the fourth study, we explored the longitudinal effect of MetS and its components on subsequent development of early or late stage AMD via the mixed model. Our study demonstrated that MetS and three of its components, namely BMI >30 kg/m^2, high glucose and high TG were predictors of progression to late-stage AMD amongst younger Australian white population aged ≤ 70 years. When we accounted for only baseline MetS components using the conventional logistic regression model, only high glucose was significantly associated with an increased 10-year cumulative incidence of late AMD amongst those aged ≤ 70 years. However, when we considered information of MetS and its components not only at baseline, but also at subsequent follow-up visits, the mixed-effects logistic regression model detected significant interaction not only between high glucose and age, but also between MetS and obesity with age, with the OR for MetS, obesity, high glucose and high TG reaching statistical significance amongst those aged ≤70 years. Hence, the mixed-effects logistic regression analysis which considered all available information of MetS components at baseline and subsequent follow-up visits, provided a more comprehensive understanding of the risks of AMD and its association with MetS and its components.

7.2 Discussion

Time-to-event outcome

From a statistical point of view, statistical methods for time-to-event data have long been staples of medical research. Within this class of methods, the proportional hazards model proposed by Cox (1972) is certainly among the most

important, with a variety of its extensions (Anderson and Gill 1982; Hougaard 2000; Therneau and Grambsch 2000; Collett 2005) and related diagnostic techniques (Therneau and Grambsch 2000; Collett 2005) becoming standard components of the medical researcher's toolbox (Finch et al. 2006; Gogas et al. 2006; Okin et al. 2006; Freedman et al. 2009; Ananthakrishnan et al. 2012). Largely, because of the increasing availability of data from longitudinal studies, which collect measurements of the same units at different time points, one class of extensions that has received a great deal of attention in recent years is the Cox proportional hazards model that includes time-dependent covariates (Aydemire et al. 1999; Fisher and Lin 1999). Like in the present thesis, the time-dependent approach makes it possible to incorporate all temporal information available by full utilization of data. In our study, applying conventional Cox regression model, using the baseline information of MetS only, failed to detect the relationship between MetS with all-cause and CVD-death. However, after accounting for further follow-up information of MetS during the entire study follow-up, the time-dependent model showed the relationship between MetS with all-cause and cause-specific mortality changed with time. Indeed, it has been shown that ignoring the changes in covariate values such as changes in MetS over the entire study follow-up may result in bias when estimating baseline effect only (Aydemire et al. 1999; Dancourt et al. 2004) and therefore, it is necessary to use appropriate method to adjust for a time-dependent covariate (Giorgi and Gouvernet 2005).

The use of time-dependent covariate in a time-to-event analysis offers exciting opportunities for exploring associations and potentially causal

mechanisms for exploring predictive relationships by using quantities that vary over time. This model also allows us to account for intra-subject correlation which arose with repeated measurements. Moreover, similar to our finding, the time-dependent model allows us to distinguish short from long term effect of exposure on outcome such as the effect of MetS on mortality at 2-, 5- and 10-year follow-up, while conventional Cox regression model fails to detect such changes over time (Collet 2003). Our study has also shown that earlier status of MetS was associated with cancer-death, while updated status of MetS was associated with all-cause and CVD-death. Indeed, utilising only the information of exposure at baseline would not be able to clarify whether earlier or most updated status of exposure associated with outcome. In addition, such studies would fail to assess the effect of changes in exposure over time. These underscore the importance of fully accounting for covariate information collected at each follow-up in order to better predict all-cause and major causes of death.

Competing risks outcome

Consistent with our result on the comparison between conventional Cox regression and competing risks models, several studies (Koller et al. 2008; Wolbers et al. 2009; Tai et al. 2010; Tai et al. 2011a; Tai et al. 2011b) have pointed out that for evaluation of multiple failure outcomes which can be regarded as competing risks, the cause-specific Cox regression model may substantially overestimate the risk of outcome of interest, because subjects with a specific event may experience other competing events in the future. They have also shown

that the use of competing risks method provides a more accurate and precise evaluation of the association between exposure and different causes of death, especially among the elderly population. This is due to the fact that competing risks model estimates the absolute risk after taking into account the presence of other competing events, while the conventional Cox model censors the competing event at the time when it occurs. The presence of competing events is an important issue in studies involving the elderly population, as the elderly tends to experience several major clinical outcomes at the same time since the prevalence of major chronic diseases tends to increase with increased age (Wolbers et al. 2009). As such, the competing risk based model helps us to reduce biases in estimates, and these biases are usually contributed by ignoring the competing event(s) (Putter et al. 2007). Our finding showed that conventional cause-specific Cox regression model overestimated the relationship between BMI and different causes of death in comparison with competing risks model. Hence, the implementation of the competing risks model avoids overestimation of the impact of exposure such as BMI on the multiple-event endpoint, as the model appropriately account for each competing risk in the analysis (Wolbers et al. 2009; Tai et al. 2010; Tai et al. 2011a; Tai et al. 2011b).

Interval-censored outcome

In epidemiological studies where subjects are seen periodically on follow-up visits, interval-censored data occur naturally (Zuma et al. 2007). In clinical or epidemiological studies, individual are repeatedly evaluated during the follow-up

schedules based on time interval (e.g. at baseline, 5- or 10-year). In such scenario, there is a probability to contract the disease (i.e. age-related cataract) during this time interval (i.e. between baseline to 5-year or between 5- to 10-year), and the exact date of the outcome/event may not be captured in this interval, and it is treated as an interval-censored data (Sun 1997). This situation is common in epidemiological and clinical studies. In such situations, the random-effects interval-censored modelling should be used to model the dependence of the onset of diseases within the interval among individuals with repeated measurements of observations (Sun 1997; Zuma et al. 2007). As explained in **Chapter 2**, in this thesis repeated measures of MetS and its components over the entire study follow-up have been shown to be highly correlated. The random-effects interval censored method accounts for intra-subject correlation which naturally arose with repeated measurements (Lam et al. 2010). Our finding also showed that when we considered only the effect of MetS components at baseline without accounting for its changing status at follow-up, we did not detect any effects of obesity or low-HDL cholesterol on cortical cataract. Indeed, the conventional fixed-effects approach ignores correlation in the data for clustered interval-censored data. As such, the standard errors thus obtained may lead to invalid statistical inference (Zuma et al. 2007). Moreover, failure to fully utilize the information that had been collected over time limits the inferences that could have been drawn especially with regards to changes in exposure effect (Rabe-Hesketh and Skrondal 2008; Tong et al. 2008; Sun et al. 2013). It is therefore important to fully accounting for covariate information collected at each follow-up visit in order for physicians to

better predict the risk of morbidities such as different types of cataract in persons at varying time-intervals.

Binomial outcome

The mixed-effects model allows repeated observations of the same person at different points in time during the overall analysis, and provides greater flexibility and more stable estimate than the traditional analysis by selecting the best-fitting structure for the data while accounting for intra-subject correlation (Margolin and Wampold 1981; Iacobucci and Wasserman 1988; Ozechowski 2007). In addition, this model is commonly used for the analysis of datasets with missing data (Verbeke and Molenberghs 2000; Gueorguieva and Krystal 2004; Torng et al. 2007). In longitudinal study design, since subjects are evaluated over time at different time periods, confronting with missing data during the follow-up period is inevitable, and it would be appropriate to adopt a mixed-effects model with such design. Our findings have shown that conventional logistic regression failed to detect the relationship between MetS, glucose and TG on late stage AMD, while these associations were found through applying mixed-effects logistic regression model. This is due to the fact that, traditional regression techniques do not recognize the clustered structure and will cause the standard errors of regression coefficients to be wrongly estimated, leading to an overstatement or understatement of statistical significance for the coefficients of both the higher and lower-level covariates. Therefore, mixed-effects logistic regression model

provides a more accurate estimate of the exposure with multiple measurements to detect associations with the risk of binary disease (Li et al. 2011).

7.3 Overall strengths and limitations of the study

As explained in **Chapter 2**, the strength of this study include a representative elderly Australian population, long-term follow-up, full utilisation of MetS information at each visit as well as high quality data collection involving standardised measures at each examination thus eliminating bias in self-reporting. Moreover, cataract diagnosis was based on standardized lens photographic grading, which have been shown to have high reproducibility (Panchapakesan et al. 1997; Kanthan et al. 2008), and the use of standard method for assessing AMD incidence and a detailed side-by-side comparison of baseline and follow-up examination photographs ensure negligible misclassification for AMD diagnosis (Tan et al. 2007). Moreover, missing data and loss to follow-up cannot be avoided in complex epidemiological studies involving long term follow-up. Missing data may result in a reduction in power and biased estimates, thus affecting the statistical findings. In this thesis, we applied longitudinal panel data analysis to overcome this problem.

However, the drawbacks of this study include the possibility of Type II error and hence lack of statistical power, which may exist especially when we analyzed the data amongst the subgroup of subjects with PSC cataract and late AMD. Further, when the p-value reported in our study is less than 0.05, we may make Type I error due to chance as several endpoints and subgroups were

evaluated. Moreover, the results could have been biased by residual confounding factors, such as varying levels of body composition, visceral adiposity or physical fitness which were not measured in this study. In addition, risk factors earlier in life (even in childhood) may have a different impact that cannot be assessed in this study. Also, assessment a few decades earlier would not be as prone to reverse causation by pre-clinical ill health.

There is also the possibility that our findings relating to the relationship between MetS (and its components) with mortality, cataract or AMD might have been confounded by the presence of pre-existing diseases such as cancer at baseline and adjustment for it might not totally account for its effect as the pre-existing disease might result in weight loss and consequently caused premature mortality. It should be noted that the magnitude of association between MetS and the respective outcomes remained unaltered regardless of whether we adjusted for the presence of each pre-existing disease such as cancer, AMI, angina and stroke individually or as a composite variable including 'any pre-existing diseases. As such, in this thesis, we presented only the results based on the composite variable of 'any pre-existing diseases'.

It would be possible that different cataract sub-types may be treated as a multinomial outcome. Moreover, it is natural that more than one type of cataract occurs in one subject (mixed cataract). Therefore, we encounter with different combination of cataract sub-types in each subject. In study 3, we considered interval-censored modelling for different sub-types of cataract as separate binary outcomes. We would not able to apply multinomial modelling, since the number

of events for mixed cataract sub-types were limited, and suggesting low statistical power to detect the actual relationships. Furthermore, early stage AMD may progress to late stage AMD, since late stage AMD is considered to be an advanced stage of AMD. As such, AMD may be treated as an ordinal outcome based on the severity of disease states such as no AMD, early AMD and late AMD to explore more complex relationships on different stages of AMD. In Study 4, we considered early or late stage AMD as separate binary outcomes, since the assumption for proportionality of odds across response categories was violated. In addition, although we have information on the eye (left or right) in which the outcomes of interest occur, the number of cortical, nuclear and PSC cataract events as well as early or late stage AMD were limited for each eye (left or right). As such, we would not be able to analyze the relationship between MetS and cataract or AMD according to the eye (ie. left or right). Moreover, subjects wearing glasses were more likely to participate in the BMES study as compared to the subjects who were not wearing glasses and refused to participate in this study. This will certainly create self-selection bias that might result in bias in estimating the effect measures for an eye disease outcome such as age-related cataract and AMD (Pan et al. 2013a; Pan et al. 2013b; Pan et al. 2013c).

7.4 Scope for future work

In this section, we elaborate on the implications this research has overall and where this work will lead to in further research and future epidemiological and clinical practice. The method for analysis of repeated measures outcomes is not

limited to those we have applied in this thesis. In medical research, we also encounter other types of outcomes: ordinal, multinomial or count data. In this section we recommend suggestions for future studies involving other outcomes which have been not evaluated in this thesis.

Ordinal outcome

Previous studies on the evaluation of exposures such as dietary fatty acid, physical activity, cardiovascular risk factor or white blood cell count with early or late stage of AMD have considered AMD as a binary outcome (Knudtson et al. 2006; Shankar et al. 2007a; Tan et al. 2007; Tan et al. 2009). Moreover, these studies have only evaluated the baseline effect of the mentioned exposures on AMD despite the longitudinal nature of data. As explained earlier, early stage AMD may progress to late stage AMD which is more severe than early stage AMD and so, it may be treated as an ordinal outcome.

The mixed-effects ordinal logistic regression may be implemented for ordinal outcomes which are repeatedly measured over the study period. Similar to the mixed-effects logistic regression model, this approach provides a more precise estimate in comparison with conventional ordinal logistic regression, by appropriately accounting for intra-subject correlation which commonly arose with repeated measures of observations. Moreover, this model can overcome missing data by full utilization of data (Li et al. 2011).

Hierarchical, multilevel or clustered data structures are often encountered in epidemiological and medical research. For example, in studying the

relationship between birth weight and maternal age, the data may be collected from a large number of maternity units located in different hospitals. Here, the individuals are said to be nested within the maternity units, and the maternity units nested within different hospitals (Goldstein et al. 2002). The maternity units may have different mean birth weights, so that knowledge of the maternity unit already conveys some information about the baby. Multilevel data structures also arise in longitudinal studies where measurements are clustered within individuals (Li et al. 2011). For example, different stage of AMD may occur in the right or left eye, although most previous studies evaluated the relationships in any eye (Knudtson et al. 2006; Shankar et al. 2007a; Tan et al. 2007; Tan et al. 2009). Nevertheless, in the medical literature, multilevel data are often analyzed using fixed effects models (Peter et al. 2003). In the case of AMD, it would be useful to apply hierarchical modelling with more than one level of random-effects; first level within individuals and second level involving the site or eye where the outcome occurs. Thus the mixed-effects ordinal logistic regression modelling may be further extended to data involving hierarchical structure (Li et al. 2011).

Multinomial outcome

There have been many longitudinal studies which have investigated the relationship between different exposures such as FPG, alcohol consumption, smoking, retinal vessel caliber, antioxidant nutrient intake or cardiovascular risk factors with risk of different sub-types of cataract, namely nuclear, cortical and PSC, cross-sectionally, despite the longitudinal nature of study design. These

studies have all considered the different cataract subtypes as separate binary outcomes (Klein et al. 1998; Kanthan et al. 2010; Kanthan et al. 2011; Tan et al. 2008a; Tan et al. 2008b; Tan et al. 2008c) although the classification of cataract subtypes, cortical, nuclear and PSC cataract, may be treated as a multinomial outcome. If the observations are independent, the multinomial or polychotomous logistic regression model (Cox 1970; Bock 1970; Nerlove and Press 1973; Placket 1974; Agresti 2012) can be used to assess the influence of covariates on the development of cataract which is classified on a nominal scale. However, in the BMES study, the subjects were repeatedly measured at scheduled follow-ups. In this case, the use of the ordinary multinomial logistic regression model assuming independence of observations would be problematic, since observations from the same cluster or subject are usually correlated (Hedeker et al. 2003). A mixed-effects multinomial logistic regression model would be appropriate for such analysis and it appropriately accounts for intra-subject correlation which arose in repeated measures data (Hedeker 2003). The analysis may also be extended to account for the occurrence of cataract in the right or left eye by means of hierarchical modelling with more than one level of random-effects as described earlier.

Count outcome

Count data frequently occurs in epidemiology and medicine. Some examples of count outcome include number of new enhancing lesions seen on monthly magnetic resonance imaging (MRI) of the brain, number of hospitalizations over a

period of time or number of patients “at risk” with a differing years of exposure. Suicide is also an example of count outcome, in which the time of happening is not predictable, but we only know how many events occur during a period of time, for example during a year. In longitudinal study design, where the exposure of interest such as emotional mood or drug abuse status were repeatedly measured over the study period, it would be useful to study the relationship between emotional mood or drug abuse with suicide by applying the mixed-effects Poisson regression model (Gibbons et al. 2008). The mixed-effects Poisson regression model accounts for intra-subject correlation arising from repeated measures, yielding a more robust estimate of the effect of interest as compared with the conventional Poisson regression model (Böckenholt et al. 2003).

7.5 Conclusion

The results of this thesis clearly demonstrate that accounting for baseline and further follow-up information allow for a more accurate and precise estimation of the effect of MetS and its components on all-cause and cause-specific mortality, age-related cataract as well as AMD. Moreover, in the analysis of competing risks outcomes, the competing risks model in comparison with the conventional cause-specific regression showed narrower 95% CIs. This avoids the potential problem of extreme parameter estimates occurring due to chance when the estimates are based on small numbers.

The advanced statistical modelling techniques, such as Cox regression model with time-dependent covariate allow researchers to handle time-dependent

covariate in order to evaluate the effect of changes in MetS over time on mortality at different time points after accounting for all available covariate information over the entire duration of study follow-up. This model also allows us to distinguish short from long term effect of MetS on mortality. Moreover, random-effects complementary log-log regression model used in this proposed thesis allows us to handle interval-censored data to explore the effect of changes in MetS over time on sub-types of cataract at different time intervals, after accounting for all available exposure information over the entire duration of study follow-up. This model also allows us to capture effect at varying time interval on different subtypes of cataract.

In addition, the proposed advanced models provide a more flexible modelling framework in terms of repeated measures, and are able to overcome the problem with missing data. Besides, they account for intra-subject correlation which arose with repeated measures, thus yielding a more accurate and stronger relationship between MetS and the respective outcomes.

Bibliography

Adams RJ, Appleton S, Wilson DH, Taylor AW, Dal Grande E, Chittleborough C, Gill T, Ruffin R (2005). Population comparison of two clinical approaches to the metabolic syndrome: implications of the new International Diabetes Federation consensus definition. *Diabetes Care* 28:2777-2779.

Adams KF, Schatzkin A, Harris TB, Kipnis V, Mouw T, Ballard-Barbash R, Hollenbeck A, Leitzmann MF (2006). Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. *The New England Journal of Medicine* 355: 763–778.

Ahmed A, Khan TE, Yasmeen T, Awan S, Islam N (2012). Metabolic syndrome in type 2 diabetes: comparison of WHO, modified ATP III & IDF criteria. *Journal of the Pakistan Medical Association* 62:569-574.

Agresti A (2012). Categorical Data Analysis (3rd Ed.), Hoboken, New Jersey: John Wiley & Sons.

Akbaraly TN, Kivimaki M, Ancelin ML, Barberger-Gateau P, Mura T, Tzourio C, Touchon J, Ritchie K, Berr C (2010). Metabolic syndrome, its components, and mortality in the elderly. *The Journal of Clinical Endocrinology & Metabolism* 95:E327-332.

Ajani UA, Lotufo PA, Gaziano JM, Lee IM, Spelsberg A, Buring JE, Willett WC, Manson JE (2004). Body mass index and mortality among US male physicians. *Annals of Epidemiology* 14:731–739.

Alberti KGMM, Zimmet P, Shaw J. Diabetes UK (2006). Metabolic syndrome - a new world-wide definition. A consensus statement from the International Diabetes Federation. *Diabetes Medicine* 23:469-480.

Alfaro DV (2006). Age-related macular degeneration: a comprehensive textbook. Philadelphia: Lippincott Williams & Wilkins.

Allison PD (1982). Discrete-time methods for the analysis of event histories. In: Leinhardt S, ed. Sociological methods and research. San Francisco, CA: Jossey-Bass Publishers: 61–98.

Ananthakrishnan AN, Higuchi LM, Huang ES, Khalili H, Richter JM, Fuchs CS, Chan AT (2012). Aspirin, nonsteroidal anti-inflammatory drug use, and risk for Crohn disease and ulcerative colitis. *Annals of Internal Medicine* 156:350–359.

Andersen PK, Gill R (1982). Cox's regression model for counting processes: a large sample study. *The Annals of Statistics* 10:1100–1120.

Anderson PJ, Critchley JAJH, Chan JCN, Cockram CS, Lee ZSK, Thomas G, Tomlinson B (2001). Factor analysis of the metabolic syndrome: obesity *vs* insulin resistance as the central abnormality. *International Journal of Obesity* 25: 1782-1788.

Attebo K, Mitchell P, Smith W (1996). Visual acuity and the causes of visual loss in Australia. The Blue Mountains Eye Study. *Ophthalmology* 103:357–364.

Aydemir U, Aydemir S, Dirschedl P (1999). Analysis of time-dependent covariates in failure time data. *Statistics in Medicine* 18:2123–2134.

Baade PD, Meng X, Youl PH, Aitken JF, Dunn J, Chambers SK (2011). The impact of body mass index and physical activity on mortality among patients with colorectal cancer in Queensland, Australia. *Cancer Epidemiology, Biomarkers & Prevention* 20:1410-1420.

Bailey IL, Bullimore MA, Raasch TW, Taylor HR (1991). Clinical grading and effects of scaling. *Investigative Ophthalmology & Visual Sciences* 32:422-32.

Balkau B, Charles MA (1999). Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR). *Diabetic Medicine* 16:442-443.

Bamia C, Halkjaer J, Lagiou P, Trichopoulos D, Tjønneland A, Berentzen TL, Overvad K, Clavel-Chapelon F, Boutron-Ruault MC, Rohrmann S, Linseisen J, Steffen A, Boeing H, May AM, Peeters PH, Bas Bueno-de-Mesquita H, van den Berg SW, Dorronsoro M, Barricarte A, Rodriguez Suarez L, Navarro C, González CA, Boffetta P, Pala V, Hallmans G, Trichopoulou A. (2010). Weight change in later life and risk of death amongst the elderly: the European Prospective Investigation into Cancer and Nutrition-Elderly Network on Ageing and Health study. *Journal of Internal Medicine* 268:133-144.

Bates DM, and Pinheiro JC (1998). Computational methods for multilevel modelling. In Technical Memorandum BL0112140-980226-01TM. Murray Hill, NJ: Bell Labs, Lucent Technologies.
http://stat.bell-labs.com/NLME/CompMulti.pdf.

Blasco-Fontecilla H, Perez-Rodriguez MM, Garcia-Nieto R, Fernandez-Navarro P, Galfalvy H, de Leon J, Baca-Garcia E (2012).Worldwide impact of economic cycles on suicide trends over 3 decades: differences according to level of development. A mixed effect model study. *British Medical Journal Open* 2.

Berrington de Gonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis RJ, Moore SC, Tobias GS, Anton-Culver H, Freeman LB, Beeson WL, Clipp SL, English DR, Folsom AR, Freedman DM, Giles G, Hakansson N, Henderson KD, Hoffman-Bolton J, Hoppin JA, Koenig KL, Lee IM, Linet MS, Park Y, Pocobelli G, Schatzkin A, Sesso HD, Weiderpass E, Willcox BJ, Wolk A, Zeleniuch-Jacquotte A, Willett WC, Thun MJ (2010). Body-mass index and mortality among 1.46 million white adults. *The New England Journal of Medicine* 363:2111-2119.

Beyersmann J, Dettenkofer M, Bertz H, Schumacher M (2007). A competing risks analysis of bloodstream infection after stem-cell transplantation using subdistribution hazards and cause-specific hazards. *Statistics in Medicine* 26:5360-5369.

Bird AC, Bressler NM, Bressler SB, Chisholm IH, Coscas G, Davis MD, de Jong PT, Klaver CC, Klein BE, Klein R (1995). An international classification and

grading system for age-related maculopathy and age-related macular degeneration. *Survey of Ophthalmology* 39:367–374.

Boberg KM, Rocca G, Egeland T, Bergquist A, Broomé U, Caballeria L, Chapman R, Hultcrantz R, Mitchell S, Pares A, Rosina F, Schrumpf E (2002). Time-dependent Cox regression model is superior in prediction of prognosis in primary sclerosing cholangitis. *Hepatology* 35:652-657.

Bock RD (1970). Estimating multinomial response relations. In Contributions to Statistics and Probability, Bose RC (ed.). University of North Carolina Press: Chapel Hill, NC.

Böckenholt U, Kamakura WA, Wedel M (2003). The structure of self-reported emotional experiences: a mixed-effects Poisson factor model. *British Journal of Mathematical and Statistical Psychology* 56:215-229.

Bosevski M, Pemovska G, Bosevska G, Georgievska-Ismail L (2010). Clinical role of estimation metabolic syndrome's components in type 2 diabetic population with symptomatic coronary artery disease- a comparison of two criteria. *Medical Archives* 64:144-146.

Breeze E, Clarke R, Shipley MJ, Marmot MG, Fletcher AE (2006). Cause-specific mortality in old age in relation to body mass index in middle age and in old age: follow-up of the Whitehall cohort of male civil servants. *International Journal of Epidemiology* 35:169–178.

Brown GC, Sharma S, Brown MM, Kistler J (2000). Utility values and age-related macular degeneration. *Archives Ophthalmology* 118:47–51.

Brown H, Prescott R (2006). Applied Mixed Models in Medicine, 2nd Edition. John Wiley and Sons.

Burke GL, Arnold AM, Bild DE, Cushman M, Fried LP, Newman A, Nunn C, Robbins J; CHS Collaborative Research Group (2001). Factors associated with healthy aging: the cardiovascular health study. *Journal of the American Geriatrics Society* 49:254-262.

Candel MJ (2012). Parallel, AA/BB, AB/BA and Balaam's design: efficient and maximin choices when testing the treatment effect in a mixed effects linear regression. *Pharmaceutical Statistics*11:97-106.

Carr MC, Brunzell JD (2004). Abdominal obesity and dyslipidemia in the metabolic syndrome: importance of type 2 diabetes and familial combined hyperlipidemia in coronary artery disease risk. *The Journal of Clinical Endocrinology & Metabolism* 89:2601-2607.

Chambless LE and Diao G (2006). Estimation of time-dependent area under the ROC curve for long-term risk prediction. *Statistics in Medicine* 25:3474–3486.

Cheung N, Wong TY (2007). Obesity and eye diseases. *Survey of Ophthalmology* 52:180-195.

Christensen E, Altman DG, Neuberger J, de Stavola BL, Tygstrup N, Williams R, the PBC1 and PBC2 trial groups (1993). Updating prognosis in primary biliary cirrhosis using a time-dependent Cox regression model. *Gastroenterology* 105:1865-1876.

Clemons TE, Milton RC, Klein R, Seddon JM, Ferris FL 3rd. Age-Related Eye Disease Study Research Group (2005). Risk factors for the incidence of advanced age-related macular degeneration in the Age-Related Eye Disease Study (AREDS) AREDS report no. 19. *Ophthalmology* 112:533–539.

Collett D (2003). Modelling survival data in medical research. 2nd ed. Chapman & Hall: Boca Raton, FL.

Congdon NG, Chang MA, Botelho P, Stark WJ, Datiles III MB. Cataract: Clinical Types. Chapter 73. http://www.online-eye-info.com/cataract-definition.html

Corrada MM, Kawas CH, Mozaffar F, Paganini-Hill A (2006). Association of body mass index and weight change with all-cause mortality in the elderly. *American Journal of Epidemiology* 163:938-949.

Cox DR (1970). Analysis of Binary Data. Chapman and Hall: London.

Cox D (1972). Regression models and life-tables (with discussion). *Journal of the Royal Statistical Society, Series B* 34:187–220.

Crowder MJ, Hand DJ (1990). Analysis of Repeated Measures. New York, NY: Chapman and Hall.

Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, Pratt M, Ekelund U, Yngve A, Sallis JF, Oja P (2003). International physical activity questionnaire: 12-country reliability and validity. *Medical & Science in Sports & Exercise* 35:1381-1395.

Cugati S, Wang JJ, Rochtchina E, Mitchell P (2007). Ten-year incidence of diabetes in older Australians: the Blue Mountains Eye Study. *The Medical Journal of Australia* 186:131-135.

Dahl AK, Fauth EB, Ernsth-Bravell M, Hassing LB, Ram N, Gerstof D (2013). Body mass index, change in body mass index, and survival in old and very old persons. *Journal of the American Geriatrics Society* 61:512-518.

Dancourt V, Quantin C, Abrahamowicz M, Binquet C, Alioum A, Faivre J (2004). Modeling recurrence in colorectal cancer. *Journal of Clinical Epidemiology* 57:243–251.

Dawber TR. (1980). The Framingham Study. The Epidemiology Atherosclerotic Disease. Cambridge, MA: Harvard University Press.

Dawber TR, Meadors GF, Moore FEJ (1951). Epidemiological approaches to heart disease: The Framingham Study. *American Journal of Public Health* 41: 279-286.

Dekker JM, Girman C, Rhodes T, Nijpels G, Stehouwer CD, Bouter LM, Heine RJ (2005). Metabolic syndrome and 10-year cardiovascular disease risk in the Hoorn Study. *Circulation* 112:666-673.

Delcourt C, Michel F, Colvez A, Lacroux A, Delage M, Vernet MH; POLA Study Group (2001). Associations of cardiovascular disease and its risk factors with age-related macular degeneration: the POLA study. *Ophthalmic Epidemiology* 8:237-49.

Devaraj S, Rosenson RS, Jialal I (2004). Metabolic syndrome: an appraisal of the pro-inflammatory and procoagulant status. *Endocrinology and Metabolism Clinics* of *North America* 33:431– 453.

Drøyvold WB, Lund Nilsen TI, Lydersen S, Midthjell K, Nilsson PM, Nilsson JA, Holmen J; Nord-Trøndelag Health Study (2005). Weight change and mortality: the Nord-Trøndelag Health Study. *Journal of Internal Medicine* 257:338-345.

Duvnjak L, Bulum T, Metelko Ž (2008). Hypertension and the metabolic syndrome. *Diabetologia Croatica* 37:suppl 4, 83-89.

Dworetzky BA, Bromfield EB, Townsend MK, Kang JH (2010). A prospective study of smoking, caffeine, and alcohol as risk factors for seizures or epilepsy in young adult women: data from the Nurses' Health Study II. *Epilepsia* 51:198-205.

Eckel RH, Grundy SM, Zimmer PZ (2005). The metabolic syndrome. *Lancet* 365: 1415-1428.

Executive Summary of the Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults (Adult Treat-ment Panel III) (2001). *Journal of the American Medical Association* 285: 2486 – 2497.

Finch A, Beiner M, Lubinski J, Lynch HT, Moller P, Rosen B, Murphy J, Ghadirian P, Friedman E, Foulkes WD, Kim-Sing C, Wagner T, Tung N, Couch F, Stoppa-Lyonnet D, Ainsworth P, Daly M, Pasini B, Gershoni-Baruch R, Eng C, Olopade OI, McLennan J, Karlan B, Weitzel J, Sun P, Narod SA, for the Hereditary Ovarian Cancer Clinical Study Group (2006). Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with a *BRCA1* or *BRCA2* mutation. *Journal of the American Medical Association* 296:185–192.

Fisher LD, Lin DY (1999). Time-dependent covariates in the Cox proportional-hazards regression model. *Annual Review of Public Health* 20:145-157.

Fitzmaurice G, Nan Laird N, Ware J (2004). Applied longitudinal analysis. New Jersey: John Wily and Sons.

Flegal KM, Graubard BI, Williamson DF, Gail MH (2005). Excess deaths associated with underweight, overweight, and obesity. *The Journal of the American Medical Association* 293:1861-1867.

Ford ES, Giles WH, Dietz WH (2002). Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *Journal of the American Medical Association* 287:356-359.

Franks PW, Olsson T (2007). Metabolic syndrome and early death: getting to the heart of the problem. *Hypertension* 49:10–12.

Friedman E (2000). The role of the atherosclerotic process in the pathogenesis of age-related macular degeneration. *American Journal of Ophthalmology* 130:658-663.

Freedman LS, Oberman B, Sadetzki S (2009). Using time-dependent covariate analysis to Warthin's tumor risk. *American Journal of Epidemiology* 170:1178-1185.

Fried LP, Kronmal RA, Newman AB, Bild DE, Mittelmark MB, Polak JF, Robbins JA, Gardin JM (1998). Risk factors for 5-year mortality in older adults: the Cardiovascular Health Study. *The Journal of the American Medical Association* 279:585-592.

Friedman E (2000). The role of the atherosclerotic process in the pathogenesis of age-related macular degeneration. *American Journal of Ophthalmology*. 130:658-663.

Fryczkowski AW, Sata SE, Hodes BL (1988). Changes in the diabetic choroidal vasculature: scanning electron microscopy findings. *Annals of Ophthalmology* 20:299–305.

Funada S, Shimazu T, Kakizaki M, Kuriyama S, Sato Y, Matsuda-Ohmori K, Nishino Y, Tsuji I (2008). Body mass index and cardiovascular disease mortality in Japan: the Ohsaki Study. *Preventive Medicine* 47:66-70.

Gibbons RD, Segawa E, Karabatsos G, Amatya AK, Bhaumik DK, Brown CH, Kapur K, Marcus SM, Hur K, Mann JJ (2008). Mixed-effects Poisson regression analysis of adverse event reports: the relationship between antidepressants and suicide. *Statistics in Medicine* 27:1814-1833.

Giorgi R, Gouvernet J (2005). Analysis of time-dependent covariates in a regressive relative survival model. *Statistics in Medicine* 24:3863–3870.

Gogas H, Ioannovich J, Dafni U, Stavropoulou-Giokas C, Frangia K, Tsoutsos D, Panagiotou P, Polyzos A, Papadopoulos O, Stratigos A, Markopoulos C, Bafaloukos D, Pectasides D, Fountzilas G, Kirkwood JM (2006). Prognostic significance of autoimmunity during treatment of melanoma with interferon. *New England Journal of Medicine* 354:709–718.

Goldstein H, Browne W, Rasbash J (2002). Multilevel modelling of medical data. *Statistics in Medicine* 21:3291-3315.

Gopinath B, Thiagalingam A, Teber E, Mitchell P (2011). Exposure to workplace noise and the risk of cardiovascular disease events and mortality among older adults. *Preventive Medicine* 53:390-394.

Grunkemeier GL, Anderson RP, Miller DC, Starr A (1997). Time-related analysis of nonfatal heart valve complications: cumulative incidence (actual) versus Kaplan-Meier (actuarial). *Circulation* 96(suppl 9):II-4.

Grunkemeier GL, Jin R, Eijkemans MJ, Takkenberg JJ (2007). Actual and actuarial probabilities of competing risks: apples and lemons. *The Annals of Thoracic Surgery* 83:1586 –1592.

Gueorguieva R, Krystal JH (2004). Move over ANOVA: progress in analyzing repeated measures data and its reflection in papers published in the Archives of General Psychiatry. *Archives of General Psychiatry* 61:310–317.

Haffner SM, Valdez RA, Hazuda HP, Mitchell BD, Morales PA, Stern MP (1992). Prospective analysis of the insulin-resistance syndrome (syndrome X). *Diabetes* 41:715–722.

Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA (1991). Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *European Journal of Epidemiology* 7:403–422.

Haibe-Kains B, Desmedt C, Sotiriou C, Bontempi G (2008). A comparative study of survival models for breast cancer prognostication based on microarray data: does a single gene beat them all? *Bioinformatics* 24:2200–2208.

Hardin JW, Hilbe JM (2007). Generalized Linear Models and Extensions. 2nd ed. College Station, TX: Stata Press.

Harrell FE Jr, Califf RM, Pryor DB, Lee KL, Rosati RA (1982). Evaluating the yield of medical tests. *The Journal of the American Medical Association* 247:2543-2546.

Harrell FE Jr, Lee KL, Califf RM, Pryor DB, Rosati RA (1984). Regression modelling strategies for improved prognostic prediction. *Statistics in Medicine* 3:143-152.

Harrell FJ Jr (2001). Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis. Springer series in statistics. New York: Springer-Verlag.

Harris T, Cook EF, Garrison R, Higgins M, Kannel W, Goldman L (1998). Body mass index and mortality among nonsmoking older persons. The Framingham Heart Study. *The Journal of the American Medical Association* 259:1520–1524.

Hartmann O, Schuetz P, Albrich WC, Anker SD, Mueller B, Schmidt T (2012). Time-dependent Cox regression: serial measurement of the cardiovascular biomarker proadrenomedullin improves survival prediction in patients with lower respiratory tract infection. *International Journal of Cardiology* 161:166-173.

Haslam DW, James WP (2005). Obesity. *Lancet* 1:1197-1209.

Heagerty PJ, Lumley T, Pepe MS (2000). Time-dependent ROC curves for censored survival data and a diagnostic marker. *Biometrics* 56:337–344.

Hedeker D (2003). A mixed-effects multinomial logistic regression model. *Statistics in Medicine* 22:1433-1446.

Hennis A, Wu SY, Li X, Nemesure B, Leske MC (2001). Lens opacities and mortality: The Barbados Eye Studies. *Ophthalmology* 108:498–504.

Hidayat AA, Fine BS (1985). Diabetic choroidopathy light and electron microscopic observations of seven cases. *Ophthalmology* 92:512–522.

Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA (1991). Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *European Journal of Epidemiology* 7:403–422.

Hougaard P (2000). Analysis of Multivariate Survival Data. Springer-Verlag: New York.

Hsu PF, Chuang SY, Cheng HM, Tsai ST, Chou P, Chen CH (2008). Clinical significance of the metabolic syndrome in the absence of established hypertension and diabetes: A community-based study. *Diabetes Research and Clinical Practice* 79:461-467.

http://www.bepress.com/harvardbiostat/paper107Yates. Comparing risk scoring systems beyond the ROC paradigm in survival analysis. Harvard University Biostatistics Working Paper Series. Working paper 107.

Hu G, Qiao Q, Tuomilehto J, Balkau B, Borch-Johnsen K, Pyorala K. DECODE Study Group (2004). Prevalence of the metabolic syndrome and its relation to all-

cause and cardiovascular mortality in nondiabetic European men and women. *Archives Internal Medicine* 164:1066-1076.

Hunt KJ, Resendez RG, Williams K, Haffner SM, Stern MP (2004). San Antonio Hearth Study. National Cholesterol Education Program versus World Health Organization metabolic syndrome in relation to all-cause and cardiovascular mortality in the San Antonio Heart Study. *Circulation* 110:1251-1257.

Iacobucci, D and Wasserman S (1988). A general framework for the statistical analysis of sequential dyadic interaction data. *Psychological Bulletin* 103:379–390.

Jacob RF, Mason RP (2005). Lipid peroxidation induces cholesterol domain formation in model membranes. *The Journal of Biological Chemistry* 280:39380-39387.

Jaggers JR, Sui X, Hooker SP, LaMonte MJ, Matthews CE, Hand GA, Blair SN. (2009). Metabolic syndrome and risk of cancer mortality in men. *European Journal of Cancer* 5:1831-1838.

Kador PF, Kinoshita JH (1984). Diabetic and galactosaemic cataracts. *CIBA Foundation Symposium* 106:110–131.

Kalbfleisch JD, Prentice RL (2002). The Statistical Analysis of Failure Time Data. Hoboken, NJ: John Wiley and Sons.

Kanthan GL, Wang JJ, Rochtchina E, Tan AG, Lee A, Chia EM, Mitchell P (2008). Ten-year incidence of age-related cataract and cataract surgery in an older Australian population. The Blue Mountains Eye Study. *Ophthalmology* 115:808-814.

Kanthan GL, Mitchell P, Burlutsky G, Wang JJ (2010). Alcohol consumption and the long-term incidence of cataract and cataract surgery: the Blue Mountains Eye Study. *American Journal of Ophthalmology* 150:434-440.e1.

Kanthan GL, Mitchell P, Burlutsky G, Wang JJ (2011). Fasting blood glucose levels and the long-term incidence and progression of cataract: the Blue Mountains Eye Study. *Acta Ophthalmologica* 89:e434-438.

Kerr KF, McClelland RL, Brown ER, Lumley T (2011). Evaluating the incremental value of new biomarkers with integrated discrimination improvement. *American Journal of Epidemiology* 174:364-374.

Klein BE, Klein R, Linton KL, Magli YL, Neider MW (1990a). Assessment of cataracts from photographs in the Beaver Dam Eye Study. *Ophthalmology* 97:1428-33.

Klein BE, Magli YL, Neider MW, Klein R (1990b). Wisconsin system for classification of cataracts from photographs (protocol). Madison, WI: University of Wisconsin-Madison; pp 1-28.

Klein BE, Klein R, Lee KE (1998). Diabetes, cardiovascular disease, selected cardiovascular disease risk factors, and the 5-year incidence of age-related cataract and progression of lens opacities: the Beaver Dam Eye Study. *American Journal of Ophthalmology* 126:782-790.

Klein BE, Klein R, Lee KE, Jensen SC (2001). Measures of obesity and age-related eye diseases. *Ophthalmic Epidemiology* 8:251-262.

Klein R, Davis MD, Magli YL, Segal P, Klein BE, Hubbard L (1991). The Wisconsin Age-Related Maculopathy Grading System. *Ophthalmology* 98:1128 – 1134.

Klein R, Klein BE, Moss SE (1992). Diabetes, hyperglycemia, and age-related maculopathy. The Beaver Dam Eye Study. *Ophthalmology* 99:1527–1534.

Klein R, Klein BE, Jeensen SC (1997). The relationship of cardiovascular disease and its risk factors to the 5-year incidence of age-related maculopathy. The Beaver Dam Eye study. *Ophthalmology* 104:1804–1812.

Klein R (2005). Epidemiology of age-related macular degeneration. In: Penfold PL, Provis JM, eds. *Macular Degeneration: Science and Medicine in Practice.* New York, NY: Springer-Verlag:79-121.

Klein R, Deng Y, Klein BE, Hyman L, Seddon J, Frank RN, Wallace RB, Hendrix SL, Kuppermann BD, Langer RD, Kuller L, Brunner R, Johnson KC, Klimov AN, Gurevich VS, Nikiforova AA, Shatilina LV, Kuzmin AA, Plavinsky

SL, Teryukova NP. (1993). Antioxidative activity of high density lipoproteins in vivo. *Atherosclerosis* 100:13–18.

Klein R, Deng Y, Klein BE, Hyman L, Seddon J, Frank RN, Wallace RB, Hendrix SL, Kuppermann BD, Langer RD, Kuller L, Brunner R, Johnson KC Thomas AM, Haan M (2007). Cardiovascular disease, its risk factors and treatment, and age-related macular degeneration: Women's Health Initiative Sight Exam ancillary study. *American Journal of Ophthalmology*. 143:473-183.

Koller MT, Schaer B, Wolbers M, Sticherling C, Bucher HC, Osswald S (2008). Death without prior appropriate implantable cardioverter-defibrillator therapy: a competing risk study. *Circulation* 117:1918 –1926.

Knudtson MD, Klein R, Klein BE (2006). Physical activity and the 15-year cumulative incidence of age-related macular degeneration: the Beaver Dam Eye Study. *British Journal of Ophthalmology* 90:1461-1463.

Kuk JL, Ardern CI (2009). Influence of age on the association between various measures of obesity and all-cause mortality. *Journal of the American Geriatrics Society* 57:2077–2084.

Kylin E (1923.) Studien ueber das Hypertonie-Hyperglykamie-Hyperurikamie Syndrom [German]. *Zentralblatt fur Innere Medizin* 44: 105–127.

Kyselová Z, Garcia SJ, Gajdosíková A, Gajdosík A, Stefek M (2005). Temporal relationship between lens protein oxidation and cataract development in streptozotocin-induced diabetic rats. *Physiological Research* 54:49-56.

Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, Salonen JT (2002). The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *Journal of the American Medical Association* 288: 2709-2716.

Lam KF, Xu Y, Cheung TL (2010). A multiple imputation approach for clustered interval-censored survival data. *Statistics in Medicine* 29:680-693.

Lebowitz MD (1996). Age, period, and cohort effects. *American Journal of Respiratory Critical Care Medicine*154:S273-S277.

Lecaire T, Palta M, Zhang H, Allen C, Klein R, D'Alessio D (2006). Lower-than-expected prevalence and severity of retinopathy in an incident cohort followed during the first 4-14 years of type 1 diabetes: the Wisconsin Diabetes Registry Study. *American Journal of Epidemiology* 164:143-150.

Lee IM, Manson JE, Hennekens CH, Paffenbarger RS Jr. (1993). Body weight and mortality. A 27-year follow-up of middle-aged men. *Journal of the American Medical Association* 270:2823-2828.

Lemieux I, Pascot A, Prud'homme D, Alméras N, Bogaty P, Nadeau A, Bergeron J, Després JP (2001). Elevated C-reactive protein: another component of the

atherothrombotic profile of abdominal obesity. *Arteriosclerosis, Thrombosis and Vascular Biology* 21:961-967.

Leske MC, Wu SY, Hennis A, Nemesure B, Yang L, Hyman L, Schachat AP; Barbados Eye Studies Group (2006). Nine-year incidence of age-related macular degeneration in the Barbados Eye Studies. *Ophthalmology* 113:29–35.

Lewis GD, Gona P, Larson MG, Plehn JF, Benjamin EJ, O'Donnell CJ, Levy D, Vasan RS, Wang TJ (2008). Exercise blood pressure and the risk of incident cardiovascular disease (from the Framingham Heart Study). *American Journal of Cardiology*101:1614-1620.

Li B, Lingsms HF, Steyerberg EW, Lesaffre E (2011). Logistic random effects regression models: a comparison of statistical packages for binary and ordinal outcomes. *BMC Medical Research Methodology* 11:77.

Lim LS, Tai ES, Aung T, Tay WT, Saw SM, Seielstad M, Wong TY (2009). Relation of age-related cataract with obesity and obesity genes in an Asian population. *American Journal of Epidemiology* 169:1267-1274.

Lindsted KD, Singh PN (1997). Body mass and 26-year risk of mortality among women who never smoked: findings from the Adventist Mortality Study. *American Journal of Epidemiology* 146: 1–11.

Maggi S, Noale M, Gallina P, Bianchi D, Marzari C, Limongi F, Crepaldi G; ILSA Working Group. (2006). Metabolic syndrome, diabetes and cardiovascular

disease in an elderly Caucasian cohort: the Italian Longitudinal Study of Aging. *The Journal of Gerontology. Series A: Biological Sciences & Medical Sciences* 61:505-510.

Malik S, Wong ND, Franklin SS, Kamath TV, L'Italien GJ, Pio JR, Williams GR (2004). Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. *Circulation*110:1245-1250.

Mann DM, Lee J, Liao Y, Natarajan S (2006). Independent effect and population impact of obesity on fatal coronary heart disease in adults. *Preventive Medicine* 42:66-72.

Margolin G and Wampold BE (1981). Sequential analysis of conflict and accord in distressed and nondistressed marital partners. *Journal of Consulting and Clinical Psychology* 49:554–567.

Maru S, van der Schouw YT, Gimbrère CH, Grobbee DE, Peeters PH (2004). Body mass index and short-term weight change in relation to mortality in Dutch women after age 50 y. *The American Journal of Clinical Nutrition* 80:231-236.

Mathieu P, Pibarot P, Despres JP (2006). Metabolic syndrome: the danger signal in atherosclerosis. *Journal of Vascular Health and Risk Management* 2:285-302.

McCarty CA, Dowrick A, Cameron J, McGrath B, Robman LD, Dimitrov P, Tikellis G, Nicolas C, McNeil J, Guymer R (2008). Novel measures of

cardiovascular health and its association with prevalence and progression of age-related macular degeneration: the CHARM Study. *BMC Ophthalmology* 8:25.

Mitchell P, Smith W, Attebo K, Wang JJ (1995). Prevalence of age-related maculopathy in Australia: the Blue Mountains Eye Study. *Ophthalmology* 102:1450–1460.

Mitchell P, Smith W, Wang JJ, Cumming RG, Leeder SR, Burnett L (1998a). Diabetes in an older Australian population. *Diabetes Research and Clinical Practice* 41:177-184.

Mitchell P, Smith W, Wang JJ (1998b). Iris color, skin sun sensitivity, and age-related maculopathy. The Blue Mountains Eye Study. *Ophthalmology* 105:1359-1363.

Mitchell P, Wang JJ (1999). Diabetes, fasting blood glucose and age-related maculopathy. The Blue Mountains Eye Study. *Australian New Zealand Journal Ophthalmology* 27:197–199.

Mitchell P, Wang JJ, Foran S, Smith W (2002). Five-year incidence of age-related maculopathy lesions: the Blue Mountains Eye Study. *Ophthalmology* 109:1092–1097.

Molenberghs G, Verbeke G (2005). Models for Discrete Longitudinal Data. Springer: Berlin.

Montgomery MP, Kamel F, Pericak-Vance MA, Haines JL, Postel EA, Agarwal A, Richards M, Scott WK, Schmidt S (2010). Overall diet quality and age-related macular degeneration. *Ophthalmic Epidemiology* 17:58-65.

Mozaffarian D, Kamineni A, Prineas RJ, Siscovick DS (2008). Metabolic syndrome and mortality in older adults: the Cardiovascular Health Study. *Archives Internal Medicine* 168:969–978.

Myrskylä M, Chang VW (2009). Weight change, initial BMI, and mortality among middle- and older-aged adults. *Epidemiology* 20:840–848.

Nakagami T; DECODA Study Group (2004). Hyperglycaemia and mortality from all causes and from cardiovascular disease in five populations of Asian origin. *Diabetologia* 47:385-394.

Nelder JA (2001). Letter to the editor. *Statistics in Medicine* 20:2205.

Nerlove M, Press SJ (1973). Univariate and multivariate log-linear and logistic models. Technical Report R-1306-EDA=NIH, Rand Corporation, Santa Monica, CA.

Neuhaus, JM (1992). Statistical methods for longitudinal and clustered designs with binary responses. *Statistical Methods in Medical Research* 1:249-273.

Panchapakesan J, Cumming RG, Mitchell P (1997). Reproducibility of the Wisconsin cataract grading system in the Blue Mountains Eye Study. *Ophthalmic Epidemiol*ogy 4:119-126.

Newman AB, Yanez D, Harris T, Duxbury A, Enright PL, Fried LP; Cardiovascular Study Research Group (2001). Weight change in old age and its association with mortality. *Journal of the American Geriatrics* Society 49:1309-1318.

Ohlson LO, Larsson B, Svärdsudd K, Welin L, Eriksson H, Wilhelmsen L, Björntorp P, Tibblin G (1985).The influence of body fat distribution on the incidence of diabetes mellitus. 13.5 years of follow-up of the participants in the study of men born in 1913. *Diabetes* 34:1055-1058.

Okin PM,Wachtell K, Devereux RB, Harris KE, Jern S, Kjeldsen SE, Julius S, Lindholm LH, Nieminen MS, Edelman JM, Hille DA, Dahlöf B (2006). Regression of electrocardiographic left ventricular hypertrophy and decreased incidence of new-onset atrial fibrillation in patients with hypertension. *Journal of the American Medical Association* 296:1242–1248.

Ozechowski TJ, Turner CW, Hops H (2007). Mixed-effects logistic regression for estimating transitional probabilities in sequentially coded observational data. *Psychological Methods*12:317-335.

Pan CW, Cheung CY, Aung T, Cheung CM, Zheng YF, Wu RY, Mitchell P, Lavanya R, Baskaran M, Wang JJ, Wong TY, Saw SM (2013a).Differential associations of myopia with major age-related eye diseases: the Singapore Indian Eye Study. *Ophthalmology* 120:284-291.

Pan CW, Cheng CY, Saw SM, Wang JJ, Wong TY (2013b). Myopia and age-related cataract: a systematic review and meta-analysis. *American Journal of Ophthalmology* 156:1021-1033.

Pan CW, Ikram MK, Cheung CY, Choi HW, Cheung CM, Jonas JB, Saw SM, Wong TY (2013c). Refractive errors and age-related macular degeneration: a systematic review and meta-analysis. *Ophthalmology* 120:2058-2065.

Parr CL, Batty GD, Lam TH, Barzi F, Fang X, Ho SC, Jee SH, Ansary-Moghaddam A, Jamrozik K, Ueshima H, Woodward M, Huxley RR; Asia-Pacific Cohort Studies Collaboration (2010). Body-mass index and cancer mortality in the Asia-Pacific Cohort Studies Collaboration: pooled analyses of 424,519 participants. *The Lancet Oncology* 11:741-752.

Paunksnis A, Bojarskiene F, Cimbalas A, Cerniauskiene LR, Luksiene DI, Tamosiunas A (2007). Relation between cataract and metabolic syndrome and its components. *European Journal of Ophthalmology* 17:605-614.

Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS (2008). Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Statistics in Medicine* 27:157–172.

Pencina MJ, D'Agostino RB Sr, Steyerberg EW (2011). Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Statistics in Medicine* 30:11-21.

Peter C, Jack V, David A (2003). Comparing hierarchical modeling with traditional logistic regression analysis among patients hospitalized with acute myocardial infarction: should we be analyzing cardiovascular outcomes data differently? *American Heart Journal* 145:27-35.

Plackett RL (1974). The Analysis of Categorical Data. Charles Grifin: London.

Pollreisz A, Schmidt-Erfurth U (2010). Diabetic cataract-pathogenesis, epidemiology and treatment. *Journal of Ophthalmol*ogy 2010:608751.

Pouliot MC, Després JP, Lemieux S, Moorjani S, Bouchard C, Tremblay A, Nadeau A, Lupien PJ (1994). Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. *American Journal of Cardiology* 73:460-468.

Prospective Studies Collaboration, Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, Qizilbash N, Collins R, Peto R (2009). Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet* 373:1083-1096.

Putter H, Fiocco M, Geskus RB (2007). Tutorial in biostatistics: competing risks and multi-state models. *Statistics in Medicine* 26:2389 –2430.

Rabe-Hesketh S. and Skrondal A (2008). Multilevel and Longitudinal Modeling Using Stata, Second Edition. College Station, Tex. Stata Press.

Rexrode KM, Carey VJ, Hennekens CH, Walters EE, Colditz GA, Stampfer MJ, Willett WC, Manson JE (1998). Abdominal adiposity and coronary heart disease in women. *Journal of the American Medical Association* 280:1843–1848.

Roper NA, Bilous RW, Kelly WF, Unwin NC, Connolly VM; South Tees Diabetes Mortality Study (2002). Cause-specific mortality in a population with diabetes: South Tees Diabetes Mortality Study. *Diabetes Care* 25:43-48.

Rothman KJ, Greenland S, Lash TL (2008). Modern Epidemiology, 3rd Edition. Philadelphia, PA: Lippincott.

Ruige JB, Assendelft WJ, Dekker JM, Kostense PJ, Heine RJ, Bouter LM (1998). Insulin and risk of cardiovascular disease: a meta-analysis. *Circulation* 97:996-1001.

Ruotolo G, Howard BV (2002). Dyslipidemia of the metabolic syndrome. *Current Cardiology Reports* 4:494-500.

Saad MF, Lillioja S, Nyomba BL, Castillo C, Ferraro R, De Gregorio M, Ravussin E, Knowler WC, Bennett PH, Howard BV, Bogardus C (1991). Racial differences in the relation between blood pressure and insulin resistance. *New England Journal of Medicine.* 324:733-739.

Sabanayagam C, Wang JJ, Mitchell P, Tan AG, Tai ES, Aung T, Saw SM, Wong TY (2011). Metabolic syndrome components and age-related cataract: the Singapore Malay eye study. *Investigative Ophthalmology & Visiual Sciences* 52:2397-2404.

Saczynski JS, Beiser A, Seshadri S, Auerbach S, Wolf PA, Au R (2010). Depressive symptoms and risk of dementia: the Framingham Heart Study. *Neurology* 75:35-41.

Saito I, Iso H, Kokubo Y, Inoue M, Tsugane S (2009a). Metabolic Syndrome and All-Cause and Cardiovascular Disease Mortality Japan Public Health Center-Based Prospective (JPHC) Study. *Circulation Journal* 73:878-884.

Saito I, Konishi M, Iso H, Inoue M, Tsugane S (2009b). Impact of weight change on specific-cause mortality among middle-aged Japanese individuals. *Journal of Epidemiology Community Health* 63:447–454.

Salminen M, Kuoppamäki M, Vahlberg T, Räihä I, Irjala K, Kivelä SL (2010). The metabolic syndrome defined by modified International Diabetes Federation criteria and mortality: a 9-year follow-up of the aged in Finland. *Diabetes Metabolism* 36:437-442.

Saydah SH, Eberhardt MS, Loria CM, Brancati FL (2002). Age and the burden of death attributable to diabetes in the United States. *American Journal of Epidemiology* 156:714-719.

Schmid C, Griffith J (1998). Multivariable classification rules: calibration and discrimination. In: Armitage P, Colton T, editors. Encyclopedia of Biostatistics. Chichester, U.K.: Wiley.

Seddon JM, Gensler G, Milton RC, Klein ML, Rifai N (2004). Association between C-reactive protein and age-related macular degeneration. *The Journal of the American Medical Association* 291:704–710.

Shankar A, Mitchell P, Rochtchina E, Wang JJ (2007b). The association between circulating white blood cell count, TG level and cardiovascular and all-cause mortality: population-based cohort study. *Atherosclerosis* 192:177-183.

Sidorenkov O, Nilssen O, Grjibovski AM (2010). Metabolic syndrome in Russian adults: associated factors and mortality from cardiovascular diseases and all causes. *BMC Public Health* 10:582.

Sim J, Wright CC (2005). The Kappa statistic in reliability studies: use, interpretation, and sample size requirements. *Physical Theraphy* 85:257-268. Review.

Singer JD, Willett JB (2003). Applied Longitudinal Data Analysis: Modeling Change and Event Occurrence. Oxford University Press:407-463.

Shankar A, Mitchell P, Rochtchina E, Tan J, Wang JJ (2007a). Association between circulating white blood cell count and long-term incidence of age-related macular degeneration: the Blue Mountains Eye Study. *American Journal of Epidemiology* 165:375-382.

Smith W, Mitchell P, Attebo K, Leeder S (1997). Selection bias from sampling frames: telephone directory and electoral roll compared with door-to-door

population census: results from the Blue Mountains Eye Study. *Australian and New Zealand Journal of Public Health* 21:127-133.

Smith W, Mitchell P, Leeder SR, Wang JJ (1998). Plasma fibrinogen levels, other cardiovascular risk factors, and age-related maculopathy: the Blue Mountains Eye Study. *Archives Ophthalmology* 116:583-587.

Snijders TAB, Bosker RJ (2012). Multilevel Analysis: An Introduction to Basic and Advanced Multilevel Modeling. 2nd edition. SAGE Publication Ltd.

Sowers JR (2003). Obesity as a cardiovascular risk factor. *American Journal of Medicine* 115:Suppl 8A:37S-41S.

Steenbergen MR (2012). HIERARCHICAL LINEAR MODELS FOR ELECTORAL RESEARCH: A Worked Example in Stata. http://www.elecdem.eu/media/universityofexeter/elecdem/pdfs/istanbulwkspjan2012/Hierarchical_Linear_Models_for_Electoral_Research_A_worked_example_in_Stata.pdf

Stern MP, Williams K, González-Villalpando C, Hunt KJ, Haffner SM (2004). Does the metabolic syndrome improve identification of individuals at risk of type 2 diabetes and/or cardiovascular disease? *Diabetes Care* 27:2676-2681.

Stessman J, Jacobs JM, Ein-Mor E, Bursztyn M (2009). Normal body mass index rather than obesity predicts greater mortality in elderly people: the Jerusalem longitudinal study. *Journal of the American Geriatrics Society* 57:2232-2238.

Stitt AW (2001). Advanced glycation: an important pathological event in diabetic and age related ocular disease. *British Journal of Ophthalmology* 85:746–753.

Stone EM (2007). Macular degeneration. *Annual Review of Medicine* 58:477-490.

Sun J (1997). Regression analysis of interval-censored failure time data. *Statistics in Medicine*16:497-504.

Sun X, Li X, Chen C, Song Y (2013). A Review of Statistical Issues with Progression-Free Survival as an Interval-Censored Time-to-Event Endpoint. *Journal of Biopharmaceutical Statistics* 23:986-1003.

Tai BC, Machin D, White I, Gebski V; EOI (The European Osteosarcoma Intergroup) (2001). Competing risks analysis of patients with osteosarcoma: a comparison of four different approaches. *Statistics in Medicine* 20:661-684.

Tai BC, Grundy RG, Machin D (2010). On the importance of accounting for competing risks in pediatric cancer trials designed to delay or avoid radiotherapy: I. Basic concepts and first analyses. *International Journal of Radiation OncologyBiologyPhysics* 76:1493-1499.

Tai BC, Grundy R, Machin D (2011a). On the importance of accounting for competing risks in pediatric brain cancer: II. Regression modeling and sample size. *International Journal of Radiation OncologyBiologyPhysics* 79:1139-1146.

Tai BC, Wee J, Machin D (2011b). Analysis and design of randomised clinical trials involving competing risks outcomes. *Trials* 12:127.

Tai BC, Machin D (2014). Regression methods for medical research. UK: John Wiley and sons Ltd.

Tan HH, McAlpine RR, James P, Thompson P, McMurdo ME, Morris AD, Evans JM; DARTS/MEMO collaboration (2004). Diagnosis of type 2 diabetes at an older age: effect on mortality in men and women. *Diabetes Care* 27:2797-2799.

Tan JS, Mitchell P, Smith W, Wang JJ (2007). Cardiovascular risk factors and the long-term incidence of age-related macular degeneration. The Blue Mountains Eye Study. *Ophthalmology* 114:1143-1150.

Tan AG, Mitchell P, Burlutsky G, Rochtchina E, Kanthan G, Islam FM, Wang JJ (2008a). Retinal vessel caliber and the long-term incidence of age-related cataract: the Blue Mountains Eye Study. *Ophthalmology* 115:1693-1698,e1.

Tan AG, Mitchell P, Flood VM, Burlutsky G, Rochtchina E, Cumming RG, Wang JJ (2008b). Antioxidant nutrient intake and the long-term incidence of age-related cataract: the Blue Mountains Eye Study. *The American Journal of Clinical Nutrition* 87:1899-1905.

Tan JS, Wang JJ, Younan C, Cumming RG, Rochtchina E, Mitchell P (2008c). Smoking and the long-term incidence of cataract: the Blue Mountains Eye Study. *Ophthalmic Epidemiology* 15:155-161.

Tan JS, Wang JJ, Mitchell P (2008d). Influence of diabetes and cardiovascular disease on the long-term incidence of cataract: the Blue Mountains eye study. *Ophthalmic Epidemiol*ogy 15:317-327.

Tan JS, Wang JJ, Flood V, Mitchell P (2009). Dietary fatty acids and the 10-year incidence of age-related macular degeneration: the Blue Mountains Eye Study. *Archives of Ophthalmology* 127:656-665.

Tayback M, Kumanyika S, Chee E (1990). Body weight as a risk factor in the elderly. *Archives Internal Medicine* 150:1065–1072.

Teucher B, Rohrmann S, Kaaks R (2010). Obesity: Focus on all-cause mortality and cancer. *Maturitas* 65:112-116.

Therneau TM, Grambsch PM (2000). Modeling Survival Data: Extending the Cox Model. Springer: New York.

Thinggaard M, Jacobsen R, Jeune B, Martinussen T, Christensen K (2010). Is the relationship between BMI and mortality increasingly U-shaped with advancing age? A 10-year follow-up of persons aged 70-95 years. *The Journal of Gerontology. Series A: Biological Sciences & Medical Sciences* 65:526-531.

Thomas F, Pannier B, Benetos A, Vischer UM (2011). The impact of the metabolic syndrome--but not of hypertension--on all-cause mortality disappears in the elderly. *Journal of Hypertension* 29:663-8.

Tomany SC, Wang JJ, Van Leeuwen R, Klein R, Mitchell P, Vingerling JR, Klein BE, Smith W, De Jong PT (2004). Risk factors for incident age-related macular degeneration: pooled findings from 3 continents. *Ophthalmology* 111:1280-1287.

Tong X, Chen MH, Sun J (2008). Regression analysis of multivariate interval-censored failure time data with application to tumorigenicity experiments. *Biometrical Journal* 50:364-374.

Tsai AC, Hsiao ML (2012). The association of body mass index (BMI) with all-cause mortality in older Taiwanese: results of a national cohort study. *Archives of Gerontology & Geriatrics* 55:217-220.

Tsang CW, Lazarus R, Smith W, Mitchell P, Koutts J, Burnett L (1998). Hematological indices in an older population sample: derivation of healthy reference values. *Clinical Chemistry* 44:96-100.

Tsiatis A (1975). A nonidentifiability aspect of the problem of competing risks. *Proceedings of the National Academy of Sciences of the United States of America* 72:20 –22.

Underwood PM (2004). Cardiovascular risk, the metabolic syndrome and the hypertriglyceridaemic waist. *Current Opinion in Lipidology* 15:495-497.

Uno H, Tian L, Cai T, Kohane IS, Wei LJ (2009). Comparing Risk Scoring Systems Beyond the ROC Paradigm in Survival Analysis. *Harvard University*

Biostatistics Working Paper Series. Working Paper 107. http://biostats.bepress.com/harvardbiostat/paper107

Varma SD, Chand D, Sharma YR, Kuck JF Jr, Richards RD (1984). Oxidative stress on lens and cataract formation: role of light and oxygen. *Current Eye Research* 3:35–57.

Verbeke G, Molenberghs G (2000). Linear Mixed Models for Longitudinal Data. Springer, New York, NY.

Vine AK, Stader J, Branham K, Musch DC, Swaroop A (2005). Biomarkers of cardiovascular disease as risk factors for age-related macular degeneration. *Ophthalmology* 112:2076-2080.

von Eckardstein A, Hersberger M, Rohrer L (2005). Current understanding of the metabolism and biological actions of HDL. *Current Opinion in Clinical Nutrition & Metabolic Care* 8:147–152.

Wang JJ, Liew G, Wong TY, Smith W, Klein R, Leeder SR, Mitchell P (2006). Retinal vascular calibre and the risk of coronary heart disease-related death. *Heart* 92:1583-1587.

Wang JJ, Mitchell P, Simpson JM, Cumming RG, Smith W (2001). Visual impairment, age-related cataract, and mortality. *Archives of Ophthalmology* 119:1186-1190.

Wang J, Ruotsalainen S, Moilanen L, Lepistö P, Laakso M, Kuusisto J (2007a). The metabolic syndrome predicts cardiovascular mortality: a 13-year follow-up study in elderly non-diabetic Finns. *European Heart Journal* 28:857-864.

Wang JJ, Rochtchina E, Lee AJ, Chia EM, Smith W, Cumming RG, Mitchell P (2007b). Ten-year incidence and progression of age-related maculopathy: the blue Mountains Eye Study. *Ophthalmology* 114:92-98.

Wannamethee SG, Shaper AG, Walker M (2001). Weight change, body weight and mortality: the impact of smoking and ill health. *International Journal of Epidemiology* 30:777–786.

Wei L, Chen P, Lee JH, Nussenblatt RB. Genetic and Epigenetic Regulation in Age-related Macular degeneration (2013). *Asia-Pacific Journal of Ophthalmology (Phila)* 2:269-274.

Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB (1998). Prediction of coronary heart disease using risk factor categories. *Circulation* 97:1837-1847.

Wolbers M, Koller MT, Witteman JC, Steyerberg EW (2009). Prognostic models with competing risks: methods and application to coronary risk prediction. *Epidemiology* 20:555-561.

Woodward M, Zhang X, Barzi F, Pan W, Ueshima H, Rodgers A, MacMahon S; Asia Pacific Cohort Studies Collaboration (2003). The effects of diabetes on the

risks of major cardiovascular diseases and death in the Asia-Pacific region. *Diabetes Care* 26:360-366.

World Health Organization (1995). Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. *World Health Organization Technical Report Series* 854:1–452.

World Health Organization (1999). Definition, Diagnosis and Classification of Diabetes Mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Geneva: WHO.

World Health Organization (WHO) (2003). International society of hypertension (ISH) statement on management of hypertension. *Journal of Hypertension* 21:1983-1992.

Wilken T (2005). The metabolic syndrome, babies and bathwater. *Diabetologia* 49:421-422.

Yates J (1982). External correspondence: decomposition of the mean probability score. *Organizational Behavior & Human Performance* 30:132–156.

Yudkin JS (2003). Adipose tissue, insulin action and vascular disease: inflammatory signals. *International Journal of Obesity* 27:Suppl 3,525-528.

Younan C, Mitchell P, Cumming R, Rochtchina E, Panchapakesan J, Tumuluri K (2003). Cardiovascular disease, vascular risk factors and the incidence of cataract

and cataract surgery: the Blue Mountains Eye Study. *Ophthalmic Epidemiology* 10:227-240.

Zambon S, Zanoni S, Romanato G, Corti MC, Noale M, Sartori L, Musacchio E, Baggio G, Crepaldi G, Manzato E (2009). Metabolic syndrome and all-cause and cardiovascular mortality in an Italian elderly population. The Progetto Veneto Anziani Study. *Diabetes Care* 32:153-159.

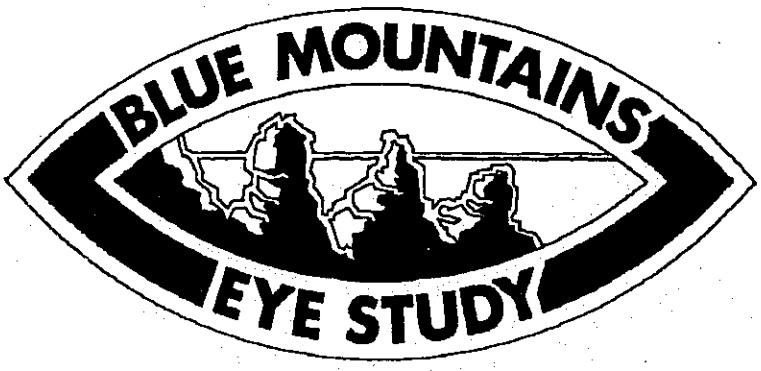
Zimmet P, Magliano D, Matsuzawa Y, Alberti G, Shaw J (2005). The metabolic syndrome: a global public health problem and a new definition. *Journal of Atherosclerosis and Thrombosis* 12:295-300.

Zuma K, Lurie M, Jorgensen M (2007). Analysis of interval-censored data from circular migrant and non-migrant sexual partnerships using the EM algorithm. *Statistics in Medicine* 26:309-319.

Blue Mountains Eye Study

Blue Mountains District Anzac Memorial Hospital
Great Western Highway, Katoomba, 2780
Telephone: (047) 820440

Eye Clinic, Westmead Hospital
Hawkesbury Rd, Westmead 2145
Telephone: (02) 633 7699, 633 7960



Questionnaire and study flow sheet

Chief Investigator — Assoc Prof Paul Mitchell

Principal Co-Investigator — Dr Karin Attebo

Other Co-Investigators — Dr Wayne Smith
Dr Robert Cumming
Mr Robert Sparkes
Professor Frank Billson

BLUE MOUNTAINS EYE STUDY QUESTIONNAIRE AND STUDY FLOW SHEET

Page 1 *(detach from rest of questionnaire after completion)*

X1. *(IDnum)* _____ ID number X2. *(IDHosp)*_____ hosp number

---

X3. *(surname)* Surname _____

X4. *(name)* First Name(s) _____

X5. *(DOB)* What is your date of birth? ___/___/___ *(calculate age)*

X6. *(age)* So you are _____ years old now ?
if <49 years stop and explain inability to include.

X7. *(address)* Your address?_____

Postcode _____

X8. *(usuadrs)* Is this your usual address? yes 1
no 2
(more than 6 months of the year)

X9. *(phno)* Your phone number? _____

X10. *(WMHpt)* Have you ever been seen at Westmead Hospital as an outpatient or admitted there? yes 1
no 2

X11.*(WMHno)* _____ *(Hospital Number)*

X12. *(rels)* Do you have any relatives living in Katoomba, Leura or Medlow Bath who are aged 49 or older? yes 1
no 2

1. Name _____

Address _____

2. Name _____

Address _____

BLUE MOUNTAINS EYE STUDY QUESTIONNAIRE AND STUDY FLOW SHEET

PHASE 1: *for completion by Examiner 1.*

A1. *(IDnum)* _____ ID number A2. *(IDHosp)*_____hosp number

A3. *(DOB)* Date of birth ___/___/___

A4. *(examday)* Exam date ___/___/9__

A5. *(examloc)*
Blue Mts Hospital 1
Nursing Home ..... 2 specify_____ code_____
Other site ..... 3 specify_____ code_____

A6. *(sex)* Sex: Female 1
Male 2

A7. *(hrstart)* Time began _____ hrs A8. *(temp)* Temperature _____ °C

Thank you for taking part in our eye study. As a part of this study we will be asking you some general questions about you, your health and your eyes. All information you provide will be strictly confidential.

A9. *(yrsBM)* How long have you lived in the Blue Mountains? _____ yrs
don't know 888

A10. *(transprt)* How did you get to the eye study today?
walked .....1 friend/rel drove 5
bus .....2 hospital bus 6
taxi .....3 voluntary driver ... 7
drove yourself ..... 4 other_____ code_____

A11. *(GP)* Who is your GP?_____

A12. *(adrGP)* In which suburb is his/her surgery? _____

A13. *(whoeye1)* Who was the last person you saw for your eyes, for glasses or any eye treatment? _____

A14. *(wheneye)* When was that? _____

A15. *(optoph)* Was it an optometrist ?... 1
or an eyedoctor ?.....2
don't know 8

A16. *(adreye)* In which suburb are his/her rooms? _____

A17. *(longeye)* How long before that had you seen someone for your eyes? _____

A18. *(whoeye2)* Who did you see? _____

If not an ophthalmologist in A18or A13, then ask:

A19. *(seenoph)* Have you ever seen an eye doctor?
yes 1
no ..... 2 *goto A22.*
don't know..8 *goto A22.*

A20. *(whooph)* Who did you see?_____

A21. *(whenoph)* When did you see him/her? _____

A22. *(birthpl)* Where were you born? _____ | code _____
(write state or territory if in Australia, country if born overseas)

A23. *(ageAust)* *If not born in Australia,* how old were you when you came to Australia? _____ yrs

---

A24. *(mumborn)* Where was your mother born? _____ | code _____
(write state or territory if in Australia, country if born overseas)

A25. *(dadborn)* Where was your father born? _____ | code _____
(write state or territory if in Australia, country if born overseas)

A26. *(race)* *Racial group:* *examiner to fill in, ask only if unsure*

White .....1 *Aboriginal* ..... 2 *Indian* 7
Negroid ..... 3 *Hispanic* 4
Oceanian .....5 *Asian* 6

A27. *(speak)* At home, do you usually speak a language other than English?

yes..... 1
no..... 2 *goto A 29.*
don't know ..... 8 *goto A 29.*

A28. *(spoken)* What language do you speak? _____ | code _____

A29. *(qualif)* After leaving school, did you get any other qualification or learn a trade?

yes 1
no ..... 2 *goto A31.*
don't know ..... 8 *goto A31.*

A30. *(qualnm)* Qualification name _____ | code _____

A31. *(jobstat)* Are you retired or still employed?

houseduties..... 1 medical disability 4
retired ..... 2 unemployed 5
employed ..... 3 other 6

A32. *(retired)* *If retired,* how old were you when you retired? _____ yrs
don't know 88

A33. *(presjob)* *If employed,* what is your present occupation?
_____ | code _____

A34. *(mainjob)* In your working life what has been your main job?
_____ | code _____

A35. *(othjobs)* Could you list other jobs you have had? (≥5 yrs) what age?

_____ | code _____ _____
_____ | code _____ _____
_____ | code _____ _____
_____ | code _____ _____
_____ | code _____ _____

A36. *(marital)* What is your marital status? *(choose most appropriate option)*

never married .....1 divorced 4
now married .....2 widowed 5
separated but not divorced 3

A37. *(spoujob) If now married or widowed:*
What kind of work does/did your spouse do for most of his/her life?

_____ | code ____

A39. *(pension)* Do you receive a pension?

yes 1
no ..... 2 *goto A 39.*
don't know..... 8 *goto A 39.*

A39. *(sort)* What sort of a pension is it?

age pension ..... 1 blind pension 4
invalid pension .... 2 other 5
veteran's 3

A40. *(other$)* Are you receiving any other income or superannuation?

yes 1
no 2
refused 3

A41. *($detail)*

source 1_____ | code ____
source 2_____ | code ____

A42. *(abode)* What sort of a place do you live in?

own house ..... 1 boarding house 6
own flat/ILU..... 2 nursing home 7
rent house ..... 3 with relatives 8
rent flat ..... 4 caravan 9
hostel ..... 5 other _____ | code ____

A43. *(wholive1)* .....and who lives with you? friend 3

nobody ..... 1 daughter 4
spouse ..... 2 son 5

A44. *(wholive2)* other _____ | code ____

A45. Do you get regular help at home from the following?

(MOW) Meals on Wheels yes .....1 no ... 2
(nurse) community nurse yes .....1 no ... 2
(hmhelp) home help yes .....1 no ... 2

A46. *(othhelp)* other _____ | code ____

A47. *(cleanhs)* Who usually cleans your house?

you ..... 1 other relative 5
spouse ..... 2 friend 6
daughter ..... 3 home help 7
son ..... 4 other_____ | code ____

A48. *(whoshop)* Who usually does your shopping?

you ..... 1 other relative 5
spouse ..... 2 friend 6
daughter 3
son ..... 4 other_____ | code ____

	Are you able to go out alone?			How often do you go?
A49. ...to do the shopping *(goshop)*	yes ... 1	no 2	A50 *(noshop)*	_____
A51. ...to visit someone *(govisit)*	yes ... 1	no 2	A52 *(novisit)*	_____
A53. ...to go to 'town' *(gotown)*	yes ... 1	no 2	A54 *(notown)*	_____

Medications

Now I would like to ask you some questions about the tablets or vitamins you've taken in the last week. May I see the medications you are taking now?

Examine contents of plastic bag. List medications,write chemist's name from bottles

B1. *(Chemist)* Chemist's Name _____

	Name of drug	code	approx period
none ☐			
B2.*(drug1)*	1 _____	|	| _____
B3.*(drug2)*	2 _____	|	| _____
B4.*(drug3)*	3 _____	|	| _____
B5.*(drug4)*	4 _____	|	| _____
B6.*(drug5)*	5 _____	|	| _____
B7.*(drug6)*	6 _____	|	| _____
B8.*(drug7)*	7 _____	|	| _____
B9.*(drug8)*	8 _____	|	| _____
B10.*(drug9)*	9 _____	|	| _____
B11.*(drug10)*	10 _____	|	| _____
B12.*(drug11)*	11 _____	|	| _____

ASK "are there any other tablets, sprays or medications you take that you have not mentioned here?"

"Can you recall any other tablets you have taken for more than 3 months in the past?"

	Name of drug	code	approx period taken
none ☐			
B13.*(tab1)*	1 _____	|	| _____
B14.*(tab2)*	2 _____	|	| _____
B15.*(tab3)*	3 _____	|	| _____
B16.*(tab4)*	4 _____	|	| _____
B17-19*tab5-7)*	5 _____	|	| _____

B20. *(aspirin)* Over the past year, about how often have you taken an **aspirin** tablet? (Solprin, Disprin, Ecotrin or Cardiprin, but not Panadol, Dymadon or Digesic)

Was it: less than once a month ..... 1 *goto B22*
more than once a month but less than once a week ..... 2 *goto B22*
once a week or more 3

B21. *(aspnum)* How many aspirin tablets do you usually take each week? _____

B22. *(aspyrs)* For how many years have you been taking this number? _____ yrs

---

B23. *(asppast)* Is that: more than 1
the same ..... 2 or
less than..... 3
the number of aspirins you were taking 10 years ago ? don't know 8

B24. *(steroid)* Have you ever taken **steroid** tablets such as Prednisone, Cortisone, or Decadron for asthma, arthritis or another condition, for longer than one month altogether? (ring steroid taken)
yes 1
no 2
don't know 8

B25. *(steryrs)* *If yes*, about how long altogether were you taking these tablets?
_____weeks _____ months _____ years

B26. *(sterdos)* What dose were you taking? _____

B27. *(stertot)* (Try to estimate total dose_____)
(say 15mg/ day for 3 mos then 5 mg/ day for 3 months)

B28. *(sterdx)* What condition did you take them for?_____
(eg asthma, arthritis) I code _____

B29. *(Becot)* Have you ever used a **Becotide** puffer, a brown coloured puffer used in asthma and other chest problems?
yes 1
no 2
don't know 8

B30. *(Becdos)* *If yes*, how often do/did you need to take it? _____
(puffs/day or week or month etc)

B31. *(sedat)* Have you ever taken tablets for "nerves" or to help you sleep like tranquilizers, antidepressants, or antianxiety drugs ?
yes ..... 1 *add name here*
no ..... 2 _____ I code _____
don't know ..... 8 _____ I code _____

B32. *(calc)* Do you take or have you ever taken calcium tablets like Sandocal, Cal-Sup or Caltrate regularly? *(at least once a week for more than a month)?*
yes..... 1 *add name here*
no ..... 2 _____ I code _____
don't know 8

Female Medical History *females only, if male, goto page 7*

Now I would like to ask you a few questions about your menstrual history

W1. *(menarch)* How old were you when you started having periods? ___ yrs DK 88

W2. *(ifmenop)* Have you stopped having periods?
yes .....1 no ... 2 *goto W7*
don't know ..... 8 *goto W5*

W3. *(menopau)* How old were you when you stopped? _____ years DK.....88

W4. *(menowhy)* Did you stop naturally or because of a hysterectomy?
naturally ..... 1 hysterectomy ..... 2 *goto W6*
other ..... 3 don't know 8

W5. *(hystrec)* Have you had a hysterectomy, that is, an operation to remove the uterus?
yes ..... 1; what age?_____ yrs
no ..... 2 don't know..8 *goto W7*

W6. *(ovarect)* Were both ovaries removed? yes..... 1; same age?____yrs
no ..... 2 don't know..88

W7. *(hormTx)* Have you ever been on hormone replacement therapy, such as oestrogens and/or progesterones for menopausal symptoms or after the menopause?
yes..... 1 don't know ..... 8 *add name here*
no ..... 2 _____|code_____

W8. *(OCP)* Have you ever taken oral contraceptive pills for birth control or other medical reasons?
yes..... 1 don't know ..... 8 *add name here*
no ..... 2 _____|code_____

W9. *(pregnan)* Have you ever been pregnant?
yes ..... 1 E48*(pregnum)* _____ times
no ..... 2 *goto W11.*
don't know..... 8 *goto W11..*

W10.*(parity)* Of these pregnancies, how many children have you had? ____children

---

W11. *(Papkno)* Have you ever heard of a **Pap Smear Test?**
yes 1
no ..... 2 don't know.....8 *goto W14.*

A Pap Smear Test, sometimes called a Pap Test, is a routine test carried out by a doctor. It is recommended for all women to detect cancer of the cervix.

W12. *(Paphad)* Have you ever had a Pap Smear Test?
yes 1
no ..... 2 don't know.....8 *goto W14.*

W13. *(PapWhen)* When did you have your last Pap Smear Test?
less than one year ago ..... 1 5 or more years ago 4
1 year to less than 3 years ago .... 2 don't know 8
3 years to less than 5 years ago ... 3

W14. *(MamKno)* Have you ever heard of a **mammogram?**
yes 1
no ..... 2 don't know.....8 *goto C1.*

A mammogram is an x-ray taken of the breasts by a machine that presses against the breast while the picture is taken.

W15. *(Mamhad)* Have you ever had a mammogram?
yes 1
no ..... 2 don't know.....8 *goto C1.*

W16. *(Mamwhen)* When did you have your last mammogram?
less than one year ago ..... 1 5 or more years ago 4
1 year to less than 3 years ago .... 2 don't know 8
3 years to less than 5 years ago ... 3

For Interviewer	DID PARTICIPANT:	yes	no	DK
D1.*(hearimp)*	Have a hearing impairment?	☐	☐	☐
D2.*(walkdif)*	Have walking difficulties?	☐	☐	☐
D3.*(cane)*	Use a cane/crutches/walker?	☐	☐	☐
D4.*(wheelch)*	Use a wheelchair?	☐	☐	☐
D5.*(cough)*	Have shortness of breath,cough continually?	☐	☐	☐
D6. *(lanprob)*	Have a language problem?	☐	☐	☐
D7.*(speechp)*	Have a speech but not a language problem?	☐	☐	☐
D8.*(dement)*	Appear demented?	☐	☐	☐

Who mainly answered the questionnaire?

D9.*(answer)*

Participant 1
Spouse 2
Son, Daughter..... 3
Sibling 4
Other relative..... 5
Friend 6
Other (specify)_____ |code___

Attach any lists of medications or medical history

Glasses Can I now please check your glasses?

C1.*(typegls)* Current glasses:

unifocal	1
bifocal	2
multifocal	3
separate pairs	4
no glasses	5
glasses not brought	6

Lens Analyzer 1) current glasses: *2) separate readers, ifworn:*

C2.*(RglDS)*
C3.*(RglDC)*

C4.*(Rglax)*

C5.*(LglDS)*
C6.*(LglDC)*
C7.*(Lglax)*

C8.*(RglDS2)*
C9.*(RglDC2)*

C10.*(Rglax2)*

C11.*(LglDS2)*
C12.*(LglDC2)*
C13.*(Lglax2)*

Humphrey autorefractor: attach printout here:

C14.*(RARac1)* C15.*(RARODS)*
C16.*(RARODC)* C17.*(RAROax)*
C18.*(RARac2)* C19.*(RARSDS)*
C20.*(RARSDC)* C21.*(RARSax)*
C22.*(LARac1)* C23. *(LARODS)*
C24.*(LARODC)* C25.*(LAROax)*
C26. *(LARac2)* C27.*(LARSDS)*
C28. *(LARSDC)* C29.*(LARSax)*

PHASE 2: *for completion by Examiner 2.*

Visual Symptoms I am going to ask you some questions about your eyes and then test your vision.

E1.*(distgls)* Do you wear glasses to see clearly in the distance, or have you in the past, (that includes bifocals or multifocals)?
yes 1
no 2
don't know.. 8

E2.*(agegls)* How old were you when you first needed to wear glasses to see clearly in the distance?
_____ years old
don't know 88

E3.*(readgls)* Do you wear reading glasses or bifocals?
yes 1
no ..... 2 *goto E5.*
don't know.. 8

E4.*(presby)* How old were you when you first needed reading glasses, bifocals or multifocals?
_____ years old
don't know 88

E5.*(timegls)* How long have you had your current glasses? _____ years
don't know 88

Reading Vision
I am now going to test how well you can read with each eye using your current reading glasses.

E6,7,8.*(rdtype)* Smallest Logmar type read **R** _____ **L** _____ **both eyes** _____

---

		able	not able
E9.*(rdnewsp)*	Can you read this newspaper paragraph?	1	2
E10.*(rdbill)*	Can you read the amount owing on this electricity bill:	1	2
E11.*(rdprice)*	Can you read the price on this can?	1	2
E12. *rdpills)*	Can you read the directions on this bottle of pills ?	1	2

E13. *(qcat)* Have you ever heard of cataracts? Yes.... 1 No... 2
E14. *(dcat)* What do you think a cataract is?

E15. *(acat)* Answer: _____
_____ code _____

E16. *(qAMD)* Have you ever heard of macular degeneration? Yes.... 1 No.... 2
E17. *(dAMD)* What do you think macular degeneration is?

E18. *(aAMD)* Answer: _____
_____ code _____

E19. *(qglauc)* Have you ever heard of glaucoma? Yes.... 1 No... 2
E20. *(dglauc)* What do you think glaucoma is?

E21. *(aglauc)* Answer: _____
_____ code _____

I am now going to test your vision with your glassses, if you wear them.

Vision Examination: Logmar visual acuity score or E - equivalent

measure at 2.4 metres (8 ft) with best distance correction; if unable to see any letters, then try at one metre

What distance was chart read? R 2.4m ☐ 1m ☐ E22. *(Rrddist)* L 2.4m ☐ 1m ☐ E23. *(Lrddist)*

CURRENT DISTANCE GLASSES yes ..... 1 no 2

at 2.4 m	Right eye					no. correct	Left eye					no. correct	
6/60	H	V	Z	D	S	____	H	V	Z	D	S	____	5
6/48	N	C	V	K	D	____	N	C	V	K	D	____	10
6/38	C	Z	S	H	N	____	C	Z	S	H	N	____	15
6/30	O	N	V	S	R	____	O	N	V	S	R	____	20
6/24	K	D	N	R	O	____	K	D	N	R	O	____	25
6/19	Z	K	C	S	V	____	Z	K	C	S	V	____	30
6/15	D	V	O	H	C	____	D	V	O	H	C	____	35
6/12	O	H	V	C	K	____	O	H	V	C	K	____	40
6/9.5	H	Z	C	K	O	____	H	Z	C	K	O	____	45
6/7.5	N	C	K	H	D	____	N	C	K	H	D	____	50
6/6	Z	H	C	S	R	____	Z	H	C	S	R	____	55
6/4.8	S	Z	R	D	N	____	S	Z	R	D	N	____	60
6/3.8	H	C	D	R	O	____	H	C	D	R	O	____	65
6/3.0	R	D	O	S	N	____	R	D	O	S	N	____	70

E24.*(RmarVA)* Logmar VA R ____ E25.*(LmarVA)* Logmar VA L ____

E26. *(RPH)* Pinhole R ____ E27. *(LPH)* Pinhole L ____

If **vision < 6/60** E28.*(RpoorVA)* R _____ E29. *(LpoorVA)* L _____

Right CF.....1 HM....2 PL.....3 NPL...4 *Left* CF..... 1 HM....2 PL.....3 NPL...4

Logmar VA modified Sheridan-Gardiner

E30.*(RSheGar)* R _____ E31.*(LSheGar)* L _____

E32. *(amblyop)* *If one eye weaker (2 line difference) ask:*

Has your Right/Left eye always been weaker?

Right eye -yes 1
Left eye -yes 2
no 3
don't know 8

E33. *(visdis)* *If visual disability, eg field defect or severe visual loss (< 6/60) in both eyes, ask:*

Have you sought help from ;

Low vision clinic 1
Royal Blind Society..... 2
Guide Dogs 3
Other _____ code _____

E34.*(demenVA)* *Did mental disability or dementia prevent measurement of VA?*

yes 1
no 2
don't know 8

at **VISUAL ACUITY WITH BEST SUBJECTIVE REFRACTION**

2.4 m	Right eye					no. correct	Left eye					no. correct	
6/60	H	V	Z	D	S	____	H	V	Z	D	S	____	5
6/48	N	C	V	K	D	____	N	C	V	K	D	____	10
6/38	C	Z	S	H	N	____	C	Z	S	H	N	____	15
6/30	O	N	V	S	R	____	O	N	V	S	R	____	20
6/24	K	D	N	R	O	____	K	D	N	R	O	____	25
6/19	Z	K	C	S	V	____	Z	K	C	S	V	____	30
6/15	D	V	O	H	C	____	D	V	O	H	C	____	35
6/12	O	H	V	C	K	____	O	H	V	C	K	____	40
6/9.5	H	Z	C	K	O	____	H	Z	C	K	O	____	45
6/7.5	N	C	K	H	D	____	N	C	K	H	D	____	50
6/6	Z	H	C	S	R	____	Z	H	C	S	R	____	55
6/4.8	S	Z	R	D	N	____	S	Z	R	D	N	____	60
6/3.8	H	C	D	R	O	____	H	C	D	R	O	____	65
6/3.0	R	D	O	S	N	____	R	D	O	S	N	____	70

E35. *{RsubjVA}* Logmar VA **Right** ____ E36.*{LsubjVA}* Logmar VA **Left** ____

Best subjective refraction RIGHT **LEFT**

E37. *{RSrefDS}* sph _____ E41. *{LSrefDS}* sph _____

E38. *{RSrefDC}* cyl _____ E42. *{LSrefDC}* cyl _____

E39. *{RSrefax}* axis _____ E43. *{LSrefax}* axis _____

E40. *{RSadd}* reading add_____ E44.*{LSadd}* reading add: _____

E45,6,7.*{newtype}* Logmar reading chart **R** _____ **L** _____both eyes _____

Contrast Sensitivity Testing (Vectorvision CSV-1000 chart) / Glare Testing (BAT)

subject wearing best distance correction

right eye

T1.*{RCSrowA}*	Row A (3cpd)	1 t	2 b	3 t	4 t	5 b	6 b	7 b	8 t
T2.*{RCSrowB}*	Row B (6cpd)	1 b	2 b	3 t	4 b	5 t	6 t	7 b	8 b
T3.*{RCSrowC}*	Row C (12cpd)	1 b	2 t	3 b	4 t	5 b	6 b	7 t	8 t
T4.*{RCSrowD}*	Row D (18cpd)	1 t	2 t	3 b	4 t	5 b	6 t	7 b	8 t

left eye

T5.*{LCSrowA}*	Row A (3cpd)	1 t	2 b	3 t	4 t	5 b	6 b	7 b	8 t
T6.*{LCSrowB}*	Row B (6cpd)	1 b	2 b	3 t	4 b	5 t	6 t	7 b	8 b
T7.*{LCSrowC}*	Row C (12cpd)	1 b	2 t	3 b	4 t	5 b	6 b	7 t	8 t
T8.*{LCSrowD}*	Row D (18cpd)	1 t	2 t	3 b	4 t	5 b	6 t	7 b	8 t

right eye with BAT (setting No. 2)

T10.*{RBatB}*	Row B (6cpd)	1 b	2 b	3 t	4 b	5 t	6 t	7 b	8 b
T11.*{RBatC}*	Row C (12cpd)	1 b	2 t	3 b	4 t	5 b	6 b	7 t	8 t

left eye with BAT (setting No. 2)

T14.*{LBatB}*	Row B (6cpd)	1 b	2 b	3 t	4 b	5 t	6 t	7 b	8 b
T15.*{LBatC}*	Row C (12cpd)	1 b	2 t	3 b	4 t	5 b	6 b	7 t	8 t

PHASE 3: *for completion by Examiner 3.*

F1. *(height)* **Height** _____ metres
reliable .....1 not done 2
unreliable.... 3 other _____(eg amputee)

F2. *(weight)* **Weight** _____ kilograms
reliable .....1 not done 2
unreliable.... 3 other _____(eg amputee)

F3. *(wtmost)* What is the most you have ever weighed ? (not counting pregnancy)
_____ stones _____ kgs don't know..... 888

Strabismus

G1.*(strab)* Have you ever been told you had a turned or lazy eye, or had treatment for any eye muscle problems?
yes.....1
no .....2 don't know.....8

G2.*(strabage)* *If yes,* how old were you when this was first noticed?_____yrs

G3.*(patch)* Did you wear a patch on one eye?
yes.....1
no .....2 don't know.....8 *goto F39.*

G4.*(agepcth)* *If yes,* From what age_____yrs G5.*(lngptch)* For how long_____

G6. *(coverT)* Perform Cover Test 6m_____

G7. *(otherT)* Other _____

Exercise

H1.*(walkex)* In the past 2 weeks, did you walk for recreation or exercise?
yes.....1 H2.*(walkhrs)* How many times? _____
no .....2 don't know.....8

H3.*(vigact)* In the past 2 weeks, did you engage in vigorous activity or exercise, which made you breathe harder or puff and pant? (eg, carrying loads, heavy gardening, chopping wood, labouring - at home, during work or anywhere else)
yes.....1
no .....2 don't know.....8

H4.*(actimes)* How many sessions of vigorous activity did you have over the 2 week period?_____

H5.*(acthrs)* How much time was spent in vigorous activity over the past 2 wks?
_____ hrs _____ mins

Cigarette smoking

H6. *(smoking)* Have you ever smoked cigarettes, cigars or a pipe regularly?
yes..... 1
no ..... 2 *goto H12.*
don't know..... 8 *goto H12.*

H7. *(smokyrs)* At what age did you start smoking regularly? _____ yrs

H8. *(smokcurr)* Have you given up smoking?
yes 1
no ..... 2 *goto G6.*

H9. *(smokcurr)* When did you last give up smoking? _____ years ago

H10. *(pastcig)* How much did you usually smoke just before you stopped?

_____ manufactured cigs/day
_____ grams "hand-rolled"
_____ cigars/week
_____ grams pipe tobacco/wk

H11. *(smoknow)* *If currently smoking:* How much do you usually smoke?

_____ manufactured cigs/day
_____ grams "hand-rolled"
_____ cigars/week
_____ grams pipe tobacco/wk

H12. *(cigspou)* Does or did your husband/ wife smoke cigarettes?

yes.....1
no .....2 don't know.....8

Caffeine intake Do you drink tea?

H13. *(tea)*
yes .....1 H14.*(Tcups)* Cups per day_____
no 2
don't know 8

H15. *(Ttype)* How do you usually make your tea?
Teabags 1
Tealeaves..... 2
Both..... 3

H16. *(coffee)* Do you drink coffee?
yes .....1 H17.*(Cofups)* Cups per day_____
no ..... 2 (exclude decaffeinated)
don't know 8

H18.*(coftype)* How do you usually make your coffee?
Instant 1
Percolated 2
Both..... 3

H19,20. *(pastcaf)* About how many cups of coffee or tea did you drink per day 10 years ago?

coffee	tea
number of cups _____	number of cups _____

Alcohol I am now going to ask you some questions to see whether alcohol is related to eye problems or whether it has any benefits for the eyes.

H21. *(alcohol)* How many days a week would you usually have an alcoholic drink now?
never.....1 *goto H24.*
<once a week 2
1-2 days a week.....3
3-4 days a week.....4
5-6 days a week.....5
every day.....6

H22. *(alctype)* What do you mostly drink?
light beer 1
beer 2
wine 3
spirit 4
other _____ code_____

H23. *(alcnum)* On the days when you have a drink, how many drinks do you usually have ?
13 or more drinks 1
9-12 drinks 2
5-8 drinks 3
3-4 drinks 4
1-2 drinks 5

H24. *(alcmore)* Has there been a period in your life when you drank quite a bit more than you do now?
yes 1
no 2
don't know..8

H25. *(alcstop)* *If yes,* how many years ago was that? _____ yrs

---

Driving and Vision: Have you ever driven a car regularly?

V1. *(drive)*
yes, still driving ... 1 *goto V3.*
yes, stopped 2
never driven..... 3 *goto V9.*

V2. *(carlast)* *If no,* when did you last drive? _____

V3. *(carvis)* Did you stop because of problems with your vision?
yes 1
no..... 2
don't know..... 8

V4. *(acciden)* Have you had any car accidents in the last year?
yes ..... 1 V4A. *(accidVA)*
no..... 2 visual contribution yes..... 1
don't know..... 8 no..... 2

V5. *(accidet)* *If yes,* number of accidents _____ don't know..8

V6. *(carabil)* Do you think your driving abilility is as good now as it used to be?
yes 1
no..... 2 don't know..... 8

V7. *(abildet)* *If no,* do you think this might be related to your vision?
yes 1
no..... 2 why _____
don't know..... 8

V8. *(carnite)* Any problems driving at night?
yes 1
no..... 2 don't know..... 8

V9. *(seenite)* Do you think you have more difficulty seeing in the dark than others of your age?
yes 1
no..... 2 don't know..... 8

V10. *(glare)* Do you think you are more sensitive than others of your age to sunlight or glare?
yes 1
no..... 2 *goto V12.*
don't know..... 8 *goto V12.*

V11. *(glareyr)* For how long has this been a problem? _____

Are you able to:

V12. *(seefar)* recognise a friend across the street? yes 1
no.....2
don't know..8

V13. *(seenear)* recognise a friend close to you? yes 1
no.....2
don't know..8

V14. *(seeTV)* recognise detail on TV? yes 1
no.....2
don't know..8

V15. *(rdnewsp)* Can you read the ordinary print in the newspaper reasonably well, that is comfortably, with or without reading glasses?
yes ..... 1 *(if yes go to V18)*
no..... 2
don't know..... 8

V16. *(lastrd)* *If no,* when were you last able to do this? _____

V17. *(magnif)* Do you need to use a magnifier to read (eg. paper)?
yes 1
no..... 2
don't know..... 8

V18.*(Vworse)* Are you aware of a deterioration of vision in one or both eyes?
yes, R eye 1
yes, L eye 2
yes, both eyes 3
no 4
don't know 8

V19.*(Rworyes)* When did your **right eye** worsen?

_____ yrs ___ mths ____wks

V20.*(Lworyes)* When did your **left eye** worsen?

___ yrs ___ mths ____wks

Did you notice any:-		how long?		how long?
V21.*(Rdistor)* distortion of straight lines?	___	_____	V26.*(Ldistor)* ___	_____
V22.*(Rpatch)* a dark patch?	___	_____	V27.*(Lpatch)* ___	_____
V23.*(Rblur)* or just blurring of vision?	___	_____	V28.*(Lblur)* ___	_____
V24.*(Rchange)* any other changes?	___	_____	V29.*(Lchange)* ___	_____

V25. *(Rdetail)* R details_____

V30. *(Ldetail)* L details_____

Hearing Have you ever had a problem with your **hearing**?

H26. *(hearing)* yes 1
no..... 2 *goto H29.*
don't know..... 8 *goto H29.*

H27.*(hearsev)* Is it? mild..... 1
moderate..... 2
severe..... 3

H28. *(hearear)* Which ear? left..... 1
right..... 2
both ears.... 3

H28A. *(hearaid)* Do you wear a hearing aid? yes 1
no ... 2
sometimes ... 3

H29. *(hearcon)* Do you have trouble in hearing normal conversation with several other people? yes 1
no 2
don't know..... 8

H30. *(heartin)* Do you have any annoying noises (ringing, buzzing, hissing) in your ears?
yes 1
no 2
don't know..... 8

Blood pressure

I am now going to check your blood pressure. *(put cuff on right arm)*

F4. *(cuff)* **Cuff size:** small .....1 adult .....2 large 3

Blood pressure (Right arm)

F5.*(systBP)* SystolicBP _____ mmHg F6.*(diastBP)* Diastolic BP _____ mmHg

---

Humphrey Visual field testing

		Right F7. *(RHumph)*	Left F8. *(LHumph)*
76-point threshold-related suprathreshold program		**H**	**H**
or	Goldmann kinetic/ static perimetry	**G**	**G**
or	Bjerrum 1 metre tangent screen	**B**	**B**

Proceed to 30-2 program if specified field defects either eye, on second day.

F9. *(Rlens)* correction used R _____ F10. *(Llens)* L _____

F11. *(Rfield)* test done yes .....1 no .....2 F12. *(Lfield)* test done yes .....1 no 2

If no,
F13. *(RVFwhy)* reason _____ *If no,* F14. *(LVFwhy)* reason _____

Slit lamp examination

Iris Colour

F15. *(Riris)* **Right eye**	F16. *(Liris)* **Left eye**
< std #1 (blue) 1	<std #1 (blue) 1
< std #2 (hazel/green)..... 2	< std #2 (hazel/green) 2
< std #3 (tan/brown)..... 3	< std #3 (tan/brown) 3
> std #3 (dark brown) 4	> std #3 (dark brown)..... 4
cannot judge/ not done 5	cannot judge/ not done 5

F17. *(occlude)* **Is angle occludable?** yes ..... 1 questionable 3
no ..... 2 can't judge 4

Intraocular pressure

F18. *(RIOP)*	R _____ mmHg	F20. *(LIOP)*	L _____ mmHg
F19. *(RIOPrel)*	unreliable 1	F21. *(LIOPrel)*	unreliable 1
	unobtainable 2		unobtainable 2

Instill dilating drops: Tropicamide 1% and Phenylephrine 10%, twice.

(End of Phase 3)

PHASE 4: *for completion by Examiner 4.*

Past Medical History

I would like to ask some questions about your general health; to find whether this is related to eye diseases.

M1.*(health)* For someone of your age, how would you rate your overall health?

excellent ..... 1 poor 4
good ..... 2 don't know..... 8
fair 3

M2.*(hosadm)* Have you had any admissions to a hospital in the last 12 months?

_____times don't know..... 88

If admitted,

M3.*(hosdis)* What for? M4.*(hosnam)* Which hospital?

1 _____
2 _____
3 _____

Has a doctor ever said that you have any of the following conditions ?

		yes	no	DK	age/yrs 1st told	Rx yrs
M5,6,6A*(hypert)*	**high blood pressure**	☐	☐	☐	_____ yrs	____
M7,8.*(angina)*	**angina**..... (chest pain form your heart)	☐	☐	☐	_____ yrs	
M9,10.*(AMI)*	**heart attack** ..... (a coronary, myocardial infarct)	☐	☐	☐	_____ yrs	
M11,12.*(stroke)*	**stroke**	☐	☐	☐	_____ yrs	
M13,14.*(cholest)*	**high cholesterol**	☐	☐	☐	_____ yrs	
M15,16.*(diabet)*	**diabetes,**	☐	☐	☐	_____ yrs	
M17.*(diadiet)*	sugar in your urine	Treated with:			diet alone?_____	yrs
M18.*(diatab)*	or high blood sugar				tablets?_____	yrs
M19.*(diains)*					insulin?_____	yrs
M20,21.*(cancer)*	**cancer**	☐	☐	☐	_____ yrs	
M22.*(CAtype)*	What type of cancer? _____					
M23.*(CAtreat)*	Treated with: surgery ..... 1 radiation ..... 2 chemotherapy 3				no treatment ..... 4 don't know 5	
M24,25.*(skinCA)*	**sunspots or skin cancer,** ... treated by freezing or surgery	☐	☐	☐	_____ yrs	
M26,27.*(Thyroid)*	**thyroid condition**	☐	☐	☐	_____ yrs	
M28. *(ThyrRx)*	Treated with: radioactive iodine..1 surgery ..... 2 thyroxine tablets ... 3 _____ code:_____					
M28a.*(Asthma)*	**asthma**	☐	☐	☐	_____ yrs	
M29,30.*(Arthrit)*	**arthritis**	☐	☐	☐	_____ yrs	
M31. *(ArthTyp)*	What type: osteoarthritis ..... 1 rheumatoid ..... 2 other ..... 3 _____ code:_____					
M31a *(Gout)*	**gout**	☐	☐	☐	_____ yrs	

M32.*(arthtab)* Have you ever taken tablets for gout or arthritis such as Zyloprim, Indocid, Voltaren, Feldene, Naprosyn, Panamax or Dymadon?

yes 1
no 2
don't know 8

add name here

_____ | code ____
_____ | code ____
_____ | code ____

M33.*(clorquin)* Have you ever taken Chloroquine or Plaquenil for arthritis or malaria?

yes 1
no 2
don't know 8

add name here

_____ | code ____
_____ | code ____

M34.*(migrain)* Have you ever had migraine headaches ?

(severe headaches, usually on one side, may have changes in vision like zig-zag lines or blurring, often nausea or vomiting and you usually need to lie down with the lights off)

yes, typical 1
yes, but atypical ... 9
no 2
don't know 8

If yes,

M34a *(mig1st)*
age started _____ yrs
M34b *(migstop)*
age stopped_____ yrs

M35.*(falls)* During the past 12 months, have you had any falls where you have landed on the ground or floor? *number of falls* _____

If fallen,

M36.*(fallvis)* How many of these do you think were due to problems with your vision?
number of falls _____

M37. *(TetYrs)* Can you recall when you had your last tetanus shot? _____ yrs ago
M38. *(TetNo)* don't know.....98 never had one..... 99

Have you had any other serious or major illnesses or operations?

M39.*(illnes1)* _____ | code ____

M40.*(illnes2)* _____ | code ____

M41.*(illnes3)* _____ | code ____

M42.*(illnes4)* _____ | code ____

M43. *(CAT)* Have you ever had a CAT scan of the head or brain?
M44. *(CATYr)*

yes 1
no..... 2
don't know..... 8

years _____

M45. *(shock)* Have you ever been in hospital with a sharp drop in your blood pressure or severe loss of blood (shock)?

yes..... 1
no 2
possible..... 3
don't know.. 8

M46.*(shokdet)* details _____

Family History We want to know if eye disease runs in families.

Have your parents or your brothers or sisters or children had:

(tick)	glauc?	cataract?	macular degen?	blind?	other eg turned eye?
I1. *(FHxmo)* mother have	____	____	____	____	_____
I2. *(FHxfa)* father have	____	____	____	____	_____
I3. *(FHxbro)* brothers /of no.	____	____	____	____	_____
I4. *(FHxsist)* sisters / of no.	____	____	____	____	_____
I5. *(FHxchil)* natural children?	____	____	____	____	_____

I6. *(alivefa)* Is your father still alive? yes ..... 1 no ..... 2 don't know..... 8

I7. *(fathage)* approx age at death _____years (if young, why?) _____

I8. *(alivemo)* Is your mother still alive? yes ..... 1 no ..... 2 don't know..... 8

I9. *(mothage)* approx age at death _____years (if young, why?) _____

I10. *(broth)* How many full brothers have you had, that is alive or dead? ___

I11. *(sist)* How many full sisters have you had, that is alive or dead? ___

I12. *(FHxdiab)* Do you have a family history of diabetes?

none	1	children	5
mother	2	maternal aunts,uncles	6
father	3	maternal grandparents	7
brothers,sisters	4	pat aunts,uncles	8
		paternal grandparents	9

Sunlight Exposure I would now like to ask you some questions about your exposure to sunlight

J1. *(colour)* As a teenager,what was the natural colour of your hair? Was it:

blonde	1	black	4
red	2	other	5
brown	3	don't know	8

J2. *(burn)* In the past, when your skin was exposed to the summer sun, did it?

- always burn, never tan 1
- usually burn, tan with difficulty..... 2
- burn and tan about average 3
- rarely burn, tan above average 4
- don't know 8

J3. *(burn-no)* How many bad sunburns, that is with soreness lasting more than a day, would you estimate you have had during your life, including childhood?

none	1	>10	4
one	2	don't know	8
2-10	3		

J4.*(skincol)* *Non-exposed skin colour:* *examiner to estimate*

very fair	1	dark olive	4
fair	2	brown	5
light olive	3	black	6

J5.*(skindam)* *Degree of sun-induced skin damage:* *examiner to estimate*

none	1	moderate	3
mild	2	severe	4

Eye medications Now a few questions about your eyes.

K1. Are you using any eyedrops at present? yes ...1 no ... 2 don't know ... 8

list: how long have you been taking these?

K2. *(drop1)* 1. _____ | code _____ _____

K3. *(drop2)* 2. _____ | code _____ _____

K4. *(drop3)* 3. _____ | code _____ _____

K5. *(drop4)* 4. _____ | code _____ _____

K6. *(stedrop)* Any steroid eye drops? yes ... 1 no ... 2 don't know ... 8

add here _____ | code _____

Eye Diseases Now about some eye conditions

K7. *(catarac)* Have you ever been told you have cataracts?

yes 1

no ..... 2 don't know ..... 8 *goto K15.*

K8. *(catadet)* details _____

K9. *(cataage)* How many years ago were you first told? ____yrs _____age

K10. *(catarop)* *If yes,* have you ever had an operation for cataract?

yes 1

no ..... 2 don't know ..... 8 *goto K15.*

K11. *(catdet)* details _____

K12. *(catawho)* Who performed it? _____

K13. *(cataYAG)* Have you had YAG laser to improve your vision after cataract surgery?

yes 1

no ..... 2 don't know 8

K14. *(catar-YAG)* details _____

K15. *(AMD)* Have you ever been told you have macular degeneration, sometimes called 'hardening of the arteries at the back of the eye', or 'degeneration of the retina'?

yes 1

no ..... 2 don't know ..... 8 *goto K20.*

K16. *(AMDdet)* details _____

K17. *(AMDage)* How many years ago were you first told? ____yrs _____age

K18. *(AMDlase)* *If yes,* have you had laser treatment for macular degeneration?

yes 1

no ..... 2 don't know ..... 8 *goto K20.*

K19. *(lasedet)* details _____

K20. *(glaucom)* Have you ever beeen told that you have glaucoma or 'raised pressure in the eyes'?

yes 1

no ..... 2 don't know ..... 8 *goto K26.*

K21. *(glaudet)* *If yes,* details _____

K22. *(glauage)* How many years ago were you first told? ____yrs _____age

K23. *(glaucRx)* Have you ever used eyedrops or medications for glaucoma?

yes 1

no ..... 2 don't know ..... 8 *goto K26.*

K24. *(glaucop)* Have you had an operation or laser treatment for glaucoma?

yes 1

no ..... 2 don't know ..... 8 *goto K26.*

K25. *(opdet)* details _____

K26. *(retina)* Have you ever been told you have a problem in the retina or the 'back of the eye'? like retinal detachment or vessel blockage or bleeding ?

yes 1
no ..... 2 don't know ..... 8 *goto K29.*

K27. *(retidet)* details _____

K28. *(retinyr)* How many years ago were you first told? ____yrs _____age

---

K29. *(injury)* Have you ever had any serious eye injury requiring doctor's care?

yes 1
no ..... 2 don't know ..... 8 *goto K31.*

K30. *(inj-det)* details_____

Any other eye problems or eye surgery that I haven't asked you about?

K31. *(eyedet1)*_____ code_____

K32. *(eyedet2)*_____ code_____

Eye Examination: Slit lamp examination

	R eye	L eye
Corneal Arcus		
	L1.*(Rarcus)*	L2. *(Larcus)*
	none....1 quest ....2 ≤180°...3 >180° 4	none....1 quest ....2 ≤180°...3 >180° 4
Pingueculum		
	L3.*(Rpingue)*	L4. *(Lpingue)*
	absent...1 quest .....2 present....3	absent...1 quest .....2 present....3
Pterygium		
	L5. *(Rpteryg)*	L6. *(Lpteryg)*
	absent...1 quest .....2 present....3 pres, axis involved 4	absent...1 quest .....2 present....3 pres, axis involved 4
Pseudoexfoliation		
	L7. *(Rexfol)*	L9. *(Lexfol)*
	absent...1 quest .....2 present....3	absent...1 quest .....2 present....3
	L8. *(Rdegree)* R degree_____	L10. *(Ldegree)* L degree_____
Corneal opacities		
	L11. *(Ropac)*	L12. *(Lopac)*
	absent...1 quest .....2 present....3 pres, axis involved 4	absent...1 quest .....2 present....3 pres, axis involved 4

Other slit lamp abnormalities

L13*(Rabn1)*_____ L14*(Labn1)*_____

L15*(Rabn2)*_____ L16*(Labn2)*_____

L17*(Rabn3)*_____ L18*(Labn3)*_____

L19*(Rabn4)*_____ L20*(Labn4)*_____

L21*(Rabn5)*_____ L22*(Labn5)*_____

		right	*left*
L23,24*(Topcon)*	*Topcon Nuclear Lens PhotographTaken*	_____	_____
L25,26*(Neitz)*	*Neitz Cortical/PSC Lens Photograph Taken*	_____	_____

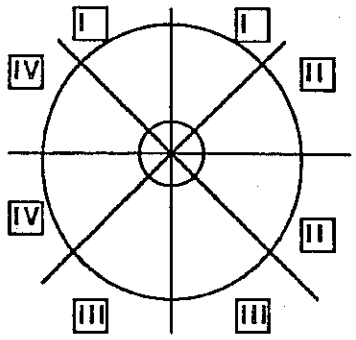
N1. *(Rphakia)* **Right Lens presence:**
phakic..... 1
aphakic, no lens ... 2
aphakic, AC IOL 3
aphakic, PC IOL 4
enucleated 5

Nuclear cataract:

N2. *(Rnuccat)* WISC	N46.*(RnucJH)* JH
≤std#1 1	 1
≤std#2 2	 2
≤std#3 3	 3
≤std#4 4	 4
>std#4 5	 5
mature..... 6	 6
can't grade... 7	 7

Cortical Cataract
N47.*(RcorJH)*
JH
none.....1
≤45°..... 2
≤90°..... 3
≤180°.....4
cortical dots. 6
can't grade....7

WISC



N23*(Rantopa)* are white anterior cortical opacities present?
absent...1 present...2 quest...3

Cortical and posterior subcapsular cataract:
record % of each lens quadrant involved for each type of opacity.

	PSC	Cortical		Vacuoles anterior	Vacuoles posterior
Quadrant I	N3_____	N4_____	N5	_____	N6 _____
Quadrant II	N7_____	N8_____	N9	_____	N10_____
Quadrant III	N11_____	N12_____	N13	_____	N14_____
Quadrant IV	N15_____	N16_____	N17	_____	N18_____
central circle	N19_____	N20_____	N21	_____	N22_____

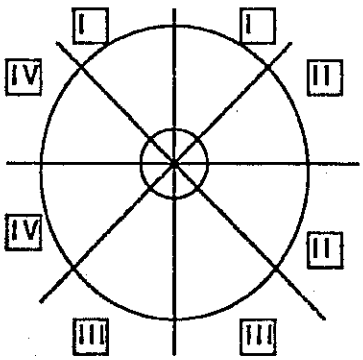
N24.*(Lphakia)* **Left Lens presence:**
phakic..... 1
aphakic, no lens ... 2
aphakic, AC IOL 3
aphakic, PC IOL 4
enucleated 5

Nuclear cataract:

N25.*(Lnuccat)* WISC	N48.*(LnucJH)* JH
≤std#1 1	 1
≤std#2 2	 2
≤std#3 3	 3
≤std#4 4	 4
>std#4 5	 5
mature..... 6	 6
can't grade...7	 7

Cortical Cataract
N49.*(LcorJH)*
JH
none.....1
≤45°..... 2
≤90°..... 3
≤180°.....4
cortical dots. 6
can't grade....7

WISC



N46.*(Lantopa)* are white anterior cortical opacities present?
absent...1 present...2 quest...3

Cortical and posterior subcapsular cataract:
record % of each lens quadrant involved for each type of opacity.

	PSC	Cortical		Vacuoles anterior	Vacuoles posterior
Quadrant I	N26_____	N27_____	N28	_____	N29 _____
Quadrant II	N30_____	N31_____	N32	_____	N33_____
Quadrant III	N34 _____	N35_____	N36	_____	N37 _____
Quadrant IV	N38_____	N39_____	N40	_____	N41 _____
central circle	N42 _____	N43_____	N44	_____	N45 _____

Fundus Examination right eye **left eye**

O1.*(RhardD)* **Hard macular drusen**
absent...1 quest .....2 present....3

O2.*(LhardD)* **Hard macular drusen**
absent...1 quest .....2 present....3

O3.*(RsoftD)* **Soft macular drusen**
absent...1 quest .....2 present....3

O4.*(LsoftD)* **Soft macular drusen**
absent...1 quest .....2 present....3

O5.*(Rpig)* **Visible Pigment**
absent...1 quest .....2 present....3

O6. *(Lpig)* **Visible Pigment**
absent...1 quest .....2 present....3

O7.*(Ratrophy)* **Geographic atrophy**
absent...1 quest .....2 present....3

O8.*(Latroph)* **Geographic atrophy**
absent...1 quest .....2 present....3

O9.*(Rdiscif)* **Disciform degeneration**
absent...1 quest .....2 present....3

O10.*(Ldiscif)* **Disciform degeneration**
absent...1 quest .....2 present....3

O11.*(Rretinop)* **Diabetic retinopathy**
absent...1 quest .....2 present....3

O12.*(Lretinop)* **Diabetic retinopathy**
absent...1 quest .....2 present....3

other retinal abnormalities
O13*(Rabnorm1)*_____
O15*(Rabnorm2)*_____
O17*(Rabnorm3)*_____
O19*(Rabnorm4)*_____

other retinal abnormalities
O14*(Labnorm1)*_____
O16*(Labnorm2)*_____
O18*(Labnorm3)*_____
O20*(Labnorm4)*_____

Estimated cause of visual loss **right eye** **left eye**
If vision in eyes is 6/12 or worse, estimate proportion caused by:

O21*(Renucl)*	enucleation	_____	O22*(Lenucl)*	enucleation	_____
O23*(Rambly)*	amblyopia	_____	O24*(Lambly)*	amblyopia	_____
O25*(Rcatara)*	cataract	_____	O26*(Lcatara)*	cataract	_____
O27*(RAMD)*	AMD	_____	O28*(LAMD)*	AMD	_____
O29*(Rretina)*	other retinal disease	____	O30*(Lretina)*	other retinal disease	_____
O31*(Rglauc)*	glaucoma	_____	O32*(Lglauc)*	glaucoma	_____
O33*(RopticN)*	other optic nerve dis	____	O34*(LopticN)*	other optic nerve dis	____
O35*(Rcornea)*	corneal disease	_____	O36*(Lcornea)*	corneal disease	_____
O37*(Rvitreo)*	vitreous media	_____	O38*(Lvitreo)*	vitreous media	_____
O39*(Runsure)*	unsure	_____	O40*(Lunsure)*	unsure	_____
O41*(Rdiseas)*	other,		O42*(Ldiseas)*	other,	
describe_____			describe_____		

O43*(colphot)* ***Colour fundus photographs taken?*** _____ _____

O44*(NFLphot)* ***Nerve Fibre Layer photographs taken?*** _____ _____

The examination is completed. Thank you very much for taking part.

O47. *(Pathday)* Date of blood test ___/___/9___
O45. *(PathT)* Take blood _____ time
O46. *(hrmeal)* How long ago did you last eat a meal? _____hours

Contents available at Sciverse ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Metabolic syndrome and mortality in the elderly: A time-dependent association

Haleh Ghaem Maralani [a], *Bee Choo Tai* [a,b,*], *Tien Y. Wong* [c,d,e], *E Shyong Tai* [f], *Jialiang Li* [g], *Jie Jin Wang* [e,h], *Paul Mitchell* [h]

[a] *Saw Swee Hock School of Public Health, National University of Singapore and National University Health System, Singapore*
[b] *Yong Loo Lin School of Medicine, National University of Singapore and National University Health System, Singapore*
[c] *Singapore Eye Research Institute, Singapore National Eye Centre, Singapore*
[d] *Department of Ophthalmology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore*
[e] *Centre for Eye Research Australia, University of Melbourne, Royal Victorian Eye and Ear Hospital, Victoria, Australia*
[f] *Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore*
[g] *Department of Statistics and Applied Probability, National University of Singapore, Singapore*
[h] *Centre for Vision Research, University of Sydney, Sydney, Australia*

ARTICLE INFO

Article history:
Received 22 June 2012
Received in revised form
1 November 2012
Accepted 8 November 2012
Published on line 30 November 2012

Keywords:
Metabolic syndrome
All-cause mortality
Cause-specific mortality
Blue Mountains Eye Study
Time-dependent

ABSTRACT

Aims: To evaluate the association between metabolic syndrome (MetS) components and mortality over time.

Methods: 3086 residents aged ≥49 years were followed in the Blue Mountains Eye Study, Australia. MetS components as defined by the International Diabetes Federation criteria were measured at baseline (1992–1994), 5-year (1997–1999) and 10-year (2002–2004). Using Cox proportional hazards and competing risks models with MetS as a time-dependent covariate, we estimated the effects of MetS on all-cause and cause-specific mortality. Time-dependent receiver-operating-characteristic curve, integrated-discrimination-improvement and net-reclassification-improvement tests assessed predicting abilities of individual and combined MetS components.

Results: Effect of MetS on mortality increased with time: all cause: 2-year: adjusted hazard ratio 0.96 [95% confidence interval 0.69–1.34]; 5-year: 1.06 [0.84–1.32]; 10-year: 1.23 [1.01–1.51]; and CHD: 2-year: 0.46 [0.20–1.03]; 5-year: 0.70 [0.41–1.21]; 10-year: 1.62 [1.02–2.59]. Conversely, MetS was associated with an increased risk of cancer death at 2-year only: 1.62 [1.01–2.62]; but not 5-year: 1.30 [0.94–1.81] or 10-year: 0.90 [0.57–1.44]. The discrimination analyses showed that different MetS components were associated with different causes of death.

Conclusions: The long-term effect of MetS on all-cause and CHD mortality in an older population was detected using time-dependent models while simulating the real scenarios of MetS changes over time.

1. Introduction

Metabolic syndrome (MetS) was first described in the 1920s as the clustering of hypertension, hyperglycemia and gout [1], with current definitions, namely European Group for the Study of Insulin Resistance (EGIR), World Health Organisation (WHO), Third Report of the National Cholesterol Education Program Adult Treatment Panel (ATP-3), and the International Diabetes Federation (IDF) [2], including components of obesity,

* *Corresponding author at*: Saw Swee Hock School of Public Health, National University of Singapore, 16 Medical Drive (MD3), Singapore 117597, Singapore. Tel.: +65 65164973; fax: +65 67791489.
E-mail address: ephtbc@nus.edu.sg (B.C. Tai).
0168-8227/$ – see front matter
http://dx.doi.org/10.1016/j.diabres.2012.11.005

insulin resistance, dyslipidemia and hypertension [1]. In middle-age populations, the adverse effect of Mets on morbidity and mortality has been established [3–5], but the utility of MetS in predicting mortality amongst the elderly is doubtful. First, underweight elderly populations may be predisposed to an increased risk of mortality [6,7]. Secondly, some MetS components, namely hypertriglyceridemia and diastolic blood pressure (BP), are not clearly related to poor health outcomes later in life [8,9]. Furthermore, the cut-off point for individual MetS components may not be appropriate for predicting mortality in the elderly population, since these distributions were often characterized in middle-age populations [10].

While many studies have examined the relationship between MetS and mortality, there are still key unanswered questions. First, the relationship between MetS with all-cause and cause-specific mortality remains unclear. Some studies showed MetS to be a predictor of all-cause [11,12] and coronary heart disease (CHD) mortality [11–13], whereas other studies demonstrated no effects of MetS on all-cause [14,15], CHD [14,15] or cardiovascular disease (CVD) [12,14,15] deaths in the elderly. Although MetS was found to predict cancer death in some studies [13,16], this relationship was not evident in one study [12].

Second, individual MetS components may have different effects on mortality. While hypertension [17], hyperglycemia [11,13,17,18], low HDL [11,13,18] and high triglyceride levels [12] have been shown to predict all-cause and CVD-death, there is inconsistency with regards to which of these MetS components better predicts mortality. Third, it remains unclear whether MetS as a whole or its individual components provide a better prediction of all-cause and cause-specific mortality [19,20]. Finally, no studies have clarified whether earlier or most updated status of MetS best predicts all-cause and cause-specific mortality.

In this study, we evaluated the effect of MetS and its components on subsequent all-cause and cause-specific mortality in an older Australian population. We fully utilized the information on MetS collected at baseline, 5-year and 10-year visits to unravel the relationship between MetS and mortality, and to determine whether this association changes with time.

2. Materials and methods

2.1. Study design

The Blue Mountains Eye Study (BMES) is a population-based cohort study of vision, common eye diseases and other health outcomes of a suburban population in the west of Sydney, Australia [21]. Between 1992 and 1994, non-institutionalised permanent residents aged 49 years and older were invited to participate in this study, and were requested to return for follow-up examinations at 5-year (1997–1999) and 10-year (2002–2004). We included 3086 participants at baseline who had complete information for the study factors. The BMES was approved by the Human Research Ethics Committee of the University of Sydney and conducted according to the Helsinki Declaration. Written informed consent was obtained from all participants at each examination. Recruitment details have been previously described [21].

2.2. Exposure measurements

At each visit, trained interviewers completed a comprehensive questionnaire comprising demographic information, smoking status, eye and general medical history including hypertension, diabetes, and pre-existing diseases (namely, cancer, angina, acute myocardial infarction (AMI), stroke and chronic lung disease) as well as medication used. Height, weight and seated BP [22] were measured. Fasting pathology tests, including total cholesterol, HDL cholesterol and triglycerides [23] and fasting plasma glucose (FPG) [24], were also measured within a month of each interview.

2.3. Definition of metabolic syndrome

It has been reported that EGIR, WHO and ATP-3 definitions for MetS were not as successful in predicting diabetes and cardiovascular disease as compared to IDF definition [2]. Thus, in this study, we define MetS based on the IDF criteria. This is a diagnostic tool for both research purpose and clinical practice and can be used relatively easily in any country by any physician to identify patients at increased risk of developing health related outcomes. Moreover, studies have suggested that the IDF criteria is more reliable for diagnosing MetS in predictive model for coronary clinical status in type 2 diabetes populations [2,25].

MetS was defined according to the IDF criteria [2] as obesity (i.e. body mass index (BMI) $>30\ kg/m^2$) plus any two of the following four factors: serum triglyceride level ≥ 1.7 mmol/L or specific treatment for this lipid abnormality; serum HDL cholesterol <1.03 mmol/L in men and <1.29 mmol/L in women, or specific treatment for this lipid abnormality; systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg, or treatment of previously diagnosed hypertension; or FPG ≥ 5.6 mmol/L, or previous diagnosis or specific treatment for type 2 diabetes.

2.4. Mortality

Deaths occurring between the baseline examination (1992–1994) and 31 December 2007 were confirmed by matching the demographic information of the participants with the Australian National Death Index (NDI), using probabilistic record linkage [26]. The causes of death were provided by the NDI using the International Classification of Diseases (ICD) 9th revision and the International Statistical Classification of Diseases, 10th revision. For example, ICD-9 codes 430.0–438.9 and ICD-10 codes 160.0–169.9 were classified as stroke-related deaths, whereas ICD-9 codes 410.0-9, 411.0-8, 412, 414.0-9, and ICD-10 codes 121.0-9, 122.0-9, 123.0-8, 124.0-9, 125.0-9 were classified as cardiovascular related deaths. The sensitivity and specificity of the Australian NDI have been estimated as 93.7% and 100% for all deaths, and 92.5% and 89.6% respectively, for cardiovascular deaths [26].

2.5. Statistical analyses

Independent sample t-test and chi-square tests were used to evaluate the relation between continuous and categorical covariates with MetS status, respectively. We utilized all information on MetS and its components that were recorded for each subject at baseline, 5-year and 10-year follow-up visits in the analysis. Data were thus available with respect to how MetS (components) might have changed in each subject throughout the study duration. Therefore, the Cox proportional hazards and competing risks regression models with time-dependent covariates [27] were used to determine the relationship between MetS and its components with all-cause and cause-specific mortality [28], and evaluate whether the association changes with time. In these models, MetS and its individual components were regarded as time-dependent covariables [27], whereas potential confounders such as age, sex, smoking, alcohol consumption, physical activity and pre-existing disease status (namely, cancer, angina, AMI, stroke and chronic lung disease), which were collected at baseline, were considered as fixed covariates.

To account for the situation where MetS, may change over time, we implemented the Cox model with time-dependent covariate and modeled the hazard function as [27]:

$$h(t) = \exp(\beta_1 \times \mathrm{MetS} + \beta_2 \times \mathrm{MetSt}) \times h_0(t)$$

where $h_0(t)$ is the baseline hazard function, and β_1 and β_2 are the regression coefficients. The model contains MetS and a second term MetSt corresponding to an interaction between MetS and the survival time. The interaction term is formed from the product of MetS and the survival time t, that is, MetSt = MetS × t. This model can be extended to include other fixed and time-dependent covariates. It allows MetS to be linearly dependent on the survival time, so we were able to estimate the hazard ratio (HR) of MetS for $t = 2$, 5 or 10 years.

We also explored possible interactions between time-dependent MetS and its components with age, sex, and pre-existing disease. Additionally, the proportional hazards assumption underlying the Cox model was checked for individual covariates and globally.

Furthermore, to assess the prognostic value of MetS components on the risk of all-cause and cause-specific mortality, we implemented the time-dependent receiver-operating-characteristic (ROC) curve for censored survival model [29] and summarized the results of area under the curve at time t (AUC(t)) using the Harrell's concordance index [30,31]. Bootstrap model was used to compare the AUC.

Since the AUC may not be sensitive enough to express the improvement of discrimination performance, we also used two other methods, namely the net reclassification improvement (NRI) and integrated discrimination improvement (IDI) as described by Pencina et al. [32], for censored survival model [33,34] to evaluate the prediction of MetS components on all-cause and cause-specific mortality risk.

All statistical evaluations were made assuming a two-sided test based on a 5% level of significance using STATA version 11 and R statistical package (www.r-project.org).

3. Results

Table 1 presents the characteristics of study subjects based on MetS status at baseline, 5- and 10-year follow-up. The mean age of the 3086 subjects was 65.9 (standard deviation (SD) 9.5) years, and 43% were male. Apart from BMI, a mandatory component of the IDF criteria, a substantial proportion had

Table 1 – Characteristics of the study population by metabolic syndrome (MetS) status at baseline, 5- and 10-year follow-up.

	Total (n = 3086)	Baseline		5-year		10-year	
		No MetS (n = 2702)	MetS (n = 384)	No MetS (n = 1772)	MetS (n = 341)	No MetS (n = 1433)	MetS (n = 199)
Mean baseline age in years (SD)	65.9 (9.5)	66.0(9.6)	65.0 (8.6)	64.8 (8.7)[f]	63.2 (7.9)	63.1 (7.7)[f]	61.0 (6.7)
Sex (%)							
Female	1759 (57.0)	1509 (55.8)[f]	250 (65.1)	1003 (56.6)[f]	217 (63.6)	837 (58.4)	130 (65.3)
Male	1327 (43.0)	1193 (44.2)	134 (34.9)	769 (43.4)	124 (36.4)	596 (41.6)	69 (34.7)
Smoking status (%)							
Current smoker	439 (14.2)	389 (14.4)	50 (13.0)	224 (12.6)	36 (10.6)	162 (11.3)	25 (12.6)
Ex-smoker	1122 (36.4)	980 (36.3)	142 (37.0)	619 (34.9)	132 (38.7)	489 (34.1)	66 (33.2)
Non-smoker	1525 (49.4)	1333 (49.3)	192 (50.0)	929 (52.4)	173 (50.7)	782 (54.6)	108 (54.2)
Any pre-existing disease[a] (%)	812 (26.3)	701 (25.9)	111 (28.9)	423 (23.9)	93 (27.3)	276 (19.3)[f]	59 (29.7)
Mean BMI (kg/m^2)(SD)	26.2 (4.4)	25.1 (3.4)[f]	33.7 (3.3)	25.7 (4.4)[f]	33.8 (3.6)	26.3 (4.2)[f]	33.5 (3.5)
Low HDL (%)[b]	1012 (32.8)	849 (31.4)[f]	163 (42.5)	372 (23.2)[f]	160 (56.9)	324 (27.3)[f]	123 (61.8)
High triglyceride (%)[c]	1283 (41.6)	989 (36.6)[f]	294 (76.6)	557 (31.4)[f]	235 (68.9)	202 (20.8)[f]	110 (61.8)
Hypertension (%)[d]	2645 (85.7)	2271 (84.1)[f]	374 (97.4)	1574 (89.7)[f]	339 (99.4)	1081 (80.8)[f]	191 (96.0)
Elevated FPG (%)[e]	547 (17.7)	400 (14.8)[f]	147 (38.3)	300 (19.9)[f]	157(40.0)	126 (8.8)[f]	77 (38.7)

BMI: body mass index; FPG: fasting plasma glucose; MetS: metabolic syndrome; SD: standard deviation.

[a] Any pre-existing disease (namely, cancer, angina, acute myocardial infarction, stroke and chronic lung disease).

[b] Serum HDL cholesterol <1.03 mmol/L in men and <1.29 mmol/L in women, or specific treatment for this lipid abnormality.

[c] Serum triglyceride level ≥1.7 mmol/L or specific treatment for this lipid abnormality.

[d] Systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, or treatment of previously diagnosed hypertension.

[e] Fasting plasma glucose≥5.6 mmol/L, or previous diagnosis or specific treatment for type 2 diabetes.

[f] $P < 0.05$.

high BP (85.7%), high triglycerides (41.6%) and low HDL-cholesterol (32.8%) at baseline (Table 1). The prevalence of MetS increased slightly to 16.1% (95% confidence interval (CI) 14.6–17.8%) after 5 years follow-up from 12.4% (95% CI 11.3–13.6%) at baseline, and was 12.2% (95% CI 10.6–13.9%) after 10 years follow-up.

3.1. *All-cause mortality*

Over a median follow-up duration of 14.6 years, 1170 (38%) deaths were reported. Among the covariates that were repeatedly measured at the baseline, 5-year and 10-year follow-up visits, without any adjustment, elevated glucose, hypertension, triglyceride and BMI showed a time-dependent association with all-cause mortality (Table 2).

Among the fixed covariates considered in this study, gender, age, pre-existing disease and smoking were associated with all-cause mortality (Table 2). Adjusting for these fixed covariates, the risk of all-cause-mortality increased gradually from 2-year to 10-year follow-up amongst those with MetS (2-year: HR 0.96 [95% CI 0.69–1.34]; 5-year: HR 1.06 [95% CI 0.84–1.32]; 10-year: HR 1.23 [95% CI 1.01–1.51]) (Table 3). However, individually, none of the MetS components appeared to have a significant effect on all-cause mortality.

3.2. *Cause-specific mortality*

Of the 1170 reported deaths, 279 (23.9%) were CHD-deaths, 130 (11.1%) were stroke-deaths and 342 (29.2%) were cancer-deaths. Individually, hypertension and high triglyceride showed a time-dependent association with stroke and cancer deaths, respectively. Further, BMI >30 was inversely associated with CHD- and stroke-deaths, with notably

Table 2 – Bivariate association between fixed and time-dependent risk factors with all-cause and cause-specific mortality.

	All-cause (n = 1170)		CHD (n = 279)		Stroke (n = 130)		Cancer (n = 342)	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Fixed covariate								
Sex (Male)	1.54 (1.37–1.72)	<0.001	1.63 (1.28–2.06)	<0.001	1.01 (0.71–1.42)	0.978	1.51 (1.22–1.87)	<0.001
Age	1.11 (1.10–1.12)	<0.001	1.10 (1.09–1.11)	<0.001	1.10 (1.08–1.12)	<0.001	1.04 (1.03–1.06)	<0.001
Smoking status								
Non-smoker	Reference (1)		Reference (1)		Reference (1)		Reference (1)	
Ex-smoker	1.39 (1.22–1.57)	<0.001	1.11 (0.86–1.44)	0.412	0.78 (0.53–1.15)	0.208	1.46 (1.16–1.85)	0.001
Current smoker	1.46 (1.24–1.73)	<0.001	1.13 (0.79–1.59)	0.514	0.88 (0.52–1.48)	0.628	1.62 (1.20–2.18)	0.002
Any, pre-existing disease[a]	2.20 (1.95–2.46)	<0.001	2.72 (2.15–3.44)	<0.001	1.61 (1.13–2.31)	0.009	1.70 (1.37–2.12)	<0.001
Time-dependent covariate								
MetS								
2-year	0.76 (0.55–1.04)	0.090	0.35 (0.16–0.78)	0.010	0.16 (0.03–0.90)	0.037	1.42 (0.88–2.29)	0.152
5-year	0.85 (0.68–1.05)	0.133	0.54 (0.32–0.93)	0.025	0.26 (0.08–0.86)	0.027	1.14 (0.82–1.57)	0.443
10-year	1.02 (0.84–1.25)	0.822	1.31 (0.83–2.08)	0.245	0.58 (0.30–1.11)	0.103	0.78 (0.49–1.24)	0.229
BMI >30								
2-year	0.58 (0.43–0.78)	<0.001	0.45 (0.25–0.82)	0.009	0.07 (0.01–0.49)	0.007	1.00 (0.63–1.58)	0.996
5-year	0.66 (0.54–0.80)	<0.001	0.60 (0.40–0.90)	0.013	0.14 (0.04–0.52)	0.003	0.88 (0.65–1.19)	0.409
10-year	0.81 (0.67–0.96)	0.017	0.98 (0.68–1.41)	0.906	0.40 (0.22–0.75)	0.004	0.71 (0.48–1.05)	0.084
Elevated glucose[b]								
2-year	1.17 (0.92–1.50)	0.207	1.32 (0.83–2.11)	0.245	0.42 (0.16–1.09)	0.074	1.16 (0.76–1.78)	0.489
5-year	1.21 (1.03–1.43)	0.024	1.34 (0.98–1.82)	0.067	0.61 (0.31–1.18)	0.142	1.20 (0.90–1.60)	0.205
10-year	1.28 (1.08–1.52)	0.005	1.36 (0.94–1.96)	0.099	1.14 (0.72–1.78)	0.578	1.27 (0.91–1.79)	0.163
Low HDL[c]								
2-year	0.97 (0.78–1.20)	0.751	1.03 (0.68–1.56)	0.894	1.11 (0.53–2.32)	0.779	0.93 (0.63–1.36)	0.705
5-year	0.94 (0.81–1.09)	0.397	0.90 (0.68–1.20)	0.487	1.02 (0.62–1.70)	0.929	0.88 (0.67–1.14)	0.323
10-year	0.89 (0.76–1.05)	0.164	0.73 (0.50–1.05)	0.090	0.89 (0.58–1.36)	0.594	0.79 (0.57–1.10)	0.162
High triglyceride[d]								
2-year	1.21 (0.99–1.48)	0.069	0.93 (0.63–1.39)	0.738	1.14 (0.57–2.27)	0.712	1.79 (1.25–2.57)	0.001
5-year	1.15 (1.01–1.32)	0.044	1.05 (0.80–1.37)	0.737	1.05 (0.66–1.69)	0.831	1.42 (1.12–1.80)	0.004
10-year	1.07 (0.92–1.24)	0.389	1.27 (0.92–1.74)	0.145	0.92 (0.62–1.37)	0.690	0.96 (0.70–1.31)	0.791
Hypertension[e]								
2-year	1.26 (0.90–1.74)	0.174	1.41 (0.73–2.75)	0.308	13.2 (3.34–51.8)	<0.001	1.02 (0.60–1.74)	0.946
5-year	1.39 (1.10–1.74)	0.443	1.52 (0.96–2.40)	0.071	8.01 (2.65–24.22)	<0.001	1.10 (0.76–1.58)	0.615
10-year	1.64 (1.28–2.09)	<0.001	1.72 (0.98–3.04)	0.060	3.50 (1.42–8.66)	0.007	1.25 (0.79–1.95)	0.338

BMI: body mass index; CHD: coronary heart disease; CI: confidence interval; HR: hazard ratio; MetS: metabolic syndrome.

[a] Any pre-existing disease (namely, cancer, angina, acute myocardial infarction, stroke and chronic lung disease).

[b] Fasting plasma glucose ≥5.6 mmol/L, or previous diagnosis or specific treatment for type 2 diabetes.

[c] Serum HDL cholesterol <1.03 mmol/L in men and <1.29 mmol/L in women, or specific treatment for this lipid abnormality.

[d] Serum triglyceride level ≥1.7 mmol/L or specific treatment for this lipid abnormality.

[e] Systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, or treatment of previously diagnosed hypertension.

Table 3 – Time-dependent effects of metabolic syndrome and its components on all-cause and cause-specific mortality, adjusted for age, gender, smoking status, pre-existing disease at baseline (namely, cancer, angina, acute myocardial infarction, stroke and chronic lung disease).

	2-year			5-year			10-year		
	No of death amongst exposed	HR (95% CI)	P-value	No of death amongst exposed	HR (95% CI)	P-value	No of death amongst exposed	HR (95% CI)	P-value
All-cause, $n = 1170$									
MetS	152 (13.0)	0.96 (0.69–1.34)	0.825	75 (13.2)	1.06 (0.84–1.32)	0.634	21 (10.7)	1.23 (1.01–1.51)	0.046
BMI >30	189 (16.2)	0.83 (0.61–1.12)	0.213	103 (18.1)	0.90 (0.74–1.11)	0.329	36 (18.3)	1.05 (0.88–1.25)	0.603
Elevated FPG[a]	272 (23.3)	0.95 (0.74–1.22)	0.695	141 (29.2)	0.97 (0.82–1.14)	0.677	29 (25.2)	0.99 (0.83–1.18)	0.895
Low HDL[b]	334 (28.6)	1.06 (0.85–1.32)	0.621	147 (30.4)	1.00 (0.85–1.17)	0.975	59 (36.0)	0.91 (0.76–1.07)	0.253
High Triglyceride[c]	517 (44.2)	1.08 (0.89–1.32)	0.475	831 (71.0)	1.03 (0.90–1.19)	0.642	33 (27.3)	0.97 (0.83–1.13)	0.655
Hypertension[d]	1043 (89.2)	0.93 (0.66–1.30)	0.667	512 (91.3)	1.02 (0.82–1.30)	0.835	157 (80.1)	1.21 (0.94–1.55)	0.139
CHD-death, $n = 279$									
MetS	32 (11.5)	0.46 (0.20–1.03)	0.060	17 (14.2)	0.70 (0.41–1.21)	0.198	8 (21.1)	1.62 (1.02–2.59)	0.044
BMI >30	44 (15.8)	0.67 (0.40–1.18)	0.850	26 (21.7)	0.89 (0.59–1.34)	0.578	11 (29.0)	1.43 (1.01–2.03)	0.045
Elevated FPG[a]	70 (25.1)	1.08 (0.71–1.64)	0.725	31 (30.4)	1.04 (0.76–1.43)	0.792	9 (47.4)	1.04 (0.71–1.51)	0.847
Low HDL[b]	71 (25.4)	1.18 (0.69–2.02)	0.541	30 (29.4)	0.94 (0.70–1.26)	0.671	11 (29.0)	0.75 (0.51–1.08)	0.124
High Triglyceride[c]	124 (44.4)	0.85 (0.57–1.27)	0.437	210 (75.3)	0.96 (0.73–1.25)	0.739	8 (40.0)	1.15 (0.84–1.58)	0.388
Hypertension[d]	254 (91.0)	1.07 (0.55–2.10)	0.829	102 (86.4)	1.13 (0.71–1.79)	0.599	30 (81.1)	1.23 (0.69–2.20)	0.488
Stroke-death, $n = 130$									
MetS	10 (7.7)	0.21 (0.04–1.18)	0.076	5 (7.0)	0.34 (0.10–1.12)	0.076	1 (4.4)	0.76 (0.39–1.46)	0.409
BMI >30	11 (8.5)	0.10 (0.02–0.70)	0.020	6 (8.5)	0.20 (0.05–0.74)	0.016	2 (8.7)	0.58 (0.31–1.08)	0.086
Elevated FPG[a]	26 (20.0)	0.36 (0.14–0.93)	0.034	16 (25.4)	0.52 (0.26–1.00)	0.051	2 (14.3)	0.97 (0.62–1.53)	0.905
Low HDL[b]	36 (27.7)	1.18 (0.57–2.43)	0.652	21 (33.3)	1.08 (0.65–1.79)	0.759	12 (40.0)	0.97 (0.63–1.48)	0.874
High Triglyceride[c]	57 (43.9)	1.10 (0.56–2.19)	0.778	91 (70.0)	1.01 (0.63–1.62)	0.975	5 (35.7)	0.89 (0.60–1.33)	0.576
Hypertension[d]	121 (93.1)	10.38 (2.57–42.1)	0.001	67 (98.5)	6.15 (2.00–18.95)	0.002	18 (85.7)	2.58 (1.03–6.43)	0.042
Cancer-death, $n = 342$									
MetS	52 (15.2)	1.62 (1.01–2.62)	0.047	19 (12.2)	1.30 (0.94–1.81)	0.113	7 (7.6)	0.90 (0.57–1.44)	0.674
BMI >30	64 (18.7)	1.21 (0.77–1.92)	0.407	26 (16.7)	1.08 (0.79–1.47)	0.638	11 (20.8)	0.88 (0.60–1.30)	0.531
Elevated FPG[a]	87 (25.4)	0.98 (0.64–1.50)	0.929	38 (28.4)	1.02 (0.76–1.35)	0.914	5 (15.6)	1.08 (0.77–1.51)	0.668
Low HDL[b]	88 (25.7)	0.98 (0.67–1.43)	0.910	41 (30.4)	0.91 (0.70–1.19)	0.497	12 (28.6)	0.81 (0.58–1.13)	0.214
High Triglyceride[c]	161 (47.1)	1.70 (1.19–2.43)	0.004	239 (69.9)	1.34 (1.05–1.72)	0.017	8 (23.5)	0.91 (0.66–1.25)	0.564
Hypertension[d]	297 (86.8)	0.83 (0.48–1.43)	0.504	141 (91.6)	0.89 (0.62–1.29)	0.537	40 (75.5)	1.00 (0.63–1.57)	0.988

BMI: body mass index; CI: confidence interval; CHD: coronary heart disease; FPG: fasting plasma glucose; HR: hazard ratio; MetS: metabolic syndrome.

[a] Fasting plasma glucose ≥5.6 mmol/L, or previous diagnosis or specific treatment for type 2 diabetes.

[b] Serum HDL cholesterol <1.03 mmol/L in men and <1.29 mmol/L in women, or specific treatment for this lipid abnormality.

[c] Serum triglyceride level ≥1.7 mmol/L or specific treatment for this lipid abnormality.

[d] Systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, or treatment of previously diagnosed hypertension.

lower risk at 2 years as compared to longer term follow-up (Table 2).

After adjusting for age, sex, smoking status and pre-existing disease status at baseline, the association between MetS and CHD-death changed with time, with increased risk of CHD-death at 10-year, and reduced risk at 2- and 5-year (2-year: HR 0.46 [95% CI 0.20–1.03]; 5-year: HR 0.70 [95% CI 0.41–1.21]; 10-year: HR 1.62 [95% CI 1.02–2.59]. Conversely, MetS was associated with a notably higher risk of cancer death at 2-year, with diminished risk by 10-year (2-year: HR 1.62 [95% CI 1.01–2.62]; 5-year: HR 1.30 [95% CI 0.94–1.81]; 10-year: HR 0.90 [95% CI 0.57–1.44]). Among the 5 MetS components, high triglyceride also exhibited a time-dependent association with cancer death, where the elevation in risk of cancer death at 2-year had dissipated by the 10-year follow-up (Table 3). There was no evidence of effect of MetS on stroke-death, although hypertension was associated with an increased risk of stroke death, with the risk at 2-year, albeit with small numbers, being higher as compared to later time periods (Table 3).

3.3. *Time-dependent ROC*

We further sought to identify the individual and specific combinations of MetS components that best predicted all-cause and cause-specific mortality (Table 4). Among the 5 individual MetS components, triglyceride was the best single predictor of all-cause and cause-specific mortality (Table 4). For all-cause mortality, the best model comprised three components and included triglyceride, HDL-cholesterol and glucose. In the case of cause-specific mortality, the best model consisted of four components and were as follows: CHD-death: triglyceride, HDL-cholesterol, glucose and BP; Stroke-death: triglyceride, HDL-cholesterol, BMI and BP; Cancer-death: triglyceride, HDL-cholesterol, glucose and BMI. In the evaluation of all-cause and cause-specific mortality, there was significant improvement to the model fit as each new component was added to the more parsimonious preceding model (all $P < 0.05$), with no further improvement thereafter. The result indicates that when MetS components were

Table 4 – Time-dependent ROC curve, integrated discrimination improvement and net reclassification improvement for prediction of all-cause and cause-specific mortality.

	MetS component(s)	Model 1			Model 2		
		Integral AUC(t) (Harrell's, c)	IDI	NRI	Integral AUC(t) (Harrell's, c)	IDI	NRI
All-cause							
Best single component of MetS	T	0.5281	–	–	0.8207	–	–
Best 2 components of Mets	T + H	0.5399[b]	0.001	0.045	0.8210	<0.001	<0.001
Best 3 components of Mets	T + H + G	0.5458[b]	0.001	0.046	0.8215	<0.001	<0.001
Best 4 components of Mets	T + H + G + BP	0.5501	0.002[c]	0.048[c]	0.8217	<0.001	<0.001
5 components of Mets	T + H + G + BP + BMI	0.5531	0.000	0.000	0.8218	<0.001	<0.001
CHD-death							
Best single component of MetS	T	0.5275	–	–	0.8723	–	–
Best 2 components of Mets	T + H	0.5407[b]	0.004	0.025	0.8727	<0.001	<0.001
Best 3 components of Mets	T + H + G	0.5485[b]	0.004[c]	0.073[c]	0.8734	<0.001	<0.001
Best 4 components of Mets	T + H + G + BP	0.6340[a]	0.007[c]	0.100[c]	0.8756	<0.001	<0.001
5 components of Mets	T + H + G + BP + BMI	0.6351	0.000	0.000	0.8756	<0.001	<0.001
Stroke-death							
Best single component of MetS	T	0.5305	–	–	0.8886	–	–
Best 2 components of Mets	T + H	0.5435[a]	0.001	0.031	0.8920	<0.001	<0.001
Best 3 components of Mets	T + H + BMI	0.5602	0.002[c]	0.065	0.8925	<0.001	<0.001
Best 4 components of Mets	T + H + BMI + BP	0.5871[a]	0.003[c]	0.092[c]	0.8972	<0.001	<0.001
5 components of Mets	T + H + BMI + BP + G	0.6030	0.000	0.000	0.8972	<0.001	<0.001
Cancer-death							
Best single component of MetS	T	0.5300	–	–	0.8096	–	–
Best 2 components of Mets	T + H	0.5418[b]	0.001	0.010	0.8103	<0.001	<0.001
Best 3 components of Mets	T + H + G	0.5474[b]	0.004	0.052	0.8111	<0.001	<0.001
Best 4 components of Mets	T + H + G + BMI	0.6050[a]	0.006[c]	0.098[c]	0.8111	<0.001	<0.001
5 components of Mets	T + H + G + BMI + BP	0.6322	0.006[c]	0.105[c]	0.8111	<0.001	<0.001

AUC(t): time-dependent area under curve; IDI: integrated discrimination improvement; NRI: net reclassification improvement; BMI: body mass index; BP: blood pressure; CHD: coronary heart disease; G: glucose; H: HDL-cholesterol; MetS: metabolic syndrome; T: triglyceride.
Note: Model 1 without including age, sex, smoking status, pre-existing disease at baseline (namely, cancer, angina, acute myocardial infarction, stroke and chronic lung disease) and Model 2 included above covariates.
[a] $P < 0.05$.
[b] $P < 0.001$, for comparison of AUC(t) with the model immediately preceding.
[c] Confidence interval for IDI and NDI estimate was significant ($P < 0.05$).

combined, the AUC improved significantly (Model 1, Table 4). However, after adjusting for age, sex, smoking status and pre-existing disease status at baseline, none of these models were statistically enhanced as compared with the preceding model (Model 2, Table 4).

3.4. *Integrated Discrimination Improvement (IDI) and Net Reclassification Improvement (NRI)*

Improvement in mortality risk reclassification was numerically better in the 4-component model. The components included triglyceride, HDL-cholesterol, glucose and BP for all-cause and CHD-death, and triglyceride, HDL-cholesterol, BMI and BP for stroke-death. For cancer-death, the improvement in discrimination persisted in the 5-component model (Model 1, Table 4). Generally, the results of IDI and NRI suggested that combined MetS-components improved the discrimination of the model significantly (Model 1) ($P < 0.05$) in the prediction of all-cause and cause-specific mortality risk among the Australian elderly population. However, there was no improvement in the discrimination of death after including age, sex, pre-existing disease and smoking status (Model 2, Table 4).

4. Discussion

In this prospective cohort study of an Australian white population participating in the BMES, we found the following: First, MetS, exhibited a time-dependent association with all-cause, CHD and cancer deaths. Secondly, the AUC(t), IDI and NRI analyses showed that different MetS components were associated with different causes of death. Finally, the inclusion of age improved the model fitting substantially as compared to any single or combined MetS components.

To the best of our knowledge, this is the first study to have fully utilized the information of MetS recorded at baseline and all-follow-up visits to determine whether its relationship with mortality changes with time. Longitudinal studies that do not account for changes in exposure over time will not be able to distinguish between short and long term effects, and hence may result in less precise estimates of the exposure effect on outcomes [27].

In contrast to all-cause and CHD death, MetS was more likely to be associated with a greater increase in risk of early cancer death after 2 years, but this increased risk was attenuated over time. This is likely due to the loss in weight of cancer patients at end stage of cancers. Previous prospective

studies adopting different definitions of MetS at baseline with follow-up duration ranging between 7 and 14 years [13,16] have also found it to predict cancer death. MetS is a multifactorial condition and the mechanisms behind its associated increase in cancer mortality are not completely understood [16]. However, excess glucose has been shown to promote the formation of reactive oxygen species, which can promote cancer development [16]. Moreover, previous studies with follow-up duration ranging between 4.4 and 12.3 years, examining the relationship between baseline MetS and all-cause or CHD mortality, have reported inconsistencies in the relationship [5,7,8,11–15]. In studying whether mortality is associated with MetS, it is important to take into account the duration of follow-up and changes in the status of MetS over time.

When we considered only the information about MetS at baseline, without taking into account changes in MetS status at follow-up, we did not detect any effects of MetS on CHD and all-cause mortality even after adjustment for age, sex, smoking and pre-existing disease status (results not shown). Therefore, the time-varying effects of MetS on all-cause and cause-specific mortality would not have been detected if we had only utilized its baseline information. The results of this study underscore that the presence of MetS at longer term follow-up (e.g. 10-year) is more likely to confer a better prediction of all-cause and CHD death. Conversely, earlier status of MetS better predicted early cancer death at 2-year than current status of MetS. This argument is plausible, since people with cancer are more likely to lose their weight over time and as BMI is a mandatory component of MetS by definition, they would not be categorized as having MetS. However, the induction period between MetS components and the incidence of cancer which had been started years before cancer-death would be another main concern.

Interestingly, consistent with the increase in AUC(*t*), the result of IDI and NRI tests showed MetS and its components improved the performance of prediction of mortality. Triglyceride was the best single predictor of all-cause and cause-specific mortality in the elderly Australian population. BMI, a mandatory MetS component based on the IDF criteria, on its own was not as good a predictor. The findings that these risk factors clustered, thus leading to an increase in mortality risk may persuade physicians to treat their patients risk factors as a whole, rather than treating each risk factor on its own [35].

Another key finding of this study was that the model fit improved significantly after adjusting for age, with more than a 1.5-fold increase in AUC(*t*). This implied that age more than any of the MetS components was the single most important predictor of death in the elderly, and thus should be appropriately accounted for in the analysis.

While this study has its strength such as a representative elderly Australian population, high quality data collection, long-term follow-up, full utilization of MetS information at each visit, and low likelihood of misclassification error due to high specificity and sensitivity of death registration, its drawbacks must also be noted. First, the limited events for stroke mortality suggest reduced statistical power when evaluating this outcome in relation to time-dependent MetS. Second, the prevalence of MetS at baseline (12.4%), 5-year (16.1%) and 10-year (12.1%) in this study was notably lower than that reported by the Cardiovascular Health Study in USA (28%) [17] and in other Australian study (23%) [36]. These differences could be due to differences in age structure and composition of the populations under study. In the former, US adults aged ≥65 years without CVD at baseline were included [36], while individuals aged ≥18 years were recruited in the latter [17].

In conclusion, the time-dependent association between MetS and all-cause, CHD- as well as cancer death underscores the importance of fully accounting for the information about MetS collected at each follow-up in order to better predict all-cause and major causes of death among the elderly. Hence, time-dependent models may be clinically more relevant, as they simulate the real clinical scenarios on changes in MetS and its components over time, in which physicians better evaluate and manage the elderly.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

The Blue Mountains Eye Study was supported by the Australian National Health and Medical Research Council [Grant Nos. 974159, 991407, 211069].

The authors are indebted to Ms Ava Grace Tan and Dr Erdahl Teber from Centre for Vision Research Westmead Millennium, Institute University of Sydney, Australia for helping us to access the data base of the Blue Mountains Eye Study.

H.G.M. researched, analyzed and wrote the manuscript. B.C.T. critically reviewed, edited and advised on the statistical analysis and writing of manuscript. T.Y.W., E.S.T., J.J.W. and P.M. reviewed, edited and contributed to the discussion of the manuscript, while, J.L. reviewed/edited the statistical analysis and results sections.

REFERENCES

[1] Alberti KGMM, Zimmet P, Shaw J, Diabetes UK. Metabolic syndrome- a new world-wide definition. A consensus statement from the International Diabetes Federation. Diabet Med 2006;23:469–80.

[2] Zimmet P, Magliano D, Matsuzawa Y, Alberti G, Shaw J. The metabolic syndrome: a global public health problem and a new definition. J Atheroscler Thromb 2005;12:295–300.

[3] Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA 2002;288:2709–16.

[4] Hunt KJ, Resendez RG, Williams K, Haffner SM, Stern MP, San Antonio Hearth Study. National Cholesterol Education Program versus World Health Organization metabolic syndrome in relation to all-cause and cardiovascular mortality in the San Antonio Heart Study. Circulation 2004;110:1251–7.

[5] Hu G, Qiao Q, Tuomilehto J, Balkau B, Borch-Johnsen K, Pyorala K, DECODE Study Group. Prevalence of the metabolic syndrome and its relation to all-cause and cardiovascular mortality in nondiabetic European men and women. Arch Intern Med 2004;164:1066–76.
[6] Flegal KM, Graubard BI, Williamson DF, Gail MH. Excess deaths associated with underweight, overweight, and obesity. JAMA 2005;293:1861–7.
[7] Berrington de Gonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis RJ, et al. Body-mass index and mortality among 1.46 million white adults. N Engl J Med 2010;363:2111–9.
[8] Fried LP, Kronmal RA, Newman AB, Bild DE, Mittelmark MB, Polak JF, et al. Risk factors for 5-year mortality in older adults: the Cardiovascular Health Study. JAMA 1998;279:585–92.
[9] Burke GL, Arnold AM, Bild DE, Cushman M, Fried LP, Newman A, et al. Factors associated with healthy aging: the cardiovascular health study. J Am Geriatr Soc 2001;49:254–62.
[10] Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation 1998;97:1837–47.
[11] Zambon S, Zanoni S, Romanato G, Corti MC, Noale M, Sartori L, et al. Metabolic syndrome and all-cause and cardiovascular mortality in an Italian elderly population. The Progetto Veneto Anziani Study. Diabetes Care 2009;32:153–9.
[12] Saito I, Iso H, Kokubo Y, Inoue M, Tsugane S. Metabolic syndrome and all-cause and cardiovascular disease mortality Japan Public Health Center-Based Prospective (JPHC). Study Circ J 2009;73:878–84.
[13] Akbaraly TN, Kivimaki M, Ancelin ML, Barberger-Gateau P, Mura T, Tzourio C, et al. Metabolic syndrome, its components, and mortality in the elderly. J Clin Endocrinol Metab 2010;95:E327–32.
[14] Salminen M, Kuoppamäki M, Vahlberg T, Räihä I, Irjala K, Kivelä SL. The metabolic syndrome defined by modified International Diabetes Federation criteria and mortality: a 9-year follow-up of the aged in Finland. Diabetes Metab 2010;36:437–42.
[15] Sidorenkov O, Nilssen O, Grjibovski AM. Metabolic syndrome in Russian adults: associated factors and mortality from cardiovascular diseases and all causes. BMC Public Health 2010;10:582.
[16] Jaggers JR, Sui X, Hooker SP, LaMonte MJ, Matthews CE, Hand GA, et al. Metabolic syndrome and risk of cancer mortality in men. Eur J Cancer 2009;5:1831–8.
[17] Mozaffarian D, Kamineni A, Prineas RJ, Siscovick DS. Metabolic syndrome and mortality in older adults: the Cardiovascular Health Study. Arch Intern Med 2008;168:969–78.
[18] Maggi S, Noale M, Gallina P, Bianchi D, Marzari C, Limongi F, et al. Metabolic syndrome, diabetes and cardiovascular disease in an elderly Caucasian cohort: the Italian Longitudinal Study of Aging. J Gerontol A Biol Sci Med Sci 2006;61:505–10.
[19] Franks PW, Olsson T. Metabolic syndrome and early death: getting to the heart of the problem. Hypertension 2007;49:10–2.
[20] Dekker JM, Girman C, Rhodes T, Nijpels G, Stehouwer CD, Bouter LM, et al. Metabolic syndrome and 10-year cardiovascular disease risk in the Hoorn Study. Circulation 2005;112:666–73.
[21] Mitchell P, Smith W, Wang JJ, Cumming RG, Leeder SR, Burnett L. Diabetes in an older Australian population. Diabetes Res Clin Pract 1998;41:177–84.
[22] 2003 World Health Organization (WHO)/International society of hypertension (ISH) statement on management of hypertension. J Hypertens 2003;21:1983-1992.
[23] Cugati S, Wang JJ, Rochtchina E, Mitchell P. Ten-year incidence of diabetes in older Australians: the Blue Mountains Eye Study. Med J Aust 2007;186:131–5.
[24] World Health Organization. Definition, Diagnosis and Classification of Diabetes Mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Geneva: WHO, 1999.
[25] Bosevski M, Pemovska G, Bosevska G, Georgievska-Ismail L. Clinical role of estimation metabolic syndrome's components in type 2 diabetic population with symptomatic coronary artery disease—a comparison of two criteria. Med Arh 2010;64:144–6.
[26] Magliano D, Liew D, Pater H, Kirby A, Hunt D, Simes J, et al. Accuracy of the Australian National Death Index: comparison with adjudicated fatal outcomes among Australian participants in the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study. Aust N Z J Public Health 2003;27:649–53.
[27] Collett D. Modelling survival data in medical research, 2nd ed., Chapman & Hall; 2003.
[28] Tai BC, Wee J, Machin D. Analysis and design of randomised clinical trials involving competing risks outcomes. Trials 2011;12:127.
[29] Chambless LE, Diao G. Estimation of time-dependent area under the ROC curve for long-term risk prediction. Stat Med 2006;25:3474–86.
[30] Harrell Jr FE, Califf RM, Pryor DB, Lee KL, Rosati RA. Evaluating the yield of medical tests. JAMA 1982;247:2543–6.
[31] Harrell Jr FE, Lee KL, Califf RM, Pryor DB, Rosati RA. Regression modelling strategies for improved prognostic prediction. Stat Med 1984;3:143–52.
[32] Pencina MJ, D'Agostino Sr RB, D'Agostino Jr RB, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27:157–72.
[33] http://www.bepress.com/harvardbiostat/paper107Yates. Comparing risk scoring systems beyond the ROC paradigm in survival analysis. Harvard University Biostatistics Working Paper Series. Working paper 107.
[34] Kerr KF, McClelland RL, Brown ER, Lumley T. Evaluating the incremental value of new biomarkers with integrated discrimination improvement. Am J Epidemiol 2011;174:364–74.
[35] Wilken T. The metabolic syndrome, babies and bathwater. Diabetologia 2005;49:421–2.
[36] Adams RJ, Appleton S, Wilson DH, Taylor AW, Dal Grande E, Chittleborough C, et al. Population comparison of two clinical approaches to the metabolic syndrome: implications of the new International Diabetes Federation consensus definition. Diabetes Care 2005;28:2777–9.

Metabolic Syndrome and Risk of Age-Related Cataract over Time: An Analysis of Interval-Censored Data Using a Random-Effects Model

Haleh Ghaem Maralani,[1,2] *Bee Choo Tai,*[1,3] *Tien Y. Wong,*[4–6] *E. Shyong Tai,*[7] *Jialiang Li,*[8] *Jie Jin Wang,*[6,9] *and Paul Mitchell*[9]

Purpose. To investigate whether the effect of metabolic syndrome (MetS) and its components on the incidence of different cataract subtypes (cortical, nuclear, and posterior subcapsular cataract [PSC]) change with time.

Methods. A prospective cohort of persons 49 years of age and older were followed over 10 years in the Blue Mountains Eye Study, west of Sydney, Australia. MetS components as defined by the International Diabetes Federation criteria were measured at baseline (1992–1994), after 5 years (1997–1999), and after 10 years (2002–2004). The incidence of different cataract subtypes was obtained from standard photographic grading at these intervals (n = 1997). Using a random-effects complementary log–log regression model with time to cataract development in discrete time interval, we estimated the effect of MetS and its components on the incidence of different cataract subtypes at different time intervals.

Results. After accounting for changes in MetS components over time and controlling for possible confounders, MetS was found to be associated with an increased 5-year incidence of cortical cataract (hazard ratio [HR] 1.48; 95% confidence interval [CI], 1.05–2.09) and PSC cataract (HR 1.75; 95% CI, 1.01–3.04). Among the five MetS components, high glucose and obesity predicted an increased 5-year incidence of cortical cataract. In addition, low high-density lipoprotein and high glucose were associated with an increased 10-year incidence of cortical and PSC cataracts, respectively.

Conclusions. Changes in MetS predicted the 5-year incidence of cortical and PSC cataracts. Different MetS components predicted the incidence of cortical and PSC cataracts at varying time intervals. (*Invest Ophthalmol Vis Sci.* 2013; 54:641–646) DOI:10.1167/iovs.12-10980

Age-related cataract is a leading cause of blindness and poor vision and a major public health concern globally.[1] Metabolic syndrome (MetS) represents a cluster of these metabolic abnormalities involving central obesity, dyslipidemia, hyperglycemia, and high blood pressure (BP).[2] A few studies have investigated the association between cataract and MetS, and whether some individual components are more important risk factors than others for specific cataract subtypes. The Blue Mountains Eye Study (BMES) previously examined baseline MetS with glucose as a mandatory component based on the World Health Organization (WHO) criteria, in relation to 10-year cumulative incidence of the three principal cataract subtypes (i.e., cortical, nuclear, and posterior subcapsular [PSC]) and showed that MetS was associated with an increased risk of all three cataract subtypes.[3] A recent cross-sectional study in Singapore confirmed the relation between baseline MetS, defined by the Third Report of the National Cholesterol Education Program Adult Treatment Panel (ATP-3) and cortical cataract, but not between MetS and either nuclear or PSC cataracts.[4] Other studies have reported that baseline body mass index (BMI), high BP, or diabetes[3,4] is associated with age-related cataracts, whereas elevated serum triglyceride (TG) was a predictor of cataracts among females in another study.[5]

However, there are a number of unanswered questions. First, previous studies used different definitions for MetS, that is, European Group for the Study of Insulin Resistance (EGIR), WHO, and ATP-3, and it has been reported that these definitions were not as successful in predicting diabetes, cardiovascular disease, and other health outcomes.[6–9] Thus, in this study, we define MetS based on the International Diabetes Federation (IDF)[10] criteria. This is a diagnostic tool for both research purposes and clinical practice, which can be used relatively easily in any country by any physician to identify patients at increased risk of developing health-related outcomes.[2] Moreover, previous studies suggested that IDF provides more reliable criteria for diagnosing MetS in a predictive model for coronary clinical status in type 2 diabetes populations.[11,12] Second, previous studies, including an earlier report of BMES,[3] used only MetS data at baseline in the evaluation of its relationship with cataracts. However, experimental studies in rats and humans have shown that the effect

From the [1]Saw Swee Hock School of Public Health, National University of Singapore and National University Health System, Singapore; the [2]Department of Epidemiology, School of Health and Nutrition, Shiraz University of Medical Sciences, Shiraz, Iran; the [3]Yong Loo Lin School of Medicine, National University of Singapore and National University Health System, Singapore; the [4]Singapore Eye Research Institute, Singapore National Eye Centre, Singapore; the Departments of [5]Ophthalmology and [7]Medicine, Yong Loo Lin School of Medicine, National University of Singapore and National University Health System, Singapore; the [6]Centre for Eye Research Australia, University of Melbourne, Royal Victorian Eye and Ear Hospital, East Melbourne, Victoria, Australia; the [8]Department of Statistics and Applied Probability, National University of Singapore, Singapore; and the [9]Centre for Vision Research, University of Sydney, Sydney, Australia.

The Blue Mountains Eye Study was supported by Australian National Health and Medical Research Council Grants 974159, 991407, and 211069.

Submitted for publication September 17, 2012; revised December 8, 2012; accepted December 14, 2012.

Disclosure: **H. Ghaem Maralani**, None; **B.C. Tai**, None; **T.Y. Wong**, None; **E.S. Tai**, None; **J. Li**, None; **J.J. Wang**, None; **P. Mitchell**, None

Corresponding author: Bee Choo Tai, Saw Swee Hock School of Public Health, National University of Singapore and National University Health System, 16 Medical Drive (MD3), Singapore 117597; ephtbc@nus.edu.sg.

of glucose and lipid abnormalities on cataract formation may change over time[12,13]; therefore, this underscores the importance of collecting further information on glucose and lipid abnormalities beyond baseline measurements to better detect cataract formation.

To our best knowledge, this is the first study to have fully utilized the information on MetS and its components that were collected not only at baseline but also at subsequent follow-up visits (i.e., after 5 and 10 years) to examine the risk of different cataract subtypes. Further, since the outcome, different cataract subtypes, was measured in a discrete time interval, we implement the random-effect complementary log–log regression since it may be more appropriate for detecting stronger and more robust relationships[14,15] between individual MetS components, than the logistic regression as used in previous studies. Thus, to evaluate the effect of MetS and its components on the incidence of different age-related cataract subtypes (i.e., cortical, nuclear, and PSC) more precisely, and to determine whether these associations changed with time, we utilized full information that was collected at each follow-up and implemented appropriate statistical models to better describe the relationships.

Methods

Study Design and Participants

The BMES is a population-based prospective cohort study of vision, common eye diseases, and other health outcomes in a suburban Australian population west of Sydney, Australia.[16] Between 1992 and 1994, noninstitutionalized permanent residents 49 years of age and older were invited to participate, and were requested to return for follow-up examinations after 5 (1997–1999) and 10 years (2002–2004). The recruitment details have been described elsewhere.[3,16,17]

The BMES, approved by the Human Research Ethics Committee of the University of Sydney, was conducted according to the Declaration of Helsinki. Written informed consent was obtained from all participants at each examination.[16] At each visit, trained interviewers completed a comprehensive questionnaire comprising demographic information, eye, and general medical history, including hypertension, diabetes, and preexisting diseases (i.e., angina, acute myocardial infarction [AMI], and stroke), as well as medication used. Height, weight, and seated BP[18] were measured. Fasting pathology tests, including high-density lipoprotein (HDL) cholesterol, TG,[19] and fasting blood sugar (FBS),[20] were also measured within 2 months of each interview. In addition, information on smoking (never, former, and current smoker) and alcohol intake were collected. Moreover, history of eye diseases including cataract, age-related macular degeneration (AMD), myopia, glaucoma, as well as family history of eye disease or blindness were obtained and recorded.[3] Eye iris color and skin sun-tanning characteristics were also estimated on a 4-point scale (always burn, never tan; usually burn, tan with difficulty; burn and tan above average; rarely burn, tan above average).[21]

Cataract Grading

Detailed cataract grading was performed according to definitions described previously.[3] Briefly, the population at risk for cataract comprised participants who had at least one follow-up visit, but whose lens photographs were retrospectively shown not to show signs of cataract at baseline. They also had complete information to define MetS at baseline. Different subtypes of cataract were determined using standard photographic grading at each of the three examinations. The Wisconsin Cataract Grading System was used to perform masked grading of the lens photographs. A 5-point scale was used to assess the presence and severity of nuclear cataract. Nuclear cataract was defined as nuclear opacity worse than standard 3. The extent of cortical or PSC cataract was determined by estimating the lens area involved in segments of a circular grid overlaying the photographs. Cortical opacity involving at least 5% of the total lens area or the presence of any PSC opacity was used to define the presence of the respective cataract subtypes.[3] Thus, distinct types of cataract were categorized and analyzed independently.

Definition of Metabolic Syndrome

Metabolic syndrome was defined according to IDF criteria[22] as obesity (BMI > 30 kg/m^2) plus any two of the following four factors: serum TG level ≥ 1.7 mM or specific treatment for this lipid abnormality; serum HDL cholesterol < 1.03 mM in males and <1.29 mM in females, or specific treatment for this lipid abnormality; systolic BP ≥ 130 mm Hg or diastolic BP ≥ 85 mm Hg, or treatment of previously diagnosed hypertension; or fasting plasma glucose ≥ 5.6 mM, or previously diagnosed type 2 diabetes.

In this study, the baseline MetS components were measured and recorded when the participant entered the study, and again at the 5- and 10-year examinations after first recruitment. Data are therefore available on how MetS and its components change in each subject throughout the study.

Statistical Analysis

The χ^2 test and independent sample t-test were used to determine the relationship between categorical and continuous covariates included in this study and the 10-year cumulative incidence of cataract, respectively.

Because an individual's MetS status as well as cataract status were prospectively evaluated at predefined time intervals (i.e., baseline, 5-year, and 10-year), the exact time that cataract—the outcome of interest—developed was therefore not known. Such information was interval censored, and thus the effect of 10-year changes in MetS and its components on the incidence of each cataract subtype was modeled using a random-effects complementary log–log regression model.[14,15] This statistical technique is readily available for survival analysis with discrete time and is one of the most frequently used discrete-time hazard functions.[23] In this study, the outcomes of interest, that is, time to development of different cataract subtypes, were included in the model based on discrete time intervals (i.e., 0–5 years or 5–10 years), in accordance with the follow-up schedule. This approach includes indicator variables for the examination time interval (0–5 and 5–10 years) as covariates.[14,15,24,25] The random-effects model accounts for possible intrasubject correlation in the assessment of MetS and its components, which were repeatedly measured at baseline, 5 years, and 10 years. Of note, when the dichotomous outcome is rare, the complementary log–log regression is more appropriate. However, Nelder (2001)[26] and Hardin and Hilbe (2007)[27] have suggested that when a binary outcome is common, the complementary log–log regression model may also fit the data well.

Age, sex, smoking, preexisting disease (i.e., angina, AMI, and stroke), family history of eye disease (i.e., cataract, AMD, myopia, glaucoma, and blindness), history of eye disease (i.e., AMD, myopia, and glaucoma), eye iris color, and skin sun-tanning characteristics were considered as possible confounders in the model building. Furthermore, we included interactions between MetS (as well as its components) and the time interval to evaluate whether its relationship with the different cataract subtypes varied according to time interval (i.e., 5- and 10-years).[24,25] We further explored possible interaction between age and sex with MetS and its components. It should be noted that for each cataract subtype, the control group included participants without the same cataract subtype. All statistical evaluations were made assuming a two-sided test based on a 5% level of significance (STATA, version 11; StataCorp, College Station, TX).

Table 1. Baseline Characteristics of Study Population according to 10-Year Cumulative Incidence of Age-Related Cataract

Characteristic	Total $n = 1997$	No Cataract $n = 1140$	Cataract $n = 857$	*P* Value
Baseline mean age (SD)	63.9 (8.3)	62.3 (8.3)	65.9 (7.8)	<0.0001
Sex (%)				
Male	844 (42.3)	517 (45.3)	327 (38.2)	0.001
Female	1153 (57.7)	623 (54.7)	530 (61.8)	
Family history of blindness (%)	83 (4.2)	39 (3.4)	44 (5.1)	0.058
Family history of any eye disease (%)*	643 (32.2)	366 (32.1)	277 (32.3)	0.918
History of any eye disease at baseline (%)†	400 (20.0)	221 (19.4)	179 (20.9)	0.407
Preexisting disease (%)‡	308 (15.4)	161 (14.1)	147 (17.2)	0.064
Smoking status (%)				
Nonsmoker	1046 (52.4)	601 (52.7)	445 (51.9)	0.416
Ex-smoker	698 (34.9)	387 (33.9)	311 (36.3)	
Current smoker	253 (12.7)	152 (13.3)	101 (11.8)	
Eye iris color (%)				
Blue	978 (49.0)	565 (49.5)	413 (48.2)	0.897
Hazel/green	572 (28.6)	323 (28.3)	249 (29.0)	
Tan/brown	251 (12.6)	144 (12.6)	107 (12.5)	
Dark brown	196 (9.8)	108 (9.5)	88 (10.3)	
Sun skin-burned (%)				
Always burn, never tan	271 (13.6)	152 (13.3)	119 (13.9)	0.927
Usually burn, tan with difficulty	496 (24.8)	288 (25.3)	208 (24.2)	
Burn and tan above average	784 (39.3)	448 (39.4)	336 (39.2)	
Rarely burn, tan above average	446 (22.3)	251 (22.0)	194 (22.7)	
MetS (%)	246 (12.3)	119 (10.4)	127 (14.8)	0.004
BMI > 30 (%)	346 (17.3)	173 (15.2)	173 (20.2)	0.004
High glucose (%)§	306 (15.3)	149 (13.1)	157 (18.3)	0.001
Low-HDL (%)‖	591 (29.6)	318 (27.9)	273 (31.9)	0.055
High TG (%)¶	815 (40.8)	461 (40.4)	354 (41.3)	0.713
High BP (%)#	1689 (84.6)	941 (82.5)	748 (87.3)	0.004

* Includes family history of cataracts, glaucoma, macular, and blindness.
† Includes history of age-related macular degeneration, myopia, and glaucoma at baseline.
‡ Includes history of angina, stroke, and acute myocardial infarction at baseline.
§ Fasting plasma glucose ≥ 5.6 mM, or previous diagnosis or specific treatment for type 2 diabetes.
‖ Serum HDL cholesterol < 1.03 mM in males and <1.29 mM in females, or specific treatment for this lipid abnormality.
¶ Serum TG level ≥ 1.7 mM or specific treatment for this lipid abnormality.
# Systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 mm Hg, or treatment of previously diagnosed hypertension.

Results

Description of Study Population

A total of 1997 subjects with complete information for the study factors at baseline contributed to the analysis of age-related cataract. Of these, 1820 individuals contributed information for the analysis of cortical cataract, 1357 for nuclear cataract, and 1962 for PSC cataract. Table 1 presents the baseline characteristics for the study subjects according to the cumulative incidence of cataract at 10 years. Over the 10-year follow-up, 857 persons (42.9%) with incident cataract were detected. Of these, 455 (25.0%) were cortical cataract, 436 (32.1%) were nuclear cataract, and 135 (6.9%) were PSC cataract. Of the 455 persons with incident cortical cataract, 252 (53.2%) had more than 5% and less than 10% severity and 213 (46.8%) had 10% or more severity in the worse eye. Of the 135 persons with incident PSC cataract, 104 (77.0%) had less than 5% severity and 31 (23.0%) had 5% or more severity in the worse eye. The mean age of participants was 63.9 years (standard deviation [SD], 8.3) with a female predominance (57.7%). Table 2 shows the changes in MetS and its components over the 10-year study follow-up. Of those included in the analysis, prevalent MetS increased slightly to 16.6% (95% confidence interval [CI], 14.9%–18.3%) after 5 years follow-up from 12.3% (95% CI, 10.9%–13.8%) at baseline, and was 12.8% (95% CI, 11.1%–14.6%) after 10 years (Table 2).

The Figure shows the changes in MetS and its components at baseline, 5-year, and 10-year follow-up among individuals with different cataract subtypes. Generally, a lower proportion of individuals with nuclear cataract had MetS or its components as compared with cortical or PSC cataract. MetS increased from baseline to 5-year follow-up

Table 2. Changes in MetS and Its Components over 10-Year Follow-Up

Factor	Baseline $n = 1997$	At 5 Years $n = 1926$	At 10 Years $n = 1463$
MetS (%)	246 (12.3)	319 (16.6)	187 (12.8)
BMI > 30 (%)	346 (17.3)	447 (23.2)	344 (23.5)
High glucose (%)*	306 (15.3)	404 (23.4)	198 (18.5)
Low-HDL (%)†	591 (29.6)	484 (28.0)	418 (32.1)
High TG (%)‡	815 (40.8)	789 (39.5)	300 (27.3)
High BP (%)§	1689 (84.6)	1750 (91.3)	1183 (82.6)

* Fasting plasma glucose ≥ 5.6 mM, or previous diagnosis or specific treatment for type 2 diabetes.
† Serum HDL cholesterol < 1.03 mM in males and <1.29 mM in females, or specific treatment for this lipid abnormality.
‡ Serum TG level ≥ 1.7 mM or specific treatment for this lipid abnormality.
§ Systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 mm Hg, or treatment of previously diagnosed hypertension.

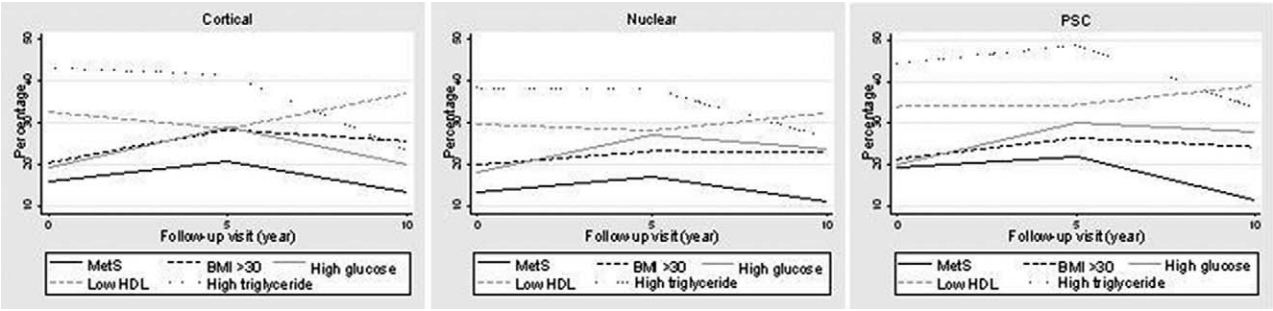


Figure. Changes in metabolic syndrome and its components at baseline, 5-year, and 10-year follow-up among individuals with cortical, nuclear, and PSC cataract.

and decreased by 10-year follow-up among all three subtypes of cataract.

MetS and Its Components and the Incidence of Age-Related Cataract

We found MetS (hazard ratio [HR] 1.48; 95% CI, 1.05–2.09), BMI > 30 (HR 1.59; 95% CI, 1.16–2.17), and elevated glucose (HR 1.60; 95% CI, 1.15–2.23) to be associated with increased 5-year incidence of cortical cataract, whereas low-HDL cholesterol (HR 1.57; 95% CI, 1.10–2.24) was associated with an excess in incidence of cortical cataract at 10-year follow-up (Table 3).

However, there was no association between MetS or any of its components with the incidence of nuclear cataract at either 5 or 10 years, even after accounting for information on MetS and its components at baseline and follow-up visits as well as controlling for confounders.

Conversely, MetS was associated with an increase in 5-year incidence of PSC cataract (HR 1.75; 95% CI, 1.01–3.04), whereas elevated glucose was associated with an increase in 10-year incidence of PSC cataract (HR 1.90; 95% CI, 1.01–3.61) (Table 3).

Discussion

In this prospective cohort study of an Australian white population participating in the BMES, we found the following: First, after accounting for baseline and further follow-up information on MetS and its components as defined by the IDF criteria, MetS, elevated glucose, and BMI levels >30 contributed to an increase in 5-year incidence of cortical cataract, whereas low-HDL cholesterol was linked to an increase in 10-year incidence of cortical cataract. Second, MetS and elevated glucose were positively associated with the incidence of PSC cataract at 5- and 10-year follow-up, respectively.

The association between elevated glucose and incidence of cortical and PSC cataract at different time intervals suggests that FBS levels best predicted late incidence of PSC cataract and early incidence of cortical cataract. Mechanisms connecting hyperglycemia with cataract include advanced glycation of lens proteins,[28] hyperosmotic effects of sorbitol on lens fibers via the aldose reductase pathway,[29] with induction of apoptosis in lens epithelial cells leading to the development of cataract.[30]

Additionally, our study demonstrated that BMI levels >30 predicted the 5-year incidence of cortical cataract, suggesting

Table 3. 10-Year Changes in MetS and Its Components on the Incidence of Age-Related Cataract

	Cortical		Nuclear		PSC	
Factor	**HR (95% CI)***	***P* Value**	**HR (95% CI)***	***P* Value**	**HR (95% CI)***	***P* Value**
Incidence at 5 years						
MetS	1.48 (1.05–2.09)	0.025	1.01 (0.75–1.36)	0.941	1.75 (1.01–3.04)	0.045
BMI > 30	1.59 (1.16–2.17)	0.004	0.84 (0.64–1.10)	0.210	1.30 (0.76–2.20)	0.337
High glucose†	1.60 (1.15–2.23)	0.006	1.13 (0.87–1.56)	0.372	1.59 (0.93–2.72)	0.091
Low-HDL‡	1.14 (0.82–1.58)	0.437	0.94 (0.73–1.22)	0.667	1.43 (0.84–2.45)	0.186
High TG§	1.09 (0.82–1.44)	0.570	0.98 (0.78–1.23)	0.874	1.44 (0.90–2.32)	0.129
High BP‖	1.12 (0.67–1.89)	0.659	1.08 (0.70–1.68)	0.720	1.10 (0.44–2.74)	0.840
Incidence at 10 years						
MetS	1.40 (0.88–2.20)	0.151	0.93 (0.54–1.61)	0.802	1.39 (0.70–2.76)	0.347
BMI > 30	1.44 (1.00–2.09)	0.051	1.24 (0.84–1.86)	0.286	1.52 (0.89–2.60)	0.127
High glucose†	1.24 (0.79–1.97)	0.349	1.30 (0.81–2.08)	0.279	1.90 (1.01–3.61)	0.048
Low-HDL‡	1.57 (1.10–2.24)	0.013	1.03 (0.69–1.54)	0.870	1.45 (0.85–2.46)	0.169
High TG§	0.76 (0.49–1.16)	0.201	0.97 (0.63–1.51)	0.903	1.50 (0.81–2.76)	0.197
High BP‖	0.96 (0.63–1.47)	0.861	1.27 (0.75–2.15)	0.378	1.11 (0.56–2.19)	0.764

* Adjusted for age, sex, eye disease at baseline (i.e., myopia, macular, and glaucoma), preexisting disease at baseline (i.e., acute myocardial infarction, angina, and stroke), and family history of blindness.

† Fasting plasma glucose ≥ 5.6 mM, or previous diagnosis or specific treatment for type 2 diabetes.

‡ Serum HDL cholesterol < 1.03 mM in males and <1.29 mM in females, or specific treatment for this lipid abnormality.

§ Serum TG level ≥ 1.7 mM or specific treatment for this lipid abnormality.

‖ Systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 mm Hg, or treatment of previously diagnosed hypertension.

that the contribution of obesity to cortical cataract formation may reduce over time. In the Singapore Malay Eye Study and another study by Lim et al.,[31] baseline BMI levels have been shown to contribute to a higher risk of cortical cataract[4] and PSC cataract.[31] The underlying mechanism behind the relationship between obesity and cataract is unclear.[32] To date, there has not been any study that examined how changes in BMI over time would affect cataract formation. However, it has been suggested that obesity was related to cataract by its associated complications such as diabetes, glucose intolerance, insulin resistance, and hyperlipidemia.[32] Moreover, it has been shown that the relationship between glucose and cholesterol with cataract formation changed over time.[12,13] Therefore, this may partly explain why the relationship between obesity and incidence of cataract may also change with time.

Moreover, our finding has shown an association between low-HDL cholesterol and an excess in 10-year incidence of cortical cataract, suggesting that it takes a longer observation time for low-HDL cholesterol to be confirmed as a predictor of cortical cataract. A previous BMES report, which considered only baseline information using logistic regression,[3] failed to detect such a relationship. This finding thus suggests the importance of full utilization of baseline and follow-up data, to better describe the discrete time to development of cataract using a complementary log–log model. Studies have suggested that inflammation and oxidative stress resulting from low-HDL cholesterol levels might contribute to cataract formation.[33–35]

Finally, as a specific entity, our finding demonstrated a positive association between MetS and 5-year incidence of cortical and PSC cataracts. In particular, MetS as a whole rather than its individual components, best predicted PSC cataract at 5 years. Interestingly, when we considered only the effect of MetS components at baseline (data not shown) without accounting for its changing status at follow-up, we did not detect any effects of BMI or low-HDL cholesterol on cortical cataract, even after adjusting for age, sex, eye diseases, and preexisting disease status. Therefore, the effects of MetS and its components on the incidence of cortical cataract at different time intervals would not have been detected if we had only utilized the baseline data.

However, based on a previous report of BMES,[3] MetS as defined by the WHO criteria, was a predictor of nuclear cataract, whereas our study did not confirm this association. We did an analysis of the data based on MetS defined by WHO criteria, which was used by a previous report of BMES. Using a complementary log–log regression model, the results of MetS defined by the IDF and WHO criteria were the same for nuclear cataract (result not shown). Therefore, this difference may be due to differences in technique and sample size. Moreover, obesity has been shown to have a different pattern in its relation with nuclear cataract, with a lower BMI level being an independent risk factor for nuclear cataract.[32] This suggests the possibility of distinct etiologic pathways for different cataract subtypes.[32] Since obesity was a mandatory component in defining MetS in our study, this may partially explain why there was no effect of MetS on nuclear cataract.

The strengths of this study include (1) its representative elderly Australian population, (2) high-quality data collection, (3) population-based study of long-term incidence of cataract, (3) full use of MetS data at each visit, (4) applying a random-effects complementary log–log regression model that can detect stronger and more robust relationships[14,15] between individual MetS components and cataract subtypes where occurrences are measured in discrete time interval, and (5) cataract diagnosis based on standardized lens photographic grading, which has been shown to have high reproducibility.[17,36] However, some drawbacks should also be noted. Statistical significance was not achieved for the relationship between MetS components and PSC cataract, mainly because of the lack of statistical power due to the limited number of PSC cases. This warrants further investigation in studies with more PSC cases.

In conclusion, changes in MetS predicted the 5-year incidence of cortical and PSC cataract. Different MetS components predicted the incidence of cortical and PSC cataracts at varying time intervals. This underscores the importance of fully accounting for the data on MetS components collected at each follow-up visit for physicians to better predict the risk of different cataract subtypes in older persons at varying time intervals.

Acknowledgments

The authors thank Elena Rochtchina, Ava Grace Tan, and Erdahl Teber (Centre for Vision Research Westmead Millennium, Institute University of Sydney, Australia) for helping us access the database of the Blue Mountains Eye Study.

References

1. Attebo K, Mitchell P, Smith W. Visual acuity and the causes of visual loss in Australia. The Blue Mountains Eye Study. *Ophthalmology*. 1996;103:357–364.
2. Alberti KGMM, Zimmet P, Shaw J. Metabolic syndrome–a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabet Med*. 2006;23:469–480.
3. Tan JS, Wang JJ, Mitchell P. Influence of diabetes and cardiovascular disease on the long-term incidence of cataract: the Blue Mountains eye study. *Ophthalmic Epidemiol*. 2008; 15:317–327.
4. Sabanayagam C, Wang JJ, Mitchell P, et al. Metabolic syndrome components and age-related cataract: the Singapore Malay eye study. *Invest Ophthalmol Vis Sci*. 2011;52:2397–2404.
5. Bojarskiene F, Cerniauskiene LR, Paunksnis A, Luksiene DI. Association of metabolic syndrome components with cataract [in Lithuanian]. *Medicina (Kaunas)*. 2006;42:115–122.
6. World Health Organization (WHO). *Definition, Diagnosis and Classification of Diabetes Mellitus and Its Complications*. Report of a WHO consultation. Geneva: WHO; 1999.
7. Balkau B, Charles MA. Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR). *Diabet Med*. 1999;16:442–443.
8. Executive Summary of the Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA*. 2001;285: 2486–2497.
9. Stern MP, Williams K, González-Villalpando C, Hunt KJ, Haffner SM. Does the metabolic syndrome improve identification of individuals at risk of type 2 diabetes and/or cardiovascular disease? *Diabetes Care*. 2004;27:2676–2681.
10. Ahmed A, Khan TE, Yasmeen T, Awan S, Islam N. Metabolic syndrome in type 2 diabetes: comparison of WHO, modified ATPIII & IDF criteria. *J Pak Med Assoc*. 2012;62:569–574.
11. Bosevski M, Pemovska G, Bosevska G, Georgievska-Ismail L. Clinical role of estimation metabolic syndrome's components in type 2 diabetic population with symptomatic coronary artery disease—a comparison of two criteria. *Med Arh*. 2010; 64:144–146.
12. Kyselová Z, Garcia SJ, Gajdosíková A, Gajdosík A, Stefek M. Temporal relationship between lens protein oxidation and cataract development in streptozotocin-induced diabetic rats. *Physiol Res*. 2005;54:49–56.

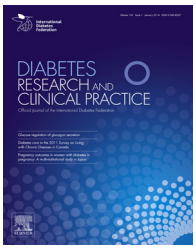
13. Jacob RF, Mason RP. Lipid peroxidation induces cholesterol domain formation in model membranes. *J Biol Chem*. 2005; 280:39380–39387.
14. Rabe-Hesketh S, Skrondal A. *Multilevel and Longitudinal Modeling Using Stata*. 2nd ed. College Station, TX: Stata Press; 2008.
15. Neuhaus JM. Statistical methods for longitudinal and clustered designs with binary responses. *Stat Methods Med Res*. 1992;1: 249–273.
16. Mitchell P, Smith W, Wang JJ, Cumming RG, Leeder SR, Burnett L. Diabetes in an older Australian population. *Diabetes Res Clin Pract*. 1998;41:177–184.
17. Kanthan GL, Wang JJ, Rochtchina E, et al. Ten-year incidence of age-related cataract and cataract surgery in an older Australian population. The Blue Mountains Eye Study. *Ophthalmology*. 2008;115:808–814.
18. Whitworth JA; World Health Organization, International Society of Hypertenion Writing Group. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. *J Hypertens*. 2003;21:1983–1992.
19. Cugati S, Wang JJ, Rochtchina E, Mitchell P. Ten-year incidence of diabetes in older Australians: the Blue Mountains Eye Study. *Med J Aust*. 2007;186:131–135.
20. World Health Organization (WHO). *Definition, Diagnosis and Classification of Diabetes Mellitus and Its Complications. Part 1: Diagnosis and Classification of Diabetes Mellitus*. Geneva: WHO; 1999.
21. Mitchell P, Smith W, Wang JJ. Iris color, skin sun sensitivity, and age-related maculopathy. The Blue Mountains Eye Study. *Ophthalmology*. 1998;105:1359–1363.
22. Zimmet P, Magliano D, Matsuzawa Y, Alberti G, Shaw J. The metabolic syndrome: a global public health problem and a new definition. *J Atheroscler Thromb*. 2005;12:295–300.
23. Singer JD, Willett JB. *Applied Longitudinal Data Analysis: Modeling Change and Event Occurrence*. Oxford, UK: Oxford University Press; 2003:407–463.
24. Allison PD. Discrete-time methods for the analysis of event histories. In: Leinhardt S, ed. *Sociological Methods and Research*. San Francisco, CA: Jossey-Bass; 1982:61–98.
25. Lecaire T, Palta M, Zhang H, Allen C, Klein R, D'Alessio D. Lower-than-expected prevalence and severity of retinopathy in an incident cohort followed during the first 4–14 years of type 1 diabetes: the Wisconsin Diabetes Registry Study. *Am J Epidemiol*. 2006;164:143–150.
26. Nelder JA. Letter to the editor. *Stat Med*. 2001;20:2205.
27. Hardin JW, Hilbe JM. *Generalized Linear Models and Extensions*. 2nd ed. College Station, TX: Stata Press; 2007.
28. Stitt AW. Advanced glycation: an important pathological event in diabetic and age related ocular disease. *Br J Ophthalmol*. 2001;85:746–753.
29. Kador PF, Kinoshita JH. Diabetic and galactosaemic cataracts. *CIBA Found Symp*. 1984;106:110–131.
30. Pollreisz A, Schmidt-Erfurth U. Diabetic cataract-pathogenesis, epidemiology and treatment. *J Ophthalmol*. 2010;2010: 608751.
31. Lim LS, Tai ES, Aung T, et al. Relation of age-related cataract with obesity and obesity genes in an Asian population. *Am J Epidemiol*. 2009;169:1267–1274.
32. Cheung N, Wong TY. Obesity and eye diseases. *Surv Ophthalmol*. 2007;52:180–195.
33. Klimov AN, Gurevich VS, Nikiforova AA, et al. Antioxidative activity of high density lipoproteins in vivo. *Atherosclerosis*. 1993;100:13–18.
34. Varma SD, Chand D, Sharma YR, Kuck JF Jr, Richards RD. Oxidative stress on lens and cataract formation: role of light and oxygen. *Curr Eye Res*. 1984;3:35–57.
35. von Eckardstein A, Hersberger M, Rohrer L. Current understanding of the metabolism and biological actions of HDL. *Curr Opin Clin Nutr Metab Care*. 2005;8:147–152.
36. Panchapakesan J, Cumming RG, Mitchell P. Reproducibility of the Wisconsin cataract grading system in the Blue Mountains Eye Study. *Ophthalmic Epidemiol*. 1997;4:119–126.

Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation



The prognostic role of body mass index on mortality amongst the middle-aged and elderly: A competing risk analysis

Haleh Ghaem Maralani [a], *Bee Choo Tai* [a,b,*], *Tien Y. Wong* [c,d,e], *E. Shyong Tai* [f], *Jialiang Li* [g], *Jie Jin Wang* [h,i], *Paul Mitchell* [h]

[a] *Saw Swee Hock School of Public Health, National University of Singapore, National University Health System, Singapore*
[b] *Yong Loo Lin School of Medicine, National University of Singapore, National University Health System, Singapore*
[c] *Singapore Eye Research Institute, Singapore National Eye Centre, Singapore*
[d] *Department of Ophthalmology, Yong Loo Lin School of Medicine, National University of Singapore, National University Health System, Singapore*
[e] *Duke-NUS Graduate Medical School, Singapore*
[f] *Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, National University Health System, Singapore*
[g] *Department of Statistics and Applied Probability, National University of Singapore, Singapore*
[h] *Centre for Vision Research, University of Sydney, Sydney, Australia*
[i] *Centre for Eye Research Australia, University of Melbourne, Royal Victorian Eye and Ear Hospital, Victoria, Australia*

ARTICLE INFO

Article history:
Received 12 April 2013
Received in revised form
25 June 2013
Accepted 25 November 2013
Available online 12 December 2013

Keywords:
All-cause mortality
Body mass index
Cause-specific mortality
Middle-aged
Elderly
Competing risks model

ABSTRACT

Aims: To determine the relationship between body mass index (BMI) including its 5-year changes and mortality, and compare the results obtained using Cox and competing risks models.

Methods: Our study subjects included 2216 persons aged ≥49 years who participated in the Blue Mountains Eye Study, Australia between 1992 and 1994, and returned for further follow-up examinations between 1997 and 1999. We examined the relationship between BMI and mortality using cubic spline. The Cox and competing risks models were used to assess the associations between baseline BMI and its 5-year changes with all-cause and cause-specific mortality.

Results: Amongst subjects aged ≤70 years, the relationship between BMI and all-cause mortality was U-shaped. For those aged >70 years, an L-shaped relationship was seen with no elevation in risk amongst the overweight/obese. Based on the competing risks model, obesity at baseline was associated with increased risk of cardiovascular death and reduction in BMI at 5-year was linked to an increase risk of cancer death amongst those aged ≤70 years. The cause-specific Cox model showed that reduction in BMI at 5-year was associated with cancer-death regardless of age, and with cardiovascular deaths among subjects aged ≤70 years. Cox regression model showed larger magnitude of effect with wider confidence interval as compared with competing risks model.

Conclusions: Conditions associated with obesity are more likely to affect mortality among subjects aged ≤70 years, but not among those aged over 70 years. Cox model shows larger magnitude of effect in comparison with competing risks model.

* *Corresponding author at*: Saw Swee Hock School of Public Health, National University of Singapore, 16 Medical Drive (MD3), Singapore 117597, Singapore. Tel.: +65 65164973; fax: +65 67791489.
E-mail address: ephtbc@nus.edu.sg (B.C. Tai).

0168-8227/$ – see front matter
http://dx.doi.org/10.1016/j.diabres.2013.11.025

1. Introduction

The prevalence of obesity in younger adults and elderly will increase, with significant consequences for public health care [1,2]. Obesity is commonly associated with hypertension, diabetes, cardiovascular disease (CVD) and disability [1,2].

Previous prospective cohort studies have tried to describe the impact of obesity on all-cause and cause-specific mortality, however, conflicting results remains amongst middle-aged and elderly, with a lack of evidence to prove the strength of association between obesity and mortality [3–12]. Variation in age of participants in different studies may contribute to the conflicting findings in these studies, with some studies suggesting that overweight and obesity may not be a risk factor for mortality in the elderly [11,12]. Moreover, the impact of changing BMI over a period of time on mortality remains uncertain [13]. Some studies reported that an increase or decrease in BMI over time predicts a greater risk of CVD, cancer or all-cause mortality among middle-aged or elderly [14–17], while others have not noted this association [4,18].

Additionally, obesity is associated with increases in mortality from multiple causes. Most studies that have examined the associations between obesity and cause-specific mortality fail to take into account ''competing risks'' from other causes of death. Cox regression model is adequate when competing risks are rare (i.e. among younger adults). However, in the presence of strong competing risks, as with frail or elderly populations [19], standard Cox regression model may substantially overestimate the absolute risk of event of interest, because subjects with a competing (and thus censored) event are treated as if they could experience the event of interest in the future [20]. In addition, predictions from a standard survival analysis in the presence of competing risks have been said to refer to the risk of failing from the event of interest in a virtual world where the competing risk is absent [21–23]. For clinical decision-making in the real world, where competing risks do occur, actual rather than virtual absolute risks are often more relevant [24,25]. Therefore, competing risks models are well suited for outcomes involving multiple failure types (such as cancer- and cardiovascular-deaths), as it appropriately account for each competing risk in the analysis, yielding a more accurate estimation of exposure (BMI) effect on different causes of death [20,26]. To our best knowledge, competing risk models have not been used to evaluate the relationship between BMI and its changes with cause-specific mortality.

Therefore, in this study, we sought to determine the associations between baseline BMI, the 5-year change in BMI, with all-cause and cause-specific mortality in the Blue Mountains Eye Study (BMES), and compare the results obtained using standard survival models such as the Kaplan–Meier and Cox with the competing risks model.

2. Materials and methods

2.1. Participants

The BMES is a prospective cohort study of vision and other health outcomes [27] in white Australians. Two adjoining urban postcode areas in the Blue Mountains area, west of Sydney, in New South Wales, Australia, were selected as target population. All non-institutionalised, permanent residents aged 49 years and over at the time of the census were eligible. Permanent residents were defined as living in the dwelling for more than six months of a year [28]. At baseline examination (1992–1994), 3654 (82.4%) of eligible subjects were interviewed and examined. At 5-year follow-up (i.e. between 1997 and 1999), 2335 participants (63.9% of the original cohort or 75.1% of survivors) were examined. Mortality subsequent to the 5-year visits was assessed via demographic data linkage to the Australian National Death Index (NDI) database. Each examination survey of this cohort was approved by the Human Research Ethics Committees of the Western Sydney Area Health Service and the University of Sydney, and the study adhered to the Helsinki Declaration. Signed informed consent was obtained from all participants at each examination. More details of the BMES have been described previously [27,28].

In this study, we included 2216 subjects with complete information from both the baseline and 5-year examinations. Participants who died shortly after the study baseline visits were excluded from the analysis as in a previous study [4], to control for the relation between reduced BMI, morbidity and early death [29].

2.2. Data collection

At each visit, a comprehensive questionnaire comprising demographic information, smoking status (current, former and never smoker), alcohol intake (gram per week) and a detailed history of diseases, including hypertension, diabetes, angina, acute myocardial infarction (AMI), stroke and cancer as well as medication was recorded at face-to-face interviews using a standardised questionnaire conducted by trained interviewers [27]. We defined pre-existing disease(s) as a binary variable based on past history or medication of at least one of the above-mentioned diseases. In addition, self-reported physical activity based on time spent on activities per week using the International Physical Activity Questionnaire [30] were collected. The activities captured included occupational, household and leisure activities.

2.3. Study factors

Participants had their weight (after removal of shoes and heavy clothing) measured by standing on an automated scale, to which a vertical height measure was attached [31]. The BMI was calculated as weight (kg)/height (m^2). Baseline BMI was re-categorised using the classification of the World Health Organisation Expert Committee on Physical Status [32]: underweight: $<18.5\ kg/m^2$, normal weight: 18.5 to $<25\ kg/m^2$, overweight: 25 to $<30\ kg/m^2$, and obese: $\geq 30\ kg/m^2$. Normal weight was considered as the reference group in all analyses.

Five-year change in BMI from baseline was categorised as follows: stable: <1 BMI unit change, gain: ≥ 1 BMI unit gain, reduction: ≥ 1 BMI unit loss [17]. Stable BMI was regarded as the reference group in all analyses involving changes in BMI from the baseline to 5-year visit.

2.4. Study outcomes

Deaths occurring after baseline recruitment (1992–1994) until 31 December 2007 were confirmed by matching the demographic information of the participants with the Australian National Death Index (NDI), by using probabilistic record linkage. Causes of death were provided by the NDI using the International Classification of Diseases (ICD) 9th revision and the International Statistical Classification of Diseases, 10th revision [33]. Cardiovascular death included the following codes from ICD-9 (3949, 4029, 4109, 4119, 4140, 4148, 4149, 4151, 4240, 4241, 4254, 4269, 4273, 4274, 4275, 4278, 4280, 4281, 4289, 4290, 4291, 4410, 4411, 4413, 4414, 4415, and 4439) and ICD-10 (I059, I10, I132, I219, I249, I251, I255, I259, I269, I271, I350, I352, I358, I429, I469, I48, I500, I514, I515, I516, I709, and I711). Stroke death (thrombotic, haemorrhagic) included the following codes from ICD-9 (430.0–438.9) and ICD-10 (160.0–169.9) [33]. In addition, cancer death was defined as C00–C97 in ICD-9 and C140–C234 in ICD-10. Deaths and cause(s) of death were confirmed by medical certifiers, which include the physician in attendance, coroner or medical examiner, regardless of whether the death occurred in a hospital or in the community [33]. The sensitivity and specificity of the Australian NDI has been estimated at 93.7% and 100% for all-cause deaths, and 92.5% and 89.6%, respectively, for cardiovascular deaths. Validation of stroke- and cancer-death was, however, not possible [33].

2.5. Statistical analyses

We first explored the relationship between baseline BMI (continuous) and the risk of death via non-parametric regression model based on cubic spline [34] with four internal knots at the 5th, 15th, 75th and 90th percentiles of the BMI distribution. In the graphical display we selected the upper bound of the reference group (normal weight) at 23.5 kg/m^2 as reference.

In examining associations between BMI and all-cause mortality, we used the Cox proportional hazards model. We implemented the competing risks model [26] to study the associations between BMI (baseline and 5-year change) with cause-specific mortality. Time-to-death (year) is the primary outcome variable. We further compared the results of the competing risks methods based on cumulative incidence [20,35–37] and competing risks regression [26,38] with the Kaplan–Meier (KM) estimates and cause-specific Cox models respectively. Of note, in the competing risks model, the effect estimate is summarised by subdistribution hazard ratio (SHR), where the subdistribution hazard is directly interpretable in terms of the cumulative incidence function [20,38].

Sex, smoking status and pre-existing disease(s) at baseline remained significant in the multivariable analyses. We further explored effect modification of age, sex and pre-existing disease(s) on BMI. The effect estimate and its 95% confidence interval (CI) were presented according to age groups, as the interaction effect was significant. The proportional hazards assumption was checked for individual covariates and globally.

All statistical evaluations were made assuming a two-sided test based on a 5% level of significance. The non-parametric plot of cubic spline was generated using R statistical package (www.r-project.org). All other statistical analyses were carried out using STATA version 11.

3. Results

3.1. Demographic profile of subjects

Table 1 provides a description of the baseline characteristics of the 2216 participants. Generally, underweight persons were more likely to be younger (65%) and predominantly female (74%). Moreover, obese persons were more likely to be younger (78%) or have a history of pre-existing disease(s) (58%) at

Table 1 – Baseline characteristics of 2216 study subjects according to BMI categories.

Variable	Total (n = 2216)	Underweight (n = 31)	Normal weight (n = 902)	Overweight (n = 907)	Obese (n = 376)	P-value
Age (year)						
≤70	1671 (75.4)	20 (64.5)	649 (71.9)	710 (78.3)	292 (77.7)	0.005
>70	545 (24.6)	11 (35.5)	253 (28.0)	197 (21.7)	84 (22.3)	
Gender (%)						
Female	1277 (57.6)	23 (74.2)	541 (60.0)	456 (50.2)	257 (68.4)	<0.001
Male	939 (42.4)	8 (25.8)	361 (40.0)	451 (49.7)	119 (31.6)	
Smoking status (%)						
Current smoker	282 (12.7)	7 (22.6)	134 (14.9)	99 (10.9)	42 (11.2)	0.068
Ex-smoker	788 (35.6)	9 (29.0)	301 (33.4)	343 (37.8)	135 (35.9)	
Nonsmoker	1146 (51.7)	15 (48.4)	467 (51.8)	465 (51.3)	199 (52.9)	
Diabetes (%)	142 (6.5)	1 (3.2)	37 (4.1)	59 (6.6)	45 (12.2)	<0.001
Hypertension (%)	680 (30.7)	4 (12.9)	230 (25.5)	287 (31.6)	159 (42.3)	<0.001
History of stroke (%)	75 (3.4)	1 (3.2)	32 (3.6)	29 (3.2)	13 (3.5)	0.980
History of angina (%)	250 (11.3)	2 (6.5)	82 (9.1)	119 (13.2)	47 (12.6)	0.031
History of AMI (%)	177 (8.0)	2 (6.5)	60 (6.7)	81 (8.9)	34 (9.1)	0.257
History of cancer (%)	170 (7.7)	79 (8.8)	2 (6.4)	59 (6.5)	30 (8.0)	0.332
Pre-existing disease(s) (%)	1025 (46.2)	373 (41.3)	9 (29.0)	423 (46.6)	220 (58.5)	<0.001

Abbreviations: AMI, acute myocardial infarction; BMI, body mass index.

baseline. There were 599 (27%) deaths reported until December 2007. Of these, 234 (39%) were cardiovascular-deaths and 167 (28%) were cancer-deaths. During a median follow-up duration of 14.7 years, 12 (39%) underweight and 109 (29%) obese subjects had died. Of the obese subjects who died during the study follow-up, the prevalence of pre-existing disease at baseline were higher amongst those aged ≤70 years than older subjects (history of diabetes 44% vs 27%, hypertension 26% vs 17%, stroke 13% vs 11%, angina 28% vs 9%, AMI 29% vs 12% and cancer 24% vs 15%) (Appendix 1).

3.2. *Relationship between baseline BMI with all-cause and cause-specific mortality*

Interaction effect was noted between age and baseline BMI for all-cause ($P = 0.049$) and cardiovascular-death ($P = 0.044$). As such, we have reported the results of our analysis according to age. Fig. 1 shows the risk of all cause-death was U shaped with the highest mortality rates at the two extreme ranges of BMI for all subjects as well as for those aged ≤70 years. However, for persons aged over 70 years at baseline, the L-shaped relationship suggests a higher risk of death amongst the underweight, with no elevation in the mortality risk for the overweight or obese, as compared with the normal weight.

Consistent with Fig. 1, Table 2 shows that for persons aged ≤70 years at baseline, there was an increased risk of all-cause mortality amongst the obese (hazard ratio (HR) 1.44, 95% CI: 1.05–1.98). There was also suggestion that being underweight may increase the risk of all-cause death. Similarly, obesity was associated with a greater risk of cardiovascular mortality in this age group based on competing risk (SHR 2.06, 95% CI 1.14–3.70) and Cox regression (HR 2.07, 95% CI 1.15–3.72) (Table 2). Amongst persons aged over 70 years, there was no evidence of association between baseline BMI and all-cause or cause-specific mortality (Table 2). Although the conclusions drawn based on the two methods were largely similar, the magnitude of effect was larger, and with wider CI based on the cause-specific Cox model as compared with the competing risk regression in most instances (Table 2).

3.3. *Changes in BMI and all-cause or cause-specific mortality*

Over the 5-year period, reduction in BMI was observed in 278 (13%) subjects, while 1098 (50%) of them experienced an increase in BMI. Generally, persons with reduced or increased BMI tended to be younger (61% and 80%, respectively). A higher proportion with pre-existing disease(s) at baseline was noted amongst those with a decrease in BMI in subsequent 5 years, as compared with the other groups (Table 3). The overall mortality rate was the highest amongst those with a BMI decrease (49%) and the lowest amongst those with a BMI increase (22%). The magnitude of 5-year changes in BMI according to age group is shown in Appendix 2. In particular, the proportion with BMI reductions among elderly subjects (< −5 [1.5%], −5 to −3 [3.7%], <−3 to −1 [11.1%]) were higher as compared to younger subjects (< −5 [0.6%], −5 to −3 [1.7%], < −3 to −1 [6.4%]). Moreover, a higher proportion of those who were obese at baseline experienced BMI reduction (16.8%) while, a lower proportion of those who were underweight at baseline experienced BMI reduction (5.0%) among those aged ≤70 years. Among the elderly subjects, the proportions with BMI reduction in the obese and underweight groups were 30.9% and 9.1%, respectively (Appendix 3).

Fig. 2 shows the Kaplan–Meier cumulative incidence curve for cancer- and cardiovascular-deaths according to changing BMI status. The estimates were larger than those obtained using the competing risks method for all BMI groups under consideration. Reduced BMI was associated with a higher risk of all-cause mortality regardless of age (Age ≤70 years: HR 2.22,

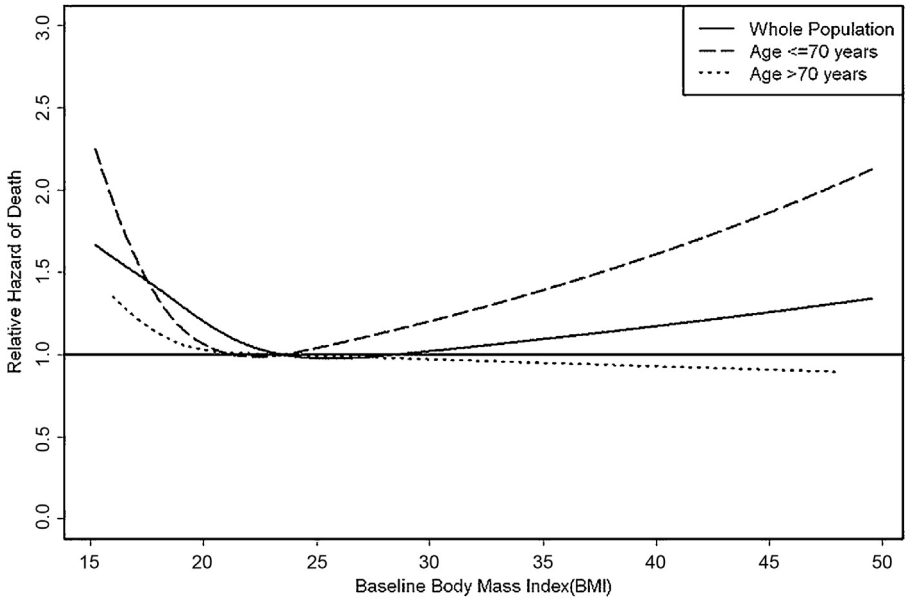


Fig. 1 – Cubic splines describing the nonlinear relationship between body mass index (kg/m^2) and the relative hazard of death. Four knots were placed at the 5th, 15th, 75th and 90th percentiles of the BMI distribution. The reference point at 23.5 is the upper bound of the reference group (i.e. normal weight).

Table 2 – Age-specific associations between baseline BMI and its 5-year changes with all/cause and cause-specific mortality according to competing risks and cause-specific Cox regression models.

	All-cause (*n* = 599)		Cancer (*n* = 167)	Cardiovascular (*n* = 234)			Cancer (*n* = 167)	Cardiovascular (*n* = 234)
	Cox-regression model		Competing risks model				Cause-specific Cox regression	
	No. of death	HR (95% CI)	No. of death	SHR (95% CI)	No. of death	SHR (95% CI)	HR (95% CI)	HR (95% CI)
Baseline BMI (kg/m^2)								
Age ≤ 70 years								
Underweight (*n* = 20)	6	1.82 (0.80–4.15)	2	0.95 (0.14–6.53)	2	1.34 (0.18–7.25)	0.96 (0.13–6.81)	1.73 (0.17–7.50)
Overweight (*n* = 710)	118	1.07 (0.82–1.41)	37	0.97 (0.61–1.54)	37	1.43 (0.84–2.42)	0.99 (0.62–1.59)	1.43 (0.85–2.41)
Obese (*n* = 292)	64	1.44 (1.05–1.98)	23	1.51 (0.88–2.59)	22	2.06 (1.14–3.70)	1.58 (0.98–2.68)	2.07 (1.15–3.72)
Age > 70 years								
Underweight (*n* = 11)	6	1.20 (0.53–2.72)	2	0.68 (0.09–4.94)	4	1.73 (0.55–5.40)	0.90 (0.12–6.64)	1.95 (0.60–5.45)
Overweight (*n* = 197)	116	0.98 (0.77–1.25)	27	1.01 (0.60–1.69)	53	0.85 (0.60–1.22)	1.02 (0.61–1.69)	0.87 (0.61–1.24)
Obese (*n* = 84)	45	0.94 (0.67–1.32)	11	1.07 (0.54–2.15)	20	0.78 (0.47–1.31)	1.12 (0.56–2.25)	0.81 (0.49–1.33)
Change in BMI (kg/m^2)								
Age ≤ 70 years								
Reduction (*n* = 169)	55	2.22 (1.60–3.09)	23	3.03 (1.76–5.23)	14	1.55 (0.83–2.89)	3.20 (1.86–5.50)	1.85 (1.02–3.46)
Gain (*n* = 875)	124	0.88 (0.68–1.14)	41	1.01 (0.63–1.60)	34	0.74 (0.46–1.18)	1.01 (0.63–1.60)	0.78 (0.49–1.25)
Age > 70 years								
Reduction (*n* = 109)	81	1.76 (1.32–2.35)	19	1.42 (0.78–2.60)	35	1.07 (0.69–1.65)	1.89 (1.04–3.43)	1.40 (0.92–2.14)
Gain (*n* = 223)	113	0.86 (0.66–1.11)	25	0.92 (0.53–1.58)	54	0.81 (0.56–1.17)	0.92 (0.52–1.58)	0.82 (0.55–1.19)

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; SHR, subdistribution hazard ratio.
Note: model is adjusted for sex, smoking status and pre-existing disease(s) at baseline. For baseline BMI, normal weight and for BMI changes, stable BMI regarded as reference group.
Stable BMI: <±1 unit BMI change, BMI gain/reduction: ±≥1 unit BMI change.

95% CI 1.60–3.09; Age >70 years: 1.76, 95% CI 1.32–2.35) (Table 2). Amongst subjects aged ≤70 years, reduction in BMI was significantly associated with cardiovascular death (HR 1.85, 95% CI: 1.02–3.46) and cancer-death (HR 3.20, 95% CI: 1.86–5.50) in the cause-specific Cox model, although this association was not confirmed by the competing risks model for cardiovascular-death (SHR 1.55, 95% CI: 0.83–2.89) (Table 2). Subjects aged >70 years with reduced BMI were also found to have an elevated risk of cancer death (HR 1.89, 95% CI: 1.04–3.43) in the cause-specific Cox model only (Table 2).

Supplementary analysis showed BMI reduction in the overweight/obese group to be significantly associated with

Table 3 – Baseline characteristics of 2216 study subjects according to 5-year changes in BMI.

	Total (*n* = 2216)	Stable BMI (*n* = 840)	Reduction (*n* = 278)	Gain (*n* = 1098)	*P*-value
Age (year)					
≤70		627 (74.6)	169 (60.8)	875 (79.7)	<0.001
>70		213 (25.4)	109 (39.2)	223 (20.3)	
Sex (%)					
Female	1277 (57.6)	421 (50.1)	181 (65.1)	675 (61.5)	<0.001
Male	939 (42.4)	419 (49.9)	97 (34.9)	423 (38.5)	
Smoking status (%)					
Current smoker	282 (12.7)	99 (11.8)	46 (16.5)	137 (12.5)	0.025
Ex-smoker	788 (35.6)	329 (39.2)	91 (32.7)	368 (33.5)	
Non-smoker	1146 (51.7)	412 (49.0)	141 (50.7)	593 (54.0)	
Diabetes (%)	142 (6.5)	54 (6.5)	32 (11.9)	56 (5.1)	<0.001
Hypertension (%)	680 (30.7)	260 (30.9)	108 (38.8)	312 (28.4)	0.003
History of stroke (%)	75 (3.4)	34 (4.1)	15 (5.4)	26 (2.4)	0.018
History of angina (%)	250 (11.3)	91 (10.9)	42 (15.2)	117 (10.7)	0.095
History of AMI (%)	177 (8.0)	58 (6.9)	29 (10.5)	90 (8.2)	0.162
History of cancer (%)	170 (7.7)	66 (7.9)	25 (9.0)	79 (7.2)	0.584
Pre-existing disease(s) (%)	1025 (46.2)	392 (46.7)	156 (56.1)	477 (43.4)	0.001

Abbreviations: AMI, acute myocardial infarction; BMI, body mass index.
Note: Stable BMI: <±1 unit BMI change, BMI gain/reduction: ±≥ 1 unit BMI change.

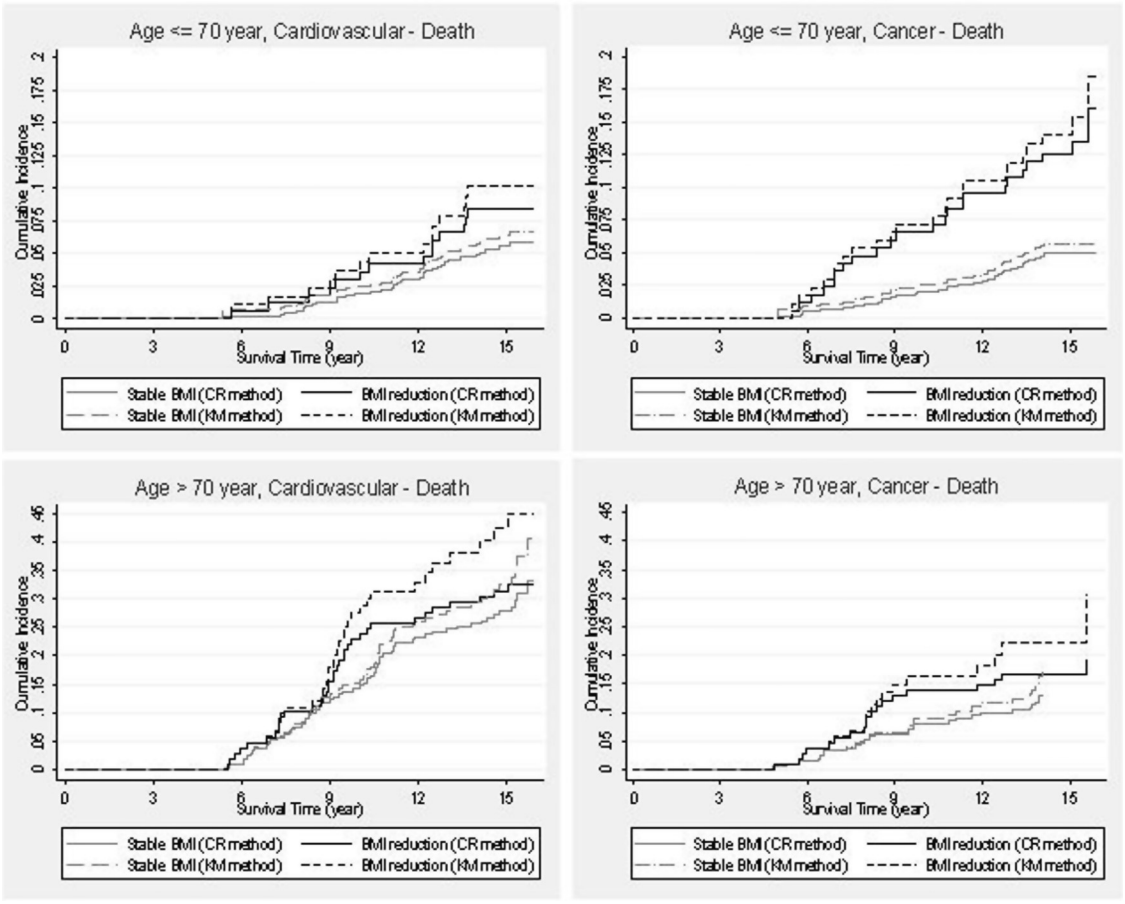


Fig. 2 – Comparison of cumulative incidence of cardiovascular and cancer mortality according to 5-year BMI changes: competing risks versus Kaplan–Meier methods. CR method: competing risks method; KM method: Kaplan–Meier method.

all-cause (Age ≤ 70: HR 2.04, 95% CI 1.38–3.01; Age > 70: HR 2.52, 95% CI 1.70–3.73) and cancer-death (Age ≤ 70: SHR, 2.33 95% CI 1.21–4.48; Age > 70: SHR 3.87 95% CI 1.69–8.90) among both age groups. Cox-specific regression model additionally showed that BMI reduction in the overweight/obese group was positively linked to increased cardiovascular mortality (HR 1.89, 95% CI 1.08–3.32) among elderly subjects (Appendix 4).

3.4. *The associations of baseline BMI and its 5-year changes with all-cause and cause-specific mortality amongst subjects without baseline pre-existing diseases*

Of the 2216 study subjects, 1191 (54%) had no history of pre-existing disease at baseline. Being underweight at baseline was associated with all-cause death in both age groups (Age ≤ 70 year: HR 3.29, 95% CI: 1.40–7.69; Age > 70 year: HR 2.82, 95% CI 1.01–7.89), while obesity was linked to increase risk of cancer-death amongst younger subjects (SHR 2.26, 95% CI 1.07–4.78) (Appendix 5). As before, the magnitude of effect was larger, and with wider CIs based on the cause-specific Cox model as compared with the competing risk regression in most instances.

With regard to BMI changes over 5-year follow-up since baseline, BMI reduction was associated with increase risk in all-cause death in both age groups (Age ≤ 70 year: HR 2.91, 95% CI: 1.78–4.75; Age > 70 year: HR 1.74, 95% CI 1.05–2.88), and cancer-death amongst those aged ≤70 years (Appendix 5). For the latter, the Cox regression model again showed a higher magnitude of effect as compared with the competing risk model.

4. Discussion

In this population-based prospective cohort study of the Australian middle-aged and elderly population, we found the following: first, amongst the younger subjects, the relationship between baseline BMI and all-cause mortality was U-shaped, with both the underweight and obese groups predisposed to have a greater risk of death; obesity was also associated with increased risk of cardiovascular death in this age group. Amongst elderly persons, an L-shaped relationship was seen: only low but not excessive BMI was found to be associated with increased risk of all-cause death. Second, a reduction in BMI between baseline and the 5-year follow-up visit was associated with all-cause mortality in both age groups and cancer deaths among those aged ≤ 70 years. Finally, the cause-specific Cox regression model showed larger

magnitude of effect of between 1 and 33%, as compared with the competing risks model.

4.1. *All-cause mortality risk*

Our study has shown that the pattern of relationship between BMI and mortality is dependent on age. The U-shaped relationship between BMI and mortality in subjects aged ≤ 70 70 years at baseline is consistent with the findings of Berrington de Gonzalez et al. [7] and Adams et al. [8]. However, this pattern of relationship was not noted amongst the elderly who were aged above 70 years. In particular, there was no elevation in risk of death amongst those who were overweight or obese. This observation is consistent with that reported by Tsai and Hsiao, who found a similar L-shaped relationship between BMI and all-cause death among Taiwanese over 65 years old [10]. The L-shaped association between baseline BMI and mortality in those of age >70 suggests that overweight/obesity does not predispose the elderly subjects to be at a greater risk of mortality. Although, it is unclear why excess weight protects older adults, we considered three possibilities. Firstly, the advantage of being overweight could be that fat mass stores energy that can be used during negative energy balance [39]. For example, extra weight could give older people reserves to recover from stresses such as surgery or pneumonia. Secondly, even though obesity is associated with higher rates of chronic disease (such as diabetes), the impact of these conditions on mortality may be reduced when they occur in elderly individuals. For example, Tan et al. showed that diabetes mellitus that was diagnosed after age of 65 was not associated with increased mortality in Scotland [40], whereas it was associated with increased mortality when diagnosed below this age. In the Asia Pacific Cohort Studies Collaboration, Woodward et al. also showed that the effect of diabetes on the risk of CVD and death decreased with increasing age at risk [41]. Thirdly, we also considered the possibility that our findings could have been confounded by the presence pre-existing diseases at baseline (i.e. cancer, AMI, angina, stroke, hypertension and diabetes) that could have resulted in weight loss and caused premature mortality. However, we analysed the data excluding subjects with these underlying conditions and again found overweight/obesity to have no association with death.

4.2. *Cause-specific mortality risk*

In our study, obesity was associated with increased risk of cardiovascular mortality in subjects aged ≤70 years. This was consistent with a study in USA that showed obesity to be associated with coronary heart disease mortality among subjects aged 35–74 years [42]. Obesity is associated with multiple cardiovascular risk factors including diabetes, hypertension and dyslipidemia [43]. As BMI reduction even in obese is a risk factor for death among both middle-aged and elderly subjects and obesity is associated with all-cause and cardiovascular death amongst subjects aged ≤70 years, it may be important to control weight and modify lifestyle years before the ageing process sets in. Moreover, our data does not necessarily suggest that weight loss may not be beneficial in some instances in older individuals because inference of causality between BMI reduction and mortality cannot be fully established.

A unique aspect of our study is the ability to demonstrate changes in BMI over time. BMI changes in fact occurred in about 60% of the study population over the 5-year period since baseline. As in previous studies [16,18,44], we also found that a reduction in BMI was associated with increased risk of all-cause mortality in both the middle-aged and the elderly. Further, BMI reduction was a predictor for cancer related mortality amongst those ≤70 years. In general, a decrease in BMI prior to death in the elderly is more likely to be related to underlying health status [29]. We therefore excluded participants who died shortly after the study baseline visits in the analysis, as did a previous study [4], and included only subjects who were alive at the 5-year follow-up visits with a minimum of 4 years follow-up duration. We also consider possible effect modification of disease status as well as medication used on BMI but found no evidence of their interactions with either baseline pre-existing disease status (no disease, prevalent disease) or status of pre-existing disease over 5-year follow-up (no disease, prevalent disease, incident disease). These analyses do not exclude the possibility that other disease could have developed during follow up that could have resulted in both weight loss and increased mortality. Considering only subjects who were free of pre-existing disease at baseline, obesity was found to be associated with cancer death only among the subgroup of healthy subjects aged ≤70 years.

Importantly, consistent with previous studies [20,26,35–37], when we analysed the relationship between baseline BMI and its 5-year changes using cause-specific Cox regression model, the effect estimates were larger than those of competing risks model by as much as 1–33%. The differences were appreciable especially in the older age group for cancer- (31%) and cardiovascular-death (33%). This finding underscores that, as population ages, the presence of competing risks would be more common especially among the frail population. Hence, we encourage the use competing risks models as a standard tool for developing predictive models involving competing risks endpoints especially among frail population, as it provides a more accurate estimate of exposure [20].

The limitations of this study need to be considered. First, there was limited number of underweight subjects resulting in low statistical power. Thus, the findings relating to the underweight should be interpreted with caution. In addition, the possibility of Type II error may exist especially when we analysed the data amongst subgroup of healthy subjects. Further, when the p value reported in our study is less than 0.05, we may make Type I error due to chance as several endpoints and subgroups were evaluated. Second, the results could have been biased by residual confounding factors, such as varying levels of body composition, visceral adiposity or physical fitness [11], which were not measured in this study. Third, we had no information about whether BMI loss was achieved intentionally or unintentionally. Fourth, the cause of mortality was determined by the NDI and the death certificates may be biased by the choices of the physicians who filled them out. The strengths of this study include its representative study population, the high quality of data collection involving standardised measures at each

examination, thus eliminating bias in self-reporting, long-term follow-up and the low likelihood of misclassification in the causes of death.

In conclusion, we have shown that the association between BMI and mortality is modified by age, with obesity associated with greater risk of all-cause and cardiovascular-specific mortality amongst subjects ≤70-years old. With respect to changes in BMI over 5 years, BMI reduction, a marker of greater severity of mortality-related diseases, was associated with increased risk of all-cause mortality regardless of age, and cancer-related mortality amongst subjects aged ≤70 years old. Competing risk model appears to provide more accurate and precise estimates for the association between BMI and cause-specific mortality.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

The Blue Mountains Eye Study was supported by the Australian National Health and Medical Research Council [grant nos. 974159, 991407, 211069].

The authors are indebted to Ms. Elena Rochtchina, Ms. Ava Grace Tan and Erdahl Teber from Centre for Vision Research Westmead Millennium, Institute University of Sydney, Australia for helping us to access the database of the Blue Mountains Eye Study.

H.G.M. researched, analysed and wrote the manuscript. B.C.T. critically reviewed, edited and advised on the statistical analysis and writing of manuscript. T.Y.W., E.S.T., J.J.W. and P.M. reviewed, edited and contributed to the discussion of the manuscript, while, J.L. reviewed/edited the statistical analysis and results sections.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabres.2013.11.025.

REFERENCES

[1] Prospective Studies Collaboration, Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, et al. Body-mass index and cause-specific mortality in 900,000 adults: collaborative analyses of 57 prospective studies. Lancet 2009;28:1083–96.
[2] Haslam DW, James WP. Obesity. Lancet 2005;1:1197–209.
[3] Teucher B, Rohrmann S, Kaaks R. Obesity focus on all-cause mortality and cancer. Maturitas 2010;65:112–6.
[4] Corrada MM, Kawas CH, Mozaffar F, Paganini-Hill A. Association of body mass index and weight change with all-cause mortality in the elderly. Am J Epidemiol 2006;163:938–49.
[5] Tayback M, Kumanyika S, Chee E. Body weight as a risk factor in the elderly. Arch Intern Med 1990;150:1065–72.
[6] Lindsted KD, Singh PN. Body mass and 26-year risk of mortality among women who never smoked: findings from the Adventist Mortality Study. Am J Epidemiol 1997;146:1–11.
[7] Berrington de Gonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis RJ, et al. Body-mass index and mortality among 1.46 million white adults. N Engl J Med 2010;363:2111–9.
[8] Adams KF, Schatzkin A, Harris TB, Kipnis V, Mouw T, Ballard-Barbash R, et al. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. N Engl J Med 2006;355:763–78.
[9] Thinggaard M, Jacobsen R, Jeune B, Martinussen T, Christensen K. Is the relationship between BMI and mortality increasingly U-shaped with advancing age? A 10-year follow-up of persons aged 70-95 years. J Gerontol Ser A: Biol Sci Med Sci 2010;65:526–31.
[10] Tsai AC, Hsiao ML. The association of body mass index (BMI) with all-cause mortality in older Taiwanese: results of a national cohort study. Arch Gerontol Geriatr 2012;55:217–20.
[11] Flegal KM, Graubard BI, Williamson DF, Gail MH. Excess deaths associated with underweight, overweight, and obesity. J Am Med Assoc 2005;293:1861–7.
[12] Kuk JL, Ardern CI. Influence of age on the association between various measures of obesity and all-cause mortality. J Am Geriatr Soc 2009;57:2077–84.
[13] Yun KE, Park HS, Song YM, Cho SI. Increases in body mass index over a 7-year period and risk of cause-specific mortality in Korean men. Int J Epidemiol 2010;39:520–8.
[14] Rosengren A, Wedel H, Wilhelmsen L. Body weight and weight gain during adult life in men in relation to coronary heart disease and mortality. A prospective population study. Eur Heart J 1999;20:269–77.
[15] Breeze E, Clarke R, Shipley MJ, Marmot MG, Fletcher AE. Cause-specific mortality in old age in relation to body mass index in middle age and in old age: follow-up of the Whitehall cohort of male civil servants. Int J Epidemiol 2006;35:169–78.
[16] Bamia C, Halkjaer J, Lagiou P, Trichopoulos D, Tjønneland A, Berentzen TL, et al. Weight change in later life and risk of death amongst the elderly: the European prospective investigation into cancer and nutrition-elderly network on ageing and health study. J Intern Med 2010;268:133–44.
[17] Myrskylä M, Chang VW. Weight change, initial BMI, and mortality among middle- and older-aged adults. Epidemiology 2009;20:840–8.
[18] Saito I, Konishi M, Iso H, Inoue M, Tsugane S. Impact of weight change on specific-cause mortality among middle-aged Japanese individuals. J Epidemiol Commun Health 2009;63:447–54.
[19] Koller MT, Schaer B, Wolbers M, Sticherling C, Bucher HC, Osswald S. Death without prior appropriate implantable cardioverter-defibrillator therapy: a competing risk study. Circulation 2008;117:1918–26.
[20] Wolbers M, Koller MT, Witteman JC, Steyerberg EW. Prognostic models with competing risks: methods and application to coronary risk prediction. Epidemiology 2009;20:555–61.
[21] Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med 2007;26:2389–430.
[22] Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. Hoboken, NJ: John Wiley and Sons; 2002.
[23] Tsiatis A. A nonidentifiability aspect of the problem of competing risks. Proc Natl Acad Sci U S A 1975;72:20–2.

[24] Grunkemeier GL, Jin R, Eijkemans MJ, Takkenberg JJ. Actual and actuarial probabilities of competing risks: apples and lemons. Ann Thorac Surg 2007;83:1586–92.
[25] Grunkemeier GL, Anderson RP, Miller DC, Starr A. Time-related analysis of nonfatal heart valve complications: cumulative incidence (actual) versus Kaplan–Meier (actuarial). Circulation 1997;96(Suppl. 9):II4.
[26] Tai BC, Wee J, Machin D. Analysis and design of randomised clinical trials involving competing risks outcomes. Trials 2011;12:127.
[27] Mitchell P, Smith W, Wang JJ, Cumming RG, Leeder SR, Burnett L. Diabetes in an older Australian population. Diabetes Res Clin Pract 1998;41:177–84.
[28] Smith W, Mitchell P, Attebo K, Leeder S. Selection bias from sampling frames: telephone directory and electoral roll compared with door-to-door population census: results from the Blue Mountains Eye Study. Aust N Z J Public Health 1997;21:127–33.
[29] Wannamethee SG, Shaper AG, Walker M. Weight change, body weight and mortality: the impact of smoking and ill health. Int J Epidemiol 2001;30:777–86.
[30] Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003;35:1381–95.
[31] Younan C, Mitchell P, Cumming R, Rochtchina E, Panchapakesan J, Tumuluri K. Cardiovascular disease, vascular risk factors and the incidence of cataract and cataract surgery: the Blue Mountains Eye Study. Ophthalmic Epidemiol 2003;10:227–40.
[32] World Health Organization. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee.In: World Health Organization technical report series. vol. 854. 1995;p. 1–452.
[33] Wang JJ, Cugati S, Knudtson MD, Rochtchina E, Klein R, Klein BE, et al. Retinal arteriolar emboli and long-term mortality: pooled data analysis from two older populations. Stroke 2006;37:1833–6.
[34] Harrell Jr FE. Regression modeling strategies: with applications to linear models, logistic regression and survival analysis. Springer series in statistics, New York: Springer-Verlag; 2001.
[35] Tai BC, Machin D, White I, Gebski V, EOI (The European Osteosarcoma Intergroup). Competing risks analysis of patients with osteosarcoma: a comparison of four different approaches. Stat Med 2001;20:661–84.
[36] Tai BC, Grundy RG, Machin D. On the importance of accounting for competing risks in pediatric cancer trials designed to delay or avoid radiotherapy: I. Basic concepts and first analyses. Int J Radiat Oncol Biol Phys 2010;76:1493–9.
[37] Tai BC, Grundy R, Machin D. On the importance of accounting for competing risks in pediatric brain cancer: II. Regression modeling and sample size. Int J Radiat Oncol Biol Phys 2011;79:1139–46.
[38] Beyersmann J, Dettenkofer M, Bertz H, Schumacher M. A competing risks analysis of bloodstream infection after stem-cell transplantation using subdistribution hazards and cause-specific hazards. Stat Med 2007;26:5360–9.
[39] Dahl AK, Fauth EB, Ernsth-Bravell M, Hassing LB, Ram N, Gerstof D. Body mass index, change in body mass index, and survival in old and very old persons. J Am Geriatr Soc 2013;61:512–8.
[40] Tan HH, McAlpine RR, James P, Thompson P, McMurdo ME, Morris AD, et al. Diagnosis of type 2 diabetes at an older age: effect on mortality in men and women. Diabetes Care 2004;27:2797–9.
[41] Woodward M, Zhang X, Barzi F, Pan W, Ueshima H, Rodgers A, et al. The effects of diabetes on the risks of major cardiovascular diseases and death in the Asia-Pacific region. Diabetes Care 2003;26:360–6.
[42] Mann DM, Lee J, Liao Y, Natarajan S. Independent effect and population impact of obesity on fatal coronary heart disease in adults. Prev Med 2006;42:66–72.
[43] Sowers JR. Obesity as a cardiovascular risk factor. Am J Med 2003;115(Suppl. 8A):37S–41S.
[44] Newman AB, Yanez D, Harris T, Duxbury A, Enright PL, Fried LP, Cardiovascular Study Research Group. Weight change in old age and its association with mortality. J Am Geriatr Soc 2001;49:1309–18.

Metabolic Syndrome and Risk of Age-related Macular Degeneration

Running title: Metabolic Syndrome and Age-related Macular Degeneration

Haleh **Ghaem Maralani**, MSc[1]; Bee Choo **Tai**, PhD[1, 2]*;

Tien Y **Wong**, MD, PhD[3,4,5];E Shyong **Tai**, MD[6]; Jialiang **Li**, PhD[7];

Jie Jin **Wang**, PhD[5,8]; Paul **Mitchell**, MD, PhD[8]

[1]Saw Swee Hock School of Public Health, National University of Singapore, and National University Health System, Singapore.

[2]Yong Loo Lin School of Medicine, National University of Singapore and National University Health System, Singapore.

[3]Singapore Eye Research Institute, Singapore National Eye Centre, Singapore.

[4]Department of Ophthalmology, Yong Loo Lin School of Medicine, National University of Singapore and National University Health System, Singapore.

[5]Duke-NUS Graduate Medical School, Singapore.

[6]Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore and National University Health System, Singapore.

[7]Department of Statistics and Applied Probability, National University of Singapore, Singapore.

[8]Centre for Vision Research, University of Sydney, Sydney, Australia.

*Correspondence:

Associate Professor Bee Choo TAI

Saw Swee Hock School of Public Health

National University of Singapore

16 Medical Drive (MD3)

Singapore 117597

Phone: (65) 65164973

Fax: (65) 67791489

Email: ephtbc@nus.edu.sg

Authors' contributions Haleh Ghaem Maralani researched, analysed and wrote the manuscript. Bee-Choo Tai critically reviewed, edited and contributed to the statistical analysis and writing of manuscript. Tien-Yin Wong, E Shyong Tai, Paul Mitchell, Jie Jin Wang, reviewed, edited and contributed to introduction and discussion sections and Jialiang Li reviewed and edited the statistical analysis and results sections. All authors approve the final version that is submitted.

Conflict of interest disclosures The authors have no proprietary or commercial interest in any of the materials discussed in this article. The authors declare no conflict of interest.

Acknowledgements

The Blue Mountains Eye Study was supported by the Australian National Health and Medical Research Council (Grant Nos. 974159, 991407, 211069).

The authors are indebted to Ms Elena Rochtchina and Ms Ava Grace Tan from the Centre for Vision Research Westmead Millennium, Institute University of Sydney, Australia for helping us to access the data base of the Blue Mountains Eye Study. The authors also thank the support of Duke-NUS/ SingHealth

Academic Medicine Research Institute and the medical editing assistance of Taara Madhavan (Associate, Clinical Sciences, Duke-NUS Graduate Medical School).

Text word count: 2511; Abstract word count: 322; No of tables: 3; No of figures: 1; No of appendix: 1 ; No of references: 37

Key words: Age-related Macular Degeneration, Blue Mountains Eye Study, Metabolic Syndrome.

Summary:

The evaluation of age modified relationship between metabolic syndrome and its components with age-related macular disease (AMD) using the mixed-effects model showed metabolic syndrome, obesity, glucose and triglyceride associated with the progression to late-stage AMD.

ABSTRACT

Purpose: To investigate the relationship between metabolic syndrome (MetS) and its components with risk of early and late stage age-related macular degeneration (AMD).

Methods: A prospective cohort of individuals aged ≥49 years were followed up over a period of 10-years in the Blue Mountains Eye Study, Australia. MetS components were measured at baseline (1992-1994), 5-year (1997-1999) and 10-year (2002-2004) follow-up. Incident cases of early and late AMD were diagnosed using standard photographic grading of retinal images of 2218 participants at risk. Mixed-effect logistic regression was conducted to explore the relationship between MetS (and its components) with subsequent development of early/late AMD.

Results: Over the 10-year follow-up, early AMD developed in 12% and late AMD in 3% of participants at risk. Amongst subjects aged ≤70 years, MetS was associated with incidence of late AMD. Of the five MetS components, obesity, high glucose and high triglyceride were associated with increased incidence of late AMD during the 10-year follow-up. There was no evidence of effect of MetS and its components on risk of early AMD.

Conclusion: MetS, obesity, high glucose, and high triglycerides were predictors of progression to late AMD. These data provide additional insights into the pathogenesis of AMD.

Age-related macular degeneration (AMD) is the leading cause of blindness and poor vision amongst elderly Caucasians in the United States,[1] Australia[2] and other western nations, with a significant impact on the quality of life of those afflicted.[3,4]

Metabolic Syndrome (MetS) represents a cluster of metabolic abnormalities involving central obesity, dyslipidemia, hyperglycemia, and high blood pressure (BP).[5] MetS components have long been postulated to be associated with AMD.[6-8] However, there have been conflicting reports about the independent associations of individual MetS components (e.g. BMI, BP or high serum lipid levels) and the development of AMD.[9-13] For example, in the Blue Mountains Eye Study (BMES), obesity was significantly associated with the prevalence of early AMD,[14] while total and high density lipoprotein (HDL) serum cholesterol were associated with incident late AMD.[15] In the Beaver Dam Eye Study, total serum cholesterol was inversely associated with incident neovascular AMD but was positively associated with incident geographic atrophy.[16] To date, most of the epidemiological data have not been consistent regarding the association of diabetes with AMD.[17-22] Furthermore, previous studies on AMD have analyzed association with individual MetS risk factors, usually measured at baseline, and in isolation.[14,15] Thus, there is uncertainty as to the relationship of a combination of risk factors, defined by the MetS, and AMD.

The aim of the current study is to examine MetS defined according to the International Diabetes Federation (IDF) criteria,[23] and risk of AMD. Furthermore, we explored age-specific (≤70 versus >70 years) relationship between MetS and

its components, which were repeatedly measured at baseline, 5- and 10-year follow-up with the subsequent development of early or late AMD via the mixed-model.

Material and Methods

Study design and participants

The BMES is a population-based cohort study of vision, common eye diseases and other health outcomes of a suburban Australian population in the west of Sydney. Details about this study are published elsewhere.[24] In brief, between 1992 and 1994, non-institutionalized permanent residents aged 49 years and older were recruited into the study. The survivors were asked to return for follow-up examinations at 5 (1997-1999) and 10 (2002-2004) years. Participants, who did not return for the 5-year follow-up, were also invited to attend the 10-year follow-up examination and had color retinal photographs for the assessment of AMD lesions.[15]

At each visit, trained interviewers filled out a comprehensive questionnaire comprising demographic information, eye and general medical history including hypertension, diabetes, and pre-existing cardiovascular disease (namely, angina, acute myocardial infarction (AMI), stroke) as well as medications used. Height, weight and seated BP[25] were measured. Fasting pathology tests, including total cholesterol (mmo/L), HDL cholesterol (mmo/L), triglyceride (mmo/L)[26] and fasting plasma glucose (FPG) (mmo/L),[27] were measured within a month of each interview and delivered by courier within the

same day to Westmead Hospital Sydney for hematology and clinical biochemistry assessment.[2] In addition, information on smoking (never, former and current smoker), alcohol consumption (gram / week), history of eye diseases including cataract, AMD, myopia and glaucoma as well as family history of these eye diseases and blindness were obtained and recorded.[15] Eye iris color (blue, hazel/ green, tan/ brown, dark brown) and skin sun-tanning characteristics were also estimated on a 4-point scale (always burn, never tan; usually burn, tan with difficulty; burn and tan above average; rarely burn, tan above average).[28] The BMES was approved by the Human Research Ethics Committee of the University of Sydney and conducted according to the Declaration of Helsinki. Written informed consent was obtained from all participants at each examination.[24]

AMD grading

The population at risk for AMD comprised participants who had at least one follow-up visit, and whose retinal photographs were retrospectively shown not to contain AMD at baseline. The primary outcomes, namely early and late stage of AMD, were repeatedly measured at baseline, 5- and 10-year follow-up. Photographic grading for AMD was based on the Wisconsin Age-Related Maculopathy Grading System.[29,30] Late-stage AMD was defined to include neovascular AMD and geographic atrophy (GA).[31] Early-stage AMD was defined as the absence of late-stage AMD and the presence of either (1) large (≥125 μm diameter) indistinct soft or reticular drusen or (2) both large distinct soft drusen and retinal pigmentary abnormalities (hyperpigmentation or

hypopigmentation),[30,31] within the macular area.[30] Patients with only distinct soft drusen or retinal pigmentary abnormalities but not both lesions at baseline who went on to develop complementary lesions that contributed to the diagnosis of early AMD were included as incident early AMD cases.

Definition of metabolic syndrome

MetS was defined according to the IDF criteria[23] as obesity (i.e. body mass index (BMI) >30 kg/m^2) plus any two of the following four factors - serum triglyceride level ≥1.7 mmol/L or specific treatment for this lipid abnormality; serum HDL cholesterol <1.03 mmol/L in men and <1.29 mmol/L in women, or specific treatment for this lipid abnormality; systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg, or treatment of previously diagnosed hypertension; or FPG ≥5.6 mmol/L, or previously diagnosed type 2 diabetes. The IDF criteria have been suggested to be more reliable for diagnosing MetS in predictive model for coronary clinical status in type 2 diabetes populations as compared with other MetS criteria such as the Third Report of the National Cholesterol Education Program Adult Treatment Panel (ATP-3), the European Group for the Study of Insulin Resistance (EGIR) and the World Health Organisation (WHO).[23]

At the time when the participant entered the study, the baseline values of MetS components were measured and recorded. The MetS components were again measured at 5- and 10-year after first recruitment. Data are thereafter available on how prevalent MetS as well as its components changes in each subject throughout the duration of study.

Statistical analysis

The χ^2 test was used to determine the relationship between categorical covariates included in this study and the 10-year cumulative incidence of both early and late stage AMD.

Mixed-effect logistic regression model[32] with repeated measurements of MetS (and its components) at baseline, 5- and 10-year follow-up visits, was used to explore the relationship between Mets and its components with the subsequent development of early or late AMD over 10-year follow-up. The mixed-effect model comprises both the fixed and random effects. The random effects are estimated when the data structure consists of repeated measures of data over time, in this case, MetS and its components as well as AMD at baseline, 5- and 10-year, within each individual. Age, sex, smoking, pre-existing cardiovascular disease (angina, AMI and stroke), family history of eye disease (cataract, AMD, myopia, glaucoma and blindness), patient's history of eye disease (cataract, myopia and glaucoma), eye iris color, and skin sun-tanning characteristics were regarded as fixed-effect covariates in the model. The regression coefficients of MetS and its components in mixed effects model may be interpreted as subject specific estimate of their effect on AMD. When repeated measures (i.e. MetS at baseline, 5- and 10-year) were made on the same subjects, it would be appropriate to adjust for possible intra-subject correlation by using random effects to achieve a more efficient and robust estimate.[32,33]

However, among the fixed effect covariates as mentioned earlier, only age, sex and pre-existing cardiovascular disease were statistically significant in the bivariate model. We further explored possible interaction between age and sex with MetS or its components in these logistic regression models. All statistical evaluations were made assuming a two-sided test based on a 5% level of significance using STATA version 11.

Results

Overall, 2218 subjects with complete information for the study factors at baseline contributed to the analysis of incidence of AMD over 10-year follow-up. Of these, 2114 contributed to the analysis of early-stage AMD and 2218 to late-stage AMD. Over the 10-year follow-up, 262 (12.4%) cases of early AMD and 70 (3.2%) cases of late AMD were detected. Of the participants included in the present study, 76.5% were aged ≤ 70 years at baseline and 58% were females. Age, sex and pre-existing cardiovascular disease were associated with both early and late AMD (Table 1).

The prevalence of MetS increased slightly to 16.4% (95% confidence interval (CI) 14.9-18.1) after 5 years of follow-up from 12.2% (95% CI 10.9-13.6) at baseline. It was 14.2% (95% CI 12.5-16.0) after 10 years of follow-up. Of the five MetS components, the prevalence of obesity increased over time (baseline 17%, 5-year 23% and 10-year 24%). The prevalence of high glucose was 15% at baseline and reached to 24% at 5- year and decreased by 10-year (21%). The prevalence of high triglyceride was highest at baseline (41%) and 5-year (40.5%)

and decreased by 10-year (28%). Moreover, the low HDL cholesterol had highest prevalence at baseline (30%) and decreased to 27% at 5-year and again slightly increased by 10-year (29%). Moreover, the 10-year changes in prevalence of high BP were as follow (baseline 85%, 5-year 91% and 10-year 81%) (Table 2).

Amongst those who developed late AMD and were aged ≤ 70 years (n=32), there were notably higher proportions with MetS, increased BMI, high glucose and high triglyceride over time. However, amongst those who developed early AMD and were aged ≤70 years, the changing status of MetS and its components was not appreciable. The observation is similar for those who developed early AMD and were age >70 years, with little change in status of MetS over time. In fact, declines in some Mets components were noted over time for early AMD (Figure 1).

Longitudinal information of MetS and its components and early or late AMD

There was no evidence of any relationship between MetS and its components with early AMD in the mixed model (Table 3). However, there was an evidence of interaction effect between MetS, obesity and high glucose with age in their relationship with late AMD (all $P < 0.05$). After adjusting for sex, pre-existing cardiovascular diseases and inclusion of interaction between age and MetS (or its components), we found that MetS was significantly associated with late AMD (Adjusted odds ratio (OR) 2.16 [95% CI 1.01-4.65], P =0.049) amongst those aged ≤70 years (Table 3). Furthermore, amongst the five MetS components, BMI >30 (adjusted OR 2.22 [95% CI 1.09-4.49], P =0.027); high glucose (Adjusted

OR 3.12 [95% CI 1.48-6.56], P =0.003) and high triglyceride (adjusted OR 2.06 [95% CI 1.01-4.22), P = 0.047) were positively linked to the incidence of late AMD during the 10-year follow-up period (Table 3).

Discussion

Our study investigated the relationship between MetS and the subsequent development of AMD over a 10 year period in a cohort of Australian white persons. We found that age modified the relationship of MetS, obesity and high glucose with late stage AMD. Amongst younger participants aged ≤70 years, MetS was associated with increase in incidence of late AMD during the 10-year follow-up. Amongst the MetS components, obesity (i.e. BMI >30), high glucose and high triglyceride were found to be significant predictors of incidence of late AMD in the younger age group. No relationship was seen for MetS and early AMD.

The finding that the associations between MetS and its components with late AMD emerged during the 10 year follow-up and that, this was observed only in those age ≤70 years at baseline add to the existing literature. For example, while Delcourt et al.,[12] and Clemons et al.,[21] have shown a significant association between obesity and late AMD, others have not confirmed this association.[8,14,34] The mechanism connecting obesity and AMD formation may be possibly explained by an increase in oxidative damage and inflammation in obese persons.[10] Obesity is also associated with an increase in C-reactive protein, a

marker for systemic inflammation which in turn is also significantly associated with AMD.[35]

We also observed an association between high glucose and late AMD in this age group. The Beaver Dam Eye Study[17,18] and the Barbados Eye Study[20] have also demonstrated an association between prevalent diabetes mellitus and any AMD. The mechanism behind the association between diabetes and AMD has been shown in eyes of long-term diabetic persons through the thickening of basement membrane of the choriocapillaris walls, luminal narrowing, dropout of the choriocapillaris, and thickening of Bruch's membrane which has been attributed to hyperglycemia.[36,37]

We further observed a positive association between high triglyceride and increased incidence of late AMD during 10-year in this group of subjects. The observed relationship may be explained by the vascular model which suggests that AMD is the result of the accumulation of lipid in the sclera and the Bruch membrane, thus progressively increasing the stiffness of these tissues.[6]

Importantly, our study examined changes in MetS over time in contrast to previous studies which only used baseline information of MetS components.[7,12,14,15,17,18] In contrast, when we analysed baseline data using the conventional logistic regression model, only high glucose was significantly associated with 10-year cumulative incidence of late AMD amongst those aged ≤ 70 years (Appendix 1). This was in contrast to the mixed model regression which we used which detected significant interaction not only between high glucose and age, but also between MetS and obesity with age, with the OR for MetS, BMI,

high glucose and high triglyceride reaching statistical significance amongst those aged ≤ 70 years. Hence, our current analysis considered all available information of Mets components at baseline and subsequent follow-up visits to provide a more comprehensive understanding of the risks of AMD associated with MetS and its components.

The strengths of this study include (a) a representative elderly Australian population; (b) high quality data collection; (c) a population-based study of long-term incidence of AMD; (d) use of standard method of assessing AMD incidence, including photographic grading by the same personnel at all examinations, and a detailed side-by-side comparison of baseline and follow-up examination photographs to ensure negligible misclassification for AMD diagnosis;[15] and (e) applying Mixed-effect logistic regression model which can detect stronger and more robust relationships[32,33] between individual MetS components and AMD where occurrence as well as study main exposure namely MetS and its components are measured during the study follow-up at baseline, 5- and 10-year. However, the drawbacks of this study should be noted. The low prevalence of Mets at baseline and follow-up visits (ranging between 12.2-16.4%) may limit our ability to detect the relationship between MetS and early AMD. In addition, the possibility of chance finding exists, especially when we analyzed the data related to late AMD in age group ≤ 70 years involving small number of cases. Further, the possibility of residual confounding effect cannot be ruled out, and the observed associations could have been due to confounding factors, not the MetS or its components per se.

In conclusion, our study demonstrated that MetS and three of its components, namely BMI >30, high glucose and high triglyceride were predictors of progression to late-stage AMD amongst younger Australian white population aged ≤70 years. MetS is not a disease in itself, but a constellation of risk factors for cardiovascular disease and our study now extends its relevance to AMD. Importantly, components of MetS are modifiable through lifestyle modification including dietary changes and increased physical activity. If confirmed in subsequent studies, these may become additional strategies for the prevention of AMD. These findings also demonstrate the efficiency of mixed-effect model and the use of multiple measurements in statistical models to detect associations with the risk of disease.

Figure legend

Figure 1. Prevalence of Metabolic Syndrome and its Components at Baseline, 5- and 10-year Follow-up among Individuals with Early and Late Stage AMD according to Age Group

AMD=age-related macular degeneration; BMI=body mass index; BP=blood pressure; MetS=metabolic syndrome; HDL=high density lipoprotein.

References

1. McCarty CA, Dowrick A, Cameron J, et al. Novel measures of cardiovascular health and its association with prevalence and progression of age-related macular degeneration: the CHARM Study. BMC Ophthalmol 2008;8:25.
2. Shankar A, Mitchell P, Rochtchina E, et al. Association between circulating white blood cell count and long-term incidence of age related macular degeneration. The Blue Mountains Eye Study. Am J Epidemiol 2007;165:375-82.
3. Brown GC, Sharma S, Brown MM, et al. Utility values and age-related macular degeneration. Arch Ophthalmol 2000;118:47–51.
4. Lim LS, Mitchell P, Seddon JM, et al. Age-related macular degeneration. Lancet 2012 379:1728-38.
5. Alberti KGMM, Zimmet P, Shaw J. Diabetes UK. Metabolic syndrome- a new world-wide definition. A consensus statement from the International Diabetes Federation. Diabetes Medicine 2006; 23:469-80.
6. Friedman E. The role of the atherosclerotic process in the pathogenesis of age-related macular degeneration. Am J Ophthalmol 2000;130:658-63.
7. Chakravarthy U, Wong TY, Fletcher A, et al. Clinical risk factors for age-related macular degeneration: a systematic review and meta-analysis. BMC Ophthalmol 2010;10:31.

8. Peeters A, Magliano DJ, Stevens J, et al. Changes in abdominal obesity and age-related macular degeneration: the Atherosclerosis Risk in Communities Study. Arch Ophthalmol 2008;126:1554-60.
9. Klein R. Epidemiology of age-related macular degeneration. In: Penfold PL, Provis JM, eds. Macular Degeneration: Science andMedicine in Practice. New York, NY: Springer-Verlag; 2005:79-121.
10. Klein R, Deng Y, Klein BE, et al. Cardiovascular disease, its risk factors and treatment, and age-related macular degeneration: Women's Health Initiative Sight Exam ancillary study. Am J Ophthalmol 2007;143:473-83.
11. Vine AK, Stader J, Branham K, et al. Biomarkers of cardiovascular disease as risk factors for age-related macular degeneration. Ophthalmology. 2005 112:2076-80.
12. Delcourt C, Michel F, Colvez A, et al. Associations of cardiovascular disease and its risk factors with age-related macular degeneration: the POLA study. Ophthalmic Epidemiol 2001;8:237-49.
13. Wong TY, Mitchell P. The eye in hypertension. Lancet. 2007;369:425-35.
14. Smith W, Mitchell P, Leeder SR, et al. Plasma fibrinogen levels, other cardiovascular risk factors, and age-related maculopathy: the Blue Mountains Eye Study. Arch Ophthalmol 1998;116:583-87.
15. Tan JSL, Mitchell P, Smith W, et al. Cardiovascular risk factors and the long-term incidence of age-related macular degeneration. The Blue Mountains Eye Study. Ophthalmology 2007;114:1143-50.

16. Tomany SC, Wang JJ, Van Leeuwen R, et al. Risk factors for incident age-related macular degeneration: pooled findings from 3 continents. Ophthalmology 2004;111:1280-7.
17. Klein R, Klein BE, Jeensen SC. The relationship of cardiovascular disease and its risk factors to the 5-year incidence of age-related maculopathy. The Beaver Dam Eye study. Ophthalmology 1997;104:1804–12.
18. Klein R, Klein BE, Moss SE. Diabetes, hyperglycemia, and age-related maculopathy. The Beaver Dam Eye Study. Ophthalmology 1992;99:1527–34.
19. Mitchell P, Wang JJ. Diabetes, fasting blood glucose and age-related maculopathy. The Blue Mountains Eye Study. Aust NZ J Ophthalmol 1999;27:197–9.
20. Leske MC, Wu SY, Hennis A, et al. Nine-year incidence of age-related macular degeneration in the Barbados Eye Studies. Ophthalmology 2006;113:29–35.
21. Clemons TE, Milton RC, Klein R, et al. Risk factors for the incidence of advanced age-related macular degeneration in the Age-Related Eye Disease Study. AREDS report No 19. Ophthalmology 2005;112:533–9.
22. Chiang PP, Lamoureux EL, Zheng Y, et al. Frequency and risk factors of non-retinopathy ocular conditions in people with diabetes: the Singapore Malay Eye Study. Diabet Med 2013;30:e32-40.

23. Zimmet P, Magliano D, Matsuzawa Y, et al. The metabolic syndrome: a global public health problem and a new definition. J Atheroscler Thromb 2005;12:295-300.
24. Mitchell P, Smith W, Wang JJ, et al. Diabetes in an older Australian population. Diabetes Res Clin Pract 1998;41:177-84.
25. 2003 World Health Organization (WHO)/ International society of hypertension (ISH) statement on management of hypertension. J Hypertens 2003;21:1983-92.
26. Cugati S, Wang JJ, Rochtchina E, et al. Ten-year incidence of diabetes in older Australians: the Blue Mountains Eye Study. Med J Aust 2007;186:131-35.
27. World health Organization. Definition, Diagnosis and Classification of Diabetes Mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Geneva: WHO, 1999.
28. Mitchell P, Smith W, Wang JJ. Iris color, skin sun sensitivity, and age-related maculopathy. The Blue Mountains Eye Study. Ophthalmology 1998;105:1359-63.
29. Mitchell P, Smith W, Attebo K, et al. Prevalence of age-related maculopathy in Australia: the Blue Mountains Eye Study. Ophthalmology 1995;102:1450–60.
30. Klein R, Davis MD, Magli YL, et al. The Wisconsin Age-Related Maculopathy Grading System. Ophthalmology 1991;98:1128 –34.

31. Bird AC, Bressler NM, Bressler SB, et al. An international classification and grading system for age-related maculopathy and age-related macular degeneration. Surv Ophthalmol 1995;39:367–74.
32. Agresti A. Categorical Data Analysis (^{3}rd Ed.), Hoboken, New Jersey: John Wiley & Sons; 2012:429-527.
33. Brown H, Prescott R. Applied Mixed Models in Medicine, 2^{nd} Edition. John Wiley and Sons; 2006: 22-30 & 215-225.
34. Klein BE, Klein R, Lee KE, et al. Measures of obesity and age-related eye diseases. Ophthalmic Epidemiol 2001;8:251–62.
35. Seddon JM, Gensler G, Milton RC, et al. Association between C-reactive protein and age-related macular degeneration. JAMA 2004;291:704–10.
36. Hidayat AA, Fine BS. Diabetic choroidopathy light and electron microscopic observations of seven cases. Ophthalmology 1985;92:512–22.
37. Fryczkowski AW, Sata SE, Hodes BL. Changes in the diabetic choroidal vasculature: scanning electron microscopy findings. Ann Ophthalmol 1988;20:299–30.

Table 1. Baseline Characteristics of Study Subjects according to 10-year Cumulative Incidence of Age-Related Macular Degeneration

	Total (n=2218)	Early AMD (n=2114)			Late AMD (n=2218)		
		No (n=1852)	Yes (n=262)	*P*-value	No (n=2148)	Yes (n=70)	*P*-value
Age (year) (%), ≤ 70	1697 (76.5)	1546 (79.0)	151 (57.6)	< 0.001	1668 (77.6)	32 (45.7)	< 0.001
>70	521 (23.5)	410 (21.0)	111 (42.4)		480 (22.4)	38 (54.3)	
Sex (%), Male	935 (42.2)	804 (43.4)	92 (35.1)	0.011	914 (42.5)	21 (30.0)	0.036
Female	1283 (57.8)	1048 (56.6)	170 (64.9)		1234 (57.4)	49 (70.0)	
Smoking status, Never	1159 (52.3)	964 (52.0)	141 (53.8)	0.492	1128 (52.5)	32 (45.6)	0.105
Former	781(35.2)	654 (35.4)	95 (36.2)		758 (35.3)	24 (33.8)	
Current	278 (12.5)	234 (12.6)	26 (10.0)		262 (12.2)	14 (20.6)	
Pre-existing cardiovascular disease (%)[a]	359 (16.2)	268 (14.5)	65 (24.8)	< 0.001	342 (15.9)	17 (24.3)	0.062
Sun skin-burned (%)							
Always burn, never tan	308 (13.9)	245 (13.2)	45 (17.2)	0.203	290 (13.5)	17 (23.9)	0.010
Usually burn, tab with difficulty	543 (24.5)	456 (24.6)	71 (27.1)		535 (24.9)	7 (10.4)	
Burn and tab above average	874 (39.4)	733 (39.6)	93 (35.5)		849 (39.5)	27 (38.8)	
Rarely burn, tab above average	493 (22.2)	418 (22.6)	53 (20.2)		474 (22.1)	19 (26.9)	
Eye iris color (%)							
Blue	1074 (48.4)	880 (47.5)	141 (53.8)	0.153	1038 (48.4)	37 (52.2)	0.056
Hazel/Green	633 (28.5)	544 (29.4)	67 (25.6)		619 (28.8)	14 (20.3)	
Tan\Brown	277 (12.5)	241 (13.0)	25 (9.5)		271 (12.6)	6 (8.7)	
Dark brown	234 (10.6)	187 (10.1)	29 (11.1)		220 (10.2)	13 (18.8)	
Family history of any eye disease (%)[b]	695 (31.3)	582 (31.4)	81 (30.9)	0.868	667 (31.0)	28 (40.0)	0.112
History of any eye disease at baseline (%)[c]	914 (41.2)	737 (39.8)	119 (45.4)	0.083	879 (40.9)	35 (50.0)	0.129
MetS (%)	271 (12.2)	236 (12.7)	24 (9.2)	0.098	263 (12.2)	8 (11.4)	0.838
BMI > 30 (%)	386 (17.4)	329 (17.8)	38 (14.5)	0.192	373 (17.4)	13 (18.6)	0.793
High glucose (%)[d]	345 (15.5)	291 (15.7)	40 (15.3)	0.853	330 (15.4)	15 (21.4)	0.168
Low-HDL (%)[e]	664 (29.9)	564 (30.4)	72 (27.5)	0.326	637 (29.7)	27 (38.6)	0.109
High triglyceride (%)[f]	916 (41.3)	765 (41.3)	110 (42.0)	0.835	882 (41.1)	34 (48.6)	0.209
High BP (%)[g]	1890 (85.2)	1565 (84.5)	229 (87.4)	0.220	1825 (85.0)	65 (92.9)	0.067

AMD= age-related macular degeneration; BMI=body mass index; MetS=metabolic syndrome; HDL=high density lipoprotein BP=blood pressure;
[a] Includes history of angina, stroke and AMI; [b]Includes family history of cataract, glaucoma, macular and blindness; [c] Includes history of cataract, myopia and glaucoma ; [d] fasting plasma glucose ≥ 5.6 mmol/L, or previous diagnosis or specific treatment for type 2 diabetes; [e] serum HDL cholesterol < 1.03 mmol/L in men and < 1.29 mmol/L in women, or specific treatment for this lipid abnormality; [f] serum triglyceride level ≥ 1.7 mmol/L or specific treatment for this lipid abnormality; [g] systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg, or treatment of previously diagnosed hypertension.

Table 2: Prevalence of MetS and its Components over 10-year Follow-up

	Baseline (n=2218)	5-year (n=2118)	10-year (n=1600)
MetS (%)	271 (12.2)	348 (16.4)	227 (14.2)
BMI > 30 (%)	386 (17.4)	488 (23.0)	379 (23.7)
High glucose (%)[a]	345 (15.5)	479 (24.0)	307 (21.5)
Low-HDL (%)[b]	664 (29.9)	548 (27.2)	586 (29.0)
High triglyceride (%)[c]	916 (41.3)	898 (40.5)	327 (27.8)
High BP (%)[d]	1890 (85.2)	1929 (91.0)	1352 (81.1)

BMI=body mass index; BP=blood pressure; MetS=metabolic syndrome; HDL=high density lipoprotein

[a] fasting plasma glucose ≥ 5.6 mmol/L, or previous diagnosis or specific treatment for type 2 diabetes; [b] serum HDL cholesterol < 1.03 mmol/L in men and < 1.29 mmol/L in women, or specific treatment for this lipid abnormality; [c] serum triglyceride level ≥ 1.7 mmol/L or specific treatment for this lipid abnormality; [d] systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg, or treatment of previously diagnosed hypertension.

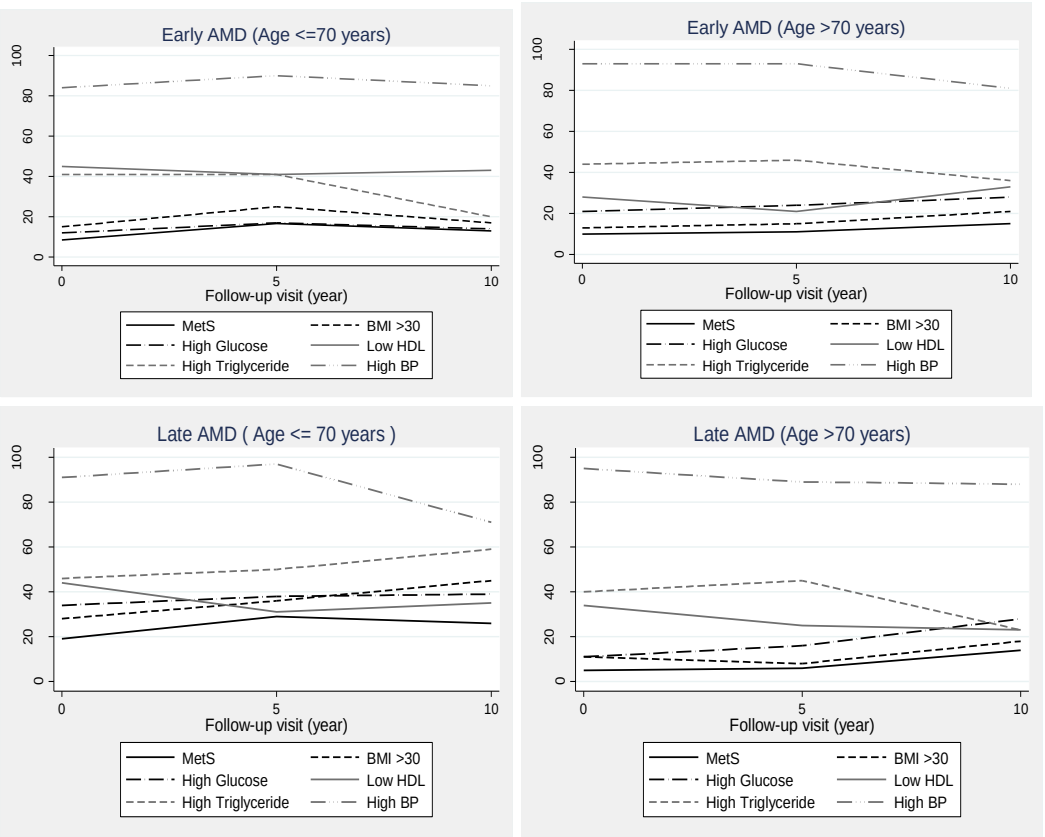
Table 3. Age-Specific Associations between Metabolic Syndrome and its Components on Incidence of Early and Late AMD over 10-year Follow-up according to Age

	Age ≤ 70 years		Age > 70 years	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Early AMD				
MetS	0.93 (0.59-1.45)	0.733	0.91 (0.44-1.90)	0.806
BMI > 30	0.88 (0.60-1.30)	0.521	0.95 (0.51-1.79)	0.879
High glucose [a]	0.77 (0.49-1.22)	0.271	1.05 (0.61-1.83)	0.855
Low-HDL [b]	0.84 (0.59-1.19)	0.324	0.66 (0.38-1.14)	0.141
High triglyceride [c]	0.60 (0.41-0.88)	0.009	1.37 (0.85-2.20)	0.202
High BP [d]	1.18 (0.74-1.87)	0.496	0.56 (0.27-1.13)	0.107
Late AMD				
MetS	2.16 (1.01-4.65)	0.049	0.42 (0.09-1.91)	0.260
BMI > 30	2.22 (1.09-4.49)	0.027	0.24 (0.05-1.11)	0.068
High glucose [a]	3.12 (1.48-6.56)	0.003	1.03 (0.38-2.76)	0.956
Low-HDL [b]	1.78 (0.89-3.57)	0.103	0.61 (0.25-1.49)	0.275
High triglyceride [c]	2.06 (1.01-4.22)	0.047	1.03 (0.47-2.25)	0.943
High BP [d]	0.84 (0.34-2.06)	0.696	0.56 (0.19-1.61)	0.278

AMD= age-related macular degeneration; BMI=body mass index; BP=blood pressure; HDL=high density lipoprotein; CI=confidence interval; OR=odds ratio.

[a] fasting plasma glucose ≥ 5.6 mmol/L, or previous diagnosis or specific treatment for type 2 diabetes; [b] serum HDL cholesterol < 1.03 mmol/L in men and < 1.29 mmol/L in women, or specific treatment for this lipid abnormality; [c] serum triglyceride level ≥ 1.7 mmol/L or specific treatment for this lipid abnormality; [d] systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg, or treatment of previously diagnosed hypertension.

*Adjusted for sex, pre-existing cardiovascular disease (namely, angina, acute myocardial infarction and stroke) and including interaction between age and MetS (or its components)



AMD=age-related macular degeneration; BMI=body mass index; BP=blood pressure; MetS=metabolic syndrome; HDL=high density lipoprotein.

Figure 1. Prevalence of Metabolic Syndrome and its Components at Baseline, 5- and 10-year Follow-up among Individuals with Early and Late Stage AMD according to Age Group

Appendix 1. Age-Specific Associations between Baseline Metabolic Syndrome and its Components with 10-year Cumulative Incidence of Early and Late AMD according to Age via Conventional Logistic Regression

	Age ≤ 70 years		Age > 70 years	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Early AMD				
MetS	0.58 (0.33-1.02)	0.056	0.98 (0.46-2.07)	0.952
BMI > 30	0.74 (0.47-1.16)	0.187	0.84 (0.43-1.63)	0.608
High glucose [a]	0.75 (0.46-1.23)	0.253	1.51 (0.85-2.70)	0.162
Low-HDL [b]	0.82 (0.57-1.18)	0.284	0.91 (0.54-1.52)	0.727
High triglyceride [c]	0.91 (0.66-1.27)	0.593	1.28 (0.80-2.03)	0.298
High BP [d]	1.07 (0.69-1.66)	0.764	0.75 (0.30-1.87)	0.537
Late AMD				
MetS	1.50 (0.61-3.70)	0.375	0.43 (0.10-1.86)	0.258
BMI > 30	1.67 (0.76-3.66)	0.198	0.61 (0.21-1.79)	0.367
High glucose [a]	2.29 (1.09-4.80)	0.029	0.61 (0.21-1.79)	0.368
Low-HDL [b]	1.84 (0.91-3.75)	0.091	1.35 (0.66-2.77)	0.410
High triglyceride [c]	1.22 (0.60-2.49)	0.589	1.01 (0.50-2.00)	0.994
High BP [d]	1.96 (0.59-6.48)	0.270	1.07 (0.24-4.76)	0.931

AMD= age-related macular degeneration; BMI=body mass index; BP=blood pressure; HDL=high density lipoprotein; CI=confidence interval; OR=odds ratio.

[a] fasting plasma glucose ≥ 5.6 mmol/L, or previous diagnosis or specific treatment for type 2 diabetes; [b] serum HDL cholesterol < 1.03 mmol/L in men and < 1.29 mmol/L in women, or specific treatment for this lipid abnormality; [c] serum triglyceride level ≥ 1.7 mmol/L or specific treatment for this lipid abnormality; [d] systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg, or treatment of previously diagnosed hypertension.

*Adjusted for sex, pre-existing cardiovascular disease (namely, angina, acute myocardial infarction and stroke) and including interaction between age and MetS (or its components)