國立臺灣大學公共衛生學院流行病學與預防醫學研究所

碩士論文

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健康生活分數對於心血管疾病的保護作用：台灣具代表性的世代研究

The protective effects between Healthy Lifestyle scores and the Risk of Cardiovascular diseases: a representative Cohort study in Taiwan

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國立臺灣大學碩士學位論文
口試委員會審定書

論文中文題目：健康生活分數對於心血管疾病的保護作用-台灣具代表性的世代研究

論文英文題目 The Protective Effects between Healthy Lifestyle Scores and the Risk of Cardiovascular diseases: a representative Cohort study in Taiwan

本論文係 蔡明潔 君（學號 R07849036）在國立臺灣大學流行病學與預防醫學研究所完成之碩士學位論文，於民國 109 年 6 月 2 日承下列考試委員審查通過及口試及格，特此證明。

口試委員：

向國龍 （簽名）

（指導教授）

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摘要

背景:

合併健康生活習慣，包括理想體重，健康飲食，適當運動，不抽菸,適量的飲酒，對於心血管疾病的保護效果過去有被證實，但是除了單純的五個健康生活習慣相加結合成健康生活分數外，沒有研究討論過在討論心血管疾病風險時是否需要加權不同的健康生活習慣，而且也不曾有研究將之與World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR) 為了預防癌症所提出的健康生活分數，或是美國心臟醫學會所提出的Life’s Simple 7健康生活分數做心血管疾病發生風險預測比較。

方法:

我們使用一個平均年齡43歲，50.2%女性的全國代表性世代追蹤資料庫【三高主題資料庫】排除掉在2002年受訪前健保資料有記錄到心血管疾病的6042位受訪者，我們定義簡單台灣健康分數為一個包含理想體重、地中海飲食、適量運動、不抽菸、規則飲酒的五個向度的加總分數。我們並且使用這五個因子對於心血管疾病多變量模型中的係數值(coefficient)做為權重，另外加總成一個權重的台灣心血管健康分數。我們並且使用WCRF/AICR 2018年對於健康生活分數的定義和美國心血管協會對於Life’s Simple 7的定義，使用三高主題資料庫去驗證這健康生活分數對於心血管疾病的保護效果，並且比較四個健康生活

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分數對於心血管疾病的預測能力。

結果:

在一個平均 13.4 年的追蹤期間，全部共有 520 個心血管疾病發生，多變量的存活分析顯示，在簡單和加權台灣健康分數最高的組別，相較分數最低的組別，心血管疾病發生率顯著的下降 56~57%，並且年紀是有意義的干擾因子。但在校正了許多臨床因子之後，WCRF/AICR 的健康生活分數和 Life’s Simple 7 卻沒有辦法觀察到顯著的保護效果。在年紀小於 60 歲的族群，因著健康生活分數的保護讓心血管疾病下降的幅度顯著的大於等於 60 歲的族群。除此之外，在 AUC 和 NRI, IDI 對模型的預測力統計量當中，簡單和權重的台灣健康生活分數相較於 WCRF/AICR 健康生活分數和 Life’s Simple 7 有較好且顯著的增加預測效果。

討論與結論:

我們證明了健康生活分數較高的人相較較低的人，心血管疾病發生率有顯著的下降，並且下降的幅度在年輕人更為明顯。進一步的研究探討綜合所有健康生活習慣對於心血管疾病的保護機轉是有必要的。

關鍵字:

健康生活分數，心血管疾病

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Abstract

Background

The protective effect of different healthy lifestyle scores for the risk of cardiovascular disease (CVD) was reported but the comparisons of performance were lack. We compared the performance measures of cardiovascular diseases from different healthy lifestyle scores among adult Taiwan.

Methods

We conducted a nationwide prospective cohort study of 6042 participants (median age 43 years, 50.2% women) in Taiwan's Hypertensive, Hyperglycemia, Hyperlipidemia Survey, 2002 who were free of CVD at baseline. Simple Taiwan healthy lifestyle score was defined as a normal body mass index, Mediterranean diet >= points, adequately physical activity 1~150 mins/week, not smoking and regular healthy drinking. A weighted healthy Taiwan healthy lifestyle score also was created, where each dichotomous lifestyle factor was first weighted according to its independent magnitude of effect. World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) cancer prevention recommended lifestyle and Life's Simple 7 following the definition proposed by the American Heart Association were all created.

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Results:

During a median 13.4 years follow-up period, totally 520 cases developed CVD events. In multivariate-adjusted Cox proportional hazard models, adherence to highest category compared with lowest one of simple Taiwan lifestyle score for hazard ratio 0.43 (95% confidence interval [CI] 0.2, 0.94) and weighted Taiwan lifestyle score for 0.44 (95%CI 0.28, 0.68) were independently and significantly (figure 1). In addition, age played a significant effect modifier for the protective effect of healthy lifestyle scores for CVD risk and more reduction of CVD incidence was observed among adults <60 years old and adults ≧60 years old. Specifically, when the simple and weighted Taiwan healthy lifestyle score were added to the classical model, the Harrell's C-statistic increasing from 0.85 to 0.86 (95% confidence interval [CI], 0.84, 087; Pdiff=0.02) in both lifestyle scores. The performance measures by integrated discriminative improvement showed significant increasing after adding simple Taiwan healthy lifestyle score (integrated discriminative improvement: 0.51, 95% CI 0.16, 0.86, P=0.002) and weighted

Taiwan lifestyle score (integrated discriminative improvement: 0.38, 95% CI 0.01,0.74, P=0.021) information.

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Conclusion:

We demonstrated that healthy lifestyle scores had protective effect of CVD, and the reduction of CVD risk was more for young adults than for old adult. Further investigations to study the mechanism of lifestyle role on CVD prevention are warranted.

Keywords:

Healthy lifestyle score，cardiovascular diseases

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Table of Contents

doi:10.6342/NTU202002676

doi:10.6342/NTU202002676

doi:10.6342/NTU202002676

List of Figures

doi:10.6342/NTU202002676

doi:10.6342/NTU202002676

List of Tables

doi:10.6342/NTU202002676

doi:10.6342/NTU202002676

doi:10.6342/NTU202002676

Chapter One：Introduction

Cardiovascular diseases are the leading cause of non- communicable disease with an estimated 31% deaths in worldwide with 17.9 million annually in 2016,[1-2] with 85% attributed to coronary heart disease related heart attack (7.4 million) and stroke (6.7 million). Cardiovascular diseases also caused 330 million years of life lost and another 35.6 million years lived with disability, [2-3] especially in the middle and low-developed country. National United declaimed a 25% relative reduction in the overall mortality from non-community disease.[1] The cardiovascular disease attributed more than 30% and landed a greatest challenges in global public health.

In response, the World Health Organization (WHO) has committed to reducing 25% premature mortality from non-communicable diseases[4-5] by 2025, and one-third premature death by 2030. Due to the possible prevention of multifactorial etiology of cardiovascular disease, primordial approach focusing on ideal weight, promotion of healthy foods (fruits, vegetables, legumes and nuts), curbing unhealthy foods (saturated fats, trans fats, refined carbohydrates), physical activity regular, tobacco control and adequate alcohol consumption[6] have been promotion.

1.1 Ideal weight

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High BMI and associated risk factors account for an estimated 9.7 million annually CVD deaths in the world, after adjusted by multi-causality and for mediation or the effects of high BMI by blood pressure, total cholesterol, and glucose.[7]

There is now an abundance of prospective cohort studying BMI as a CVD risk factor in most regions. Recent researches pooled cohorts and trials not only by age and sex but also by ethnicity and region, especially in western and Asia populations. Although east Asia is the largest number of deaths attributable to the high BMI associated factors, especially those attributable to high blood pressure, the relative risk for the effects of BMI and CVD are similar between Asian and western population.[7-8]

Considering the variety of BMI attributable CVD death stratify according to age in different income level countries, in high-income countries 24% of deaths attributable below 70 years of age and 76% in people aged 70 years and older. Respectively, 43% and 57% in low- and middle-income countries.

Obesity, as measured by body mass index (BMI), was a growing public health issue and increasing disease burden since 1990. Obesity had contributed estimated 4.0 million deaths globally and two third of deaths related to high BMI were due to

doi:10.6342/NTU202002676

cardiovascular disease.[9] Various groups of researchers have worked with the causal relationship between obesity and cardiovascular diseases. For example, Toledo had reported a monotonic linear association between body mass index (BMI) and the cardiovascular risk factors (hypertension, diabetes mellitus and/or metabolic syndrome) already increased at a threshold of BMI as 22 kg/m2 in young adults. The multivariate-adjusted odds ratio for the cardiovascular risk factors for BMI 22-25.9 kg/m2, 25-29.0 kg/m2, >30 kg/m2, compared with BMI <22 kg/m2, were 1.3, 2.7 and 4.0, respectively among 10639 participants follow up 2-6 years. Eckel has demonstrated an meta-analysis of obesity participants with metabolic health, defined as absence of metabolic syndrome, compared to healthy normal-weight, unhealthy normal weight and unhealthy obesity participants with relative risk as 1.45, 0.48 and 0.43, respectively.[10] Riaz has investigated 5 studies with 881,692 participants in an meta-analysis and revealed obesity with a significant higher risk of coronary artery disease (OR, 1.2, 95% CI, 1.02-1.41) but no association between obesity and stroke (OR, 1.02; 95% CI, 0.95-1.09).[11] Although most of studies has been consistently shown the association between obesity and coronary artery disease, overall cardiovascular disease outcome including coronary artery disease and stroke remains controversial. Furthermore, the evidence of preventive cardiovascular disease by obesity as regard to other healthy lifestyle factors were insufficiency.

doi:10.6342/NTU202002676

1.2 Mediterranean diet

The optimal diet to decreasing incidence of CVD, including high intakes of vegetables and fruits, nuts and seeds, whole grains, fiber and fish and low intakes of processed meat, trans fat, sugar-sweetened beverages and other low processed carbohydrates, and salt. Although all agree the important role of optimal lifestyle to protective CVD risks from healthy diet, which diet pattern had more benefit to decrease CVD risks are still controversial. The diet-CVD associations tend to be affected by multiplicity of comparisons, correlated among various components and behavior and social-economic factors, influenced by systematic and random measurement errors and remain selective reporting. Nonetheless, the various diet patterns complicated not only their etiology overlaps but also the potential for substitution. All of above limitations impede the robust elucidation of the presence and magnitudes of causal associations.[12] When considering region and area, the food people intake had personal traits and eating habits with traditional dietary patterns. In east Asia, high salt intake and low trans fat were noted from evidence compared with western countries.[13-17]

Mediterranean diet are the major food groups instead of nutrition and other diet compounds of whole grains/cereals, refined grains/cereals, vegetables, fruits, nuts,

doi:10.6342/NTU202002676

legumes, eggs, dairy products, fish, red meat, processed meat and sugar sweetened beverages. Recent nutrition and chronic disease research have suggested food-based groups may indeed facilitate processes beneficial to the reduction of coronary heart disease, stroke and heart failure.[18] These specific benefits include increased the primary prevention of cardiovascular diseases with greater amount of whole grains, vegetables, fruits, nuts, legumes, dairy and fish but lower consumption of red and processed meat, eggs and sugar sweetened beverages.

Mediterranean diet pattern is a healthy dietary pattern, originally noticeable from three rural Greek villages since 25 years ago.[19-20] The Mediterranean diet pattern has 9 components, including vegetables, legumes, fruits and nuts, fish, dairy products, cereals, meat and meat products, ethanol and monounsaturated vs saturated fat ratio regarding the reduction of mortality. Compared to a typical Western diet, the Mediterranean diet comprises low in saturated fat, high in monounsaturated fat (mainly from olive oil), high in complex carbohydrates (from grains and legumes), and high in fiber (mostly from vegetables and fruits). Total fat may be as high (around 40% of total energy intake) as equal to Western diet, but the difference of Mediterranean is the 2 times even higher monounsaturated: saturated fat ratio. Various groups of researchers have worked with the provocation of dietary

doi:10.6342/NTU202002676

components, the biological interaction between different diet components and the associated prevention of metabolic disease, cardiovascular disease and the reduction of mortality,[21] To date, Mediterranean is challenged by major difficulties in implementing and validation of this protective dietary pattern in other geographical and culture areas.

1.3 Physical activity

Recently decades, epidemiological theorists and researchers were investigating the concept of the association of physical activity and cardiovascular disease. Literatures have noted the evidence between the association. A study of combined BMI and physical activity and the risk of hypertension, diabetes and metabolic syndrome showed physical activity with lower odds of combined end-points (adjusted odds ratio: 0.8) for >15 METs-h/week.[22]

Physical inactivity and insufficient activity attributes global 2.5 million CVD death and results in large CVD burden especially in high-income countries. (A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: A systematic analysis for the global burden of disease study 2010. Lancet. 2012;380:2224-2260) Since 1950s, observational

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studies had indicated decreasing sedentary lifestyle and increasing physical activity were associated with the prevention of CVD incidence but the association was influenced by the same sources of error and bias such considering in diet and BMI. The non-linear dose-response relationship were reported that the benefits of additional activity seem larger at low baseline activity level than among the population had already high activity level original.[23-24]

1.4 Tobacco control-- Non-smoking

Most of the previous studies on smoking described a causal association on the cardiovascular disease. Smoker compared to non-smoker with a significant estimated pooled odds ratio (OR) of 1.61 (95% CI, 1.34-1.93) in the meta-analysis.[25] Considering coronary artery disease, the men with smoking 1 cigarette per day and 20 cigarette per day compared with those without smoking had increasing relative risk 1.48 and 2.04, respectively by an meta-analysis of 55 publications including 141 cohort studies. In regards to women, the relative risks were 1.57 and 2.84, respectively.[26] The smoking status, containing current or former, compared with non-smoking both were observed significant higher risk of stroke, as 1.92 (95% CI: 1.49-2.48) and 1.30(95% CI: 0.93-1.81), respectively.[25] More literature explored the proatherogenic effect of smoking and resulted in the rising risk of cardiovascular

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diseases. [27] Smoking cessation is an important and effectively preventive cardiovascular outcome.

1.5 Adequate Alcohol Consumption

Although alcohol has been consistently shown to be associated with cancers of the oral cavity, esophagus and larynx, hypertension, liver cirrhosis, chronic pancreatitis and injuries and violence, an association between alcohol and cardiovascular disease outcomes remains controversial.[28] A J-shaped relation was described in multiple articles. Corrao had demonstrated a protective threshold values as consumption of alcohol less than 72g/day with minimal relative risk of 0.8 at 20g/day, and a significant growing risk since 89g/day.[28] Ronksley had reported light to moderate drinking with reducing risk of coronary heart mortality as 1-2 drinks a day and of stroke mortality as ≤1 drink a day. Compared with non-drinking, Light to moderate drinking had lower relative risk for cardiovascular disease mortality, incident coronary heart disease, coronary heart disease mortality, incident stroke and stroke mortality were 0.75 (95% CI, 0.70-0.80), 0.71 (0.66-0.77), 0.75(0.68-0.81), 0.98 (0.91-1.06) AND 1.06(0.91-1.23), respectively.[29] Mostofsky also explored moderate alcohol consumption had protective effect for myocardial infarction, hemorrhagic stroke (relative risk: 0.7) and ischemic stroke (relative risk 0.81) but heavy alcohol

doi:10.6342/NTU202002676

drinking increasing the odds of cardiovascular disease.[30] However, the type of alcohol is variety and drinking culture is so different worldwide with complex social-psychological issue. The clear definition of non-harmful alcohol lifestyle remains controversial.

Although the cardioprotective effect from the light or moderate drinking is still controversial, many observational studies investigated that compared with non-drinkers, light to moderate drinking is associated lower risk of CVD and diabetes.[31] A causal association between mild to moderate alcohol and ischemic heart disease and stroke were also supported by Mendelian randomization, which conduct genetic variants involved in alcohol metabolism as proxies for lifelong differences in alcohol consumption. (90) However, an increased risk of ischemic heart disease, stroke and atrial fibrillation were noted from heavy drinking accompanied with binge drinking episodes. (91-93)

1.6 Combined healthy lifestyle factors

Recent prevention medical research has explored that combined multiple healthy lifestyle behaviors compared with single one may indeed facilitate processes beneficial to the prevention of cardiovascular disease[32] (table 1). For example,

doi:10.6342/NTU202002676

Stampfer,[33] Cardi,[34] Carlsson,[35] Paynter,[36] and Diaz-Gutierrez[37] had demonstrated the population with optimal healthy lifestyles with decreasing incidence of overall cardiovascular disease (range from 0.22 to 0.45) compared with non-optimal ones. Stampfer,[33] Akesson,[38-39] Ford,[40] Ahmed,[41] Hoevenaar-Blom,[42] Chomistek,[43] Hulsegge,[44] Lv,[45] were all reported those adherence to combined healthy lifestyle behaviors with lower odds (ranging from 0.08 to 0.54) of developing coronary artery disease compared with those with non-adherence. Ford,[40] Myint,[46] Zhang,[47] Larsson,[48] Lv[45] has suggested that participants with ideal healthy lifestyle factors had reducing the risk of ischemic stroke (ranging from 0.30 to o.50). Besides the benefits of reducing cardiovascular risk in individual, combined healthy lifestyles factor had significantly population attributable fraction (ranging from 0.23-0.68) of the cardiovascular disease.[33, 38, 43, 45, 47, 49-51] Most of the studied population were from developed countries, in which the characteristics of public health challenging are non-communicated disease, like in Europe,[35, 37-40, 46-48, 51-52] and in United status[33-34, 36, 41, 43, 49-50, 53] and one of them in China.[45] While the investigations in the most prevalent areas of cardiovascular diseases such as the undeveloped or developing countries are lack. In additions, more and more studies focused on not only the reduction of the risk but also what components of the population would modify the benefits of combined lifestyle factors to cardiovascular disease, such as gender,[35, 51-52] age,[54] and the

doi:10.6342/NTU202002676

prevalence of diabetes. However, the evidence of most beneficial population who should be enhanced the healthy lifestyle factors was not sufficient and needs further study.

1.7 Weighted combined healthy lifestyle score

Most studies combine the lifestyle score with each of healthy lifestyle factor weighted equally. The combination of lifestyle with the same weight with an assumption of each factor with the same effect in lifestyle score but easily leading to misclassification bias. Agha had reported the association between weighted healthy lifestyle score and heart failure with the similar effect as non-weighted healthy lifestyle score.[49]

1.8 Healthy lifestyle score from World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR)

Seminal work on defining the prevention of cancer was carried out by hundreds of studies, still the reference point for virtually all discussion of the healthy lifestyle factors, such as diet pattern, the ideal weight, the exposure to alcohol or tobacco, in relation to cancer. Since 20 years ago, the large international, multi-center prospective cohort study, European Prospective Investigation in to Cancer and Nutrition

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(EPIC),[55-57] was initiated to confirmed the common sense of the foods with lower cancer risk, such as fruits and vegetables, the higher cancer risk, like fat, and meat, and the food with uncertain role of cancer risk, for example, dairy products and fish. In 2007, World Cancer Research Fund/ American Institute for Cancer Research reported the Second Expert Report on lifestyle recommendations[58] for potentially reducing cancer risk in adults based on the comprehensive meta-analysis of over 500 investigations. The recommendation defined a well-being healthy lifestyle to prevent the incidence of cancer including maintaining the body mass index in the normal range, having sufficiently physical activity, prevention of alcohol exposure and living in healthy diet pattern. The healthy diet pattern contained adequacy and moderation. We summary the components of adequacy and moderation, that for adequacy comprised (1) fruits and vegetables, excluded potatoes, beans, corn, and peas, (2) unprocessed grains/cereals (3) legumes; and fir the moderation comprised (1) red meat, including beef, ham, bacon, sausages, liver, sweet breads, (2) sugar‐sweetened beverages, including fruit drinks, fruit juices, carbonated drinks and sugar in coffee or tea (3) sodium. Little literature has been published on the area of the diet recommendation from World Cancer Research Fund/ American Institute for Cancer Research and the association of the cardiovascular disease risk.

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1.9 Healthy lifestyle score of Life's Simple 7

As developed by the Goals and Metrics Committee of the Strategic Planning Task Force of the AHA (American Heart Association) in 2009, the 2020 Impact Goals for the organization was the reduction of 20% deaths from CVD and stroke.[59] American Heart Association's had defined a construct of ideal cardiovascular health with four favorable health behaviors, including abstinence from smoking within the last year, ideal body mass index (BMI), physical activity at goal, and consumption of a dietary pattern that promotes cardiovascular health, and three health factors, such as serum total cholesterol < 200 mg/dL, blood pressure <= 120/80 mmHg, and no diabetes. and risk factors to improve cardiovascular primordial prevention. The seven including ideal weight, healthy diet, adequate physical activity, quit alcohol and the healthy cardio-prevention metrics

The association defined a new healthy concept, cardiovascular healthy which named “Life's Simple 7”, facilitate the preventions of cardiovascular disease and stroke, included increasing the factor adherence to healthy lifestyle, contained nonsmoking, non-obesity (body mass index less than 25 kg/m^2), achievement of the ideal physical activity) and healthy diet, and increase the healthy factors, such as untreated total cholesterol less than 200mg/dL, untreated blood pressure less than 120/80 mmHg and

doi:10.6342/NTU202002676

untreated fasting plasma glucose less than 100mg/dL. According to the Life's Simple 7 categories, adults in optimal level, intermediate level and poor level have unequal risk of cardiovascular events. Nearly one hundred groups of researchers have worked with the implication and validation of the Life's Simple 7 to different population, age, gender and race.[60-67] Most of the previous studies on the Life's Simple 7 described on the countries in other than Asia. The studies supported the effectiveness to improve the cardiovascular healthy in community and in early lifetime. We didn't find any publications that reported a prospective cohort investigating the Life's Simple 7 in Asia population.

1.10 Taiwanese Survey on Hypertension, Hyperglycemia, and Hyperlipidemia (TwSHHH)

Taiwanese Survey on Hypertension, Hyperglycemia, and Hyperlipidemia (TwSHHH) were launched in 2002 with 7578 participants, as a sub-set for hypertension, hyperglycemia and hyperlipidemia, from Taiwanese National Health Interview Survey (NHIS) to examine the risk factor for chronic metabolic disease in Taiwanese. As a random sampling and the link of national health insurance research database, the participants of TwSHHH could represented a national-wide population and high quality national prospective cohort with primary data information.

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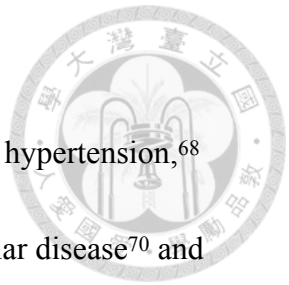

TwSHHH have supported many publications, providing insight into hypertension,[68] hyperglycemia, hyperlipidemia, metabolic syndrome,[69] cardiovascular disease[70] and mortality[71] as well as illuminating the role of diet, lifestyle, and genetics in chronic disease prevention. The TwSHHH studies provided evidence specific to Taiwan area that allows individuals, health care providers, and policy makers to reach informed decisions.

1.11 Hypothesis and Research Gap

The protective effects between combined healthy lifestyle factor as lifestyle score and the risk of CVD had evidence in previous studies, especially in American and European race. However, it is unclear in Asia population whether adherence to healthy lifestyle score could further lead to the reduction in the lifetime risk of CVD and the magnitude of population attribution fraction of healthy lifestyle score on the incidence of CVD. Further, the non-weighted healthy lifestyle score assumed all lifestyle factors with the same magnitude of effect and potentially leaded to the misclassification bias. A demonstration of beneficial influence of weighted healthy lifestyle score from the reducing CVD risk has important clinical implication. Healthy lifestyle score from the recommendation of WCRF/AICR has been shown to

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favorably influence of cancer risk but little evidence about CVD risk. Therefore, to exam the impact of a healthy lifestyle score from WCRF/ACIR on CVD risk is of particular interest. In addition, beside combined healthy lifestyle factors and healthy lifestyle score from WCRF/ACIR, healthy lifestyle score from American Heart Association namely Life's Simple 7 has been proposed the inverse association of CVD risk. However, we were particularly interested in the predictive performance of CVD among combined healthy lifestyle factors, healthy lifestyle score from WCRF/AICR and Life's Simple 7. Finally, age as a potential effect modifier on the association between healthy lifestyle score and CVD has been studied in a secondary data but no validation in primary analysis. Further evidence was lack whether targeting younger adult for primordial prevention of CVD would be more feasible compared with older adults in clinical studies.

Accordingly, the current study sought to assess whether a healthy lifestyle score, as captured by a combination of non-obesity BMI, healthy dietary quality, physical activity, non-smoking and adequate drinking is associated with CVD risk in a representative cohort of Taiwan adults from the Taiwanese Survey on Hypertension, Hyperglycemia, and Hyperlipidemia. Furthermore, we weighted each lifestyle factor according to its independent magnitude of effect on CVD and estimate the impact.

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In additional, we evaluated the performance ability of different healthy lifestyle score on predicting the CVD risk.

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Chapter Two：Materials and Method

2.1 Study design and participants

We conducted analyses in Taiwan's Hypertensive, Hyperglycemia, Hyperlipidemia Survey, 2002. (Taiwan's Triple High Survey, 2002,TwSHHH) 44, a prospective cohort of 6706 participants (age>= 15 years old)in 2002. The protocol was reviewed and approved by the Research Ethics Committee of National Taiwan University Hospital. The committee was organized under and operated in accordance with the Good Clinical Practice Guidelines (NTUH-REC Number: 201901103W [Institutional Review Board reference, IRB]). Taiwan's Triple High Survey, 2002 was using face-to-face questionnaire interviews during March 11.2002 to August 10, 2002 and recruited 7578 random sample from Taiwan National Health Interview Survey.45-46 Participants enrolled in Taiwan's Triple High Survey, 2002 provided information on medical history, lifestyle factors and blood drawing data. In 2007, the follow-up of the Triple High cohort was done again as Taiwan's Triple High Survey, 2007. With the informed consent of eligible participants, the Taiwan's triple high cohort were linked to the National Health Insurance Research Database from January 1, 2000 to December 31, 2015. The National Health Insurance program is a universal, single-payer, and compulsory health insurance system that covers 99% of the 23 million residents in Taiwan. The National Health Insurance included ambulatory care,

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inpatient care, dental service, prescription drugs, registration file, and scrambled identification numbers released for public access and International Classification of Disease-9 and 10 (ICD-9 and ICD-10) codes of discharge diagnosed. In the current investigation, the Taiwan's Triple High Survey, 2002 was used as baseline information. All eligible participants in this study were excluded if prior to the enrollment date of 2002 Taiwan's Triple High Survey (1) they hadn't been 20 years old (2) they had pregnancy within 1 year (3) they had records of coronary artery disease and ischemic stroke from National Health Insurance (4) their identical numbers linking to Taiwan National Health Interview Survey or National Health Insurance Research Database were missing.

2.2 Assessment of health lifestyle factors

We considered five lifestyle factors: ideal body mass index (BMI) (table 2), alternative Mediterranean diet pattern (table 3), achievement of the physical active goal (table 4), non-smoking status (table 5), and healthy alcohol consumption (table 6). BMI was calculated as weight in kilograms divided by the square of height in meters from self-reported data in 2002 but the measurement from trained questionnaire staff in 2007 and categorized as non-obesity (BMI < 27) and obesity (BMI≧27) according to Taiwan Recommendation (table 2). Data used to generate the

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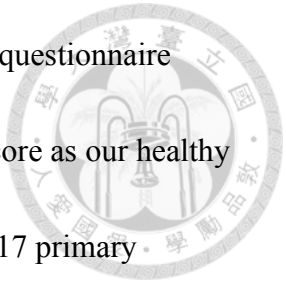

healthy diet patterns were derived from a simplified food frequency questionnaire with 20 items of food. We used the alternative Mediterranean diet score as our healthy dietary score. The alternative Mediterranean diet included 11 of the 17 primary criteria contained in the Mediterranean dietary score (table 3): fresh vegetables, legumes, fresh fruits, dairy products (milk, goat's milk, fermented milk, cheese, yogurt, Yakult), grains (rice or noodle), meat (beef, pork, goat, chicken), fish, eggs, sweets (cookies, candies, chocolate, cakes, bread, ice cream, milkshake), nonalcoholic beverages (cola, soda or sweet-beverage), saturated lipid (burger, French frizzed, pizza). The alternative Mediterranean diet score was calculated by the frequency of intake and summed across all 11 components. Participants with an alternative Mediterranean diet score less than 6 points were assigned to non-adherence of alternative Mediterranean diet as zero point. Those with an alternative Mediterranean diet score of six or more than six points were assigned to adherence of alternative Mediterranean diet score as 1 point.

Physical activity during the past 2 weeks were categorized as adequate active (1~50, 51~100, 101~150 minutes/week) and non-optimal active including inactive (0 minute/week) or overactive (> 150 minutes/week) (table 4). Smoking status was categorized as current Smoking≧20 year, current smoking < 20 year, quit smoking < 1 year, quit smoking≧1 year and never smoking (table 5). The participants were

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questioned about the usually drinking status and categorized as frequency alcohol consumption (dinking every day with undrunk, half-drunk or drunk; drinking per 2 days with half-drunk or drunk; drinking once a week with drunk) or few (drinking less than once a week or drinking per 2 days with undrunk) or non-alcohol consumption (table 6). A detailed description of the questions and definition on ideal BMI, healthy diet, adequate physical activity, non-smoking status and frequency alcohol consumption was based on the current literature, recommended guidelines but also on levels realistically obtainable within the general population.

2.3 Simple Taiwan healthy lifestyle scores

We created a simple pragmatic combined healthy lifestyle score. We created a healthy lifestyle score to sum each dichotomous lifestyle factor as "optimal" versus "nonoptimal" as follows: normal BMI (BMI < 25 kg/m2) versus obese (BMI >=25 kg/m2), alternative Mediterranean diet 6 or higher points versus less than 6 points, ideal physical activity versus unideal physical activity , never smoking versus current or quit smoking and healthy drinking versus no drinking (table 7). The participants received 1 point for each optimal criterion met, and points were summed to obtain a HL-score ranging from 0 (nonoptimal) to 5 (optimal). Participants scored one point for each of the following health lifestyle criterion met: healthy diet, non-harmful

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alcohol, non-obesity, adequate physical activity and non-current smoking. Participants could therefore have a total health lifestyle score ranging from 0-5 and were divided into five lifestyle groups: unhealthy lifestyle (none, one; 0–1), intermediate unhealthy lifestyle (two healthy lifestyle factors; 2), intermediate lifestyle (three healthy lifestyle factors; 3) intermediate healthy lifestyle (four healthy lifestyle factors; 4) healthy lifestyle (five healthy lifestyle factors; 5).

2.4 Weighted Taiwan healthy lifestyle score

A weighted healthy lifestyle-score named the Taiwan healthy lifestyle score also was created, where each dichotomous lifestyle factor was first weighted according to its independent magnitude of effect (ex: beta coefficient adjusted for the other dichotomized lifestyle factors) on cardiovascular disease risk (table 8). Taiwan healthy lifestyle score was obtained from the sum of the weighted points attained by each individual, which range from 0 (Nonoptimal) to 17 (optimal). Taiwan healthy lifestyle score was classified into 4 groups for analyzing as quintile of people for comparing with healthy lifestyle score.

2.5 The World Cancer Research Fund International/ American Institute for Cancer Research (WCRF/AICR) lifestyle score

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In accordance with WCRF/AICR 2018 definition, the WCRF/AICR lifestyle score was created which was a composite numerical measure of the adherence of health lifestyle and consisting of 7 main components, with each scored based on a 0, 0.25, 0.5 and 1 scale (0 point = least healthy; 10 points = most healthy) (table 9). According to recommendation of be a healthy weight, BMI was categorized as 18.5–24.9 kg/m2, 25–29.9 kg/m2 and either <18.5 or ≥30 kg/m2 for analyses. For being physically active, total moderate-vigorous physical activity was categorized as ≥150 mins/week, 75–<150 mins/week and <75 mins/week. For health dietary habits, fruits and vegetables were categorized according to the frequency of intake as one of them every day, one of them 1~5 times per week or both of them less than once/week; the frequency of bean intake was categorized as intake of bean every day , 1~5 times per week or less than 1 time per week. For limited consumption of "fast foods" and other processed foods high in fat, starches or sugars, the frequency of French fried or pizza intake was representative ultra-processed foods (aUPFs) and categorized tertiles. For limited consumption of red and processed meat, the frequency of pork, beef, goat, chicken and burger intake were representative and categorized tertiles, too. Limited consumption of sugar-sweetened drinks was defined by no intake of cola, soda and other sweetened drinks, < 3 times per week or ≧3 times per week. Participants was categorized into no drinking, few drinking and frequency drinking for the

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recommendation of limited alcohol consumption. All points of 7 components was sumed as WCRF/AICR healthy lifestyle score .

2.6 Life's Simple 7 score

Based on the 2019 AHA update criteria of cardiovascular health, the Life's Simple 7 score in our study included core health behaviors (weight, diet, physical activity and smoking) and health factors (cholesterol, blood pressure and glucose control). We defined the health heart participants with body mass index of >= 30, 25~29.9 and < 25 kg/m2 as poor health, intermediate health and ideal health (table 10). We categorized achievement of the alternative ideal health diet (table 11) of Life's Simple 7: >= 7 times per week of fruits and vegetables; >= 1 times per week of fish; >= 1 cup per day of grains (rice and noodles); >= 7 times per week of legumes; < 1 time per week of sugar-sweetened beverages (cola, soda and other sweetened beverages); < 1 time per week of processed meat (beef, pork, goat, and burgers) and < 1 time per week of saturated fat (French fried and pizza). We calculated the frequency of intake and summed across all food items. Participants with an alternative ideal health diet of Life's Simple 7 scoring 0~2, 3~4 and 5~7 points had poor health, intermediate health and ideal health, respectively. The weekly time of physical activity were derived from interview. We calculated the frequency of bouts of exercise by multiplying the times

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of each bouts by the frequency in previous two weeks and summed across all exercise. The achievement of physical active goal were categorized according to Life's Simple 7 (poor health: 0 min/week; Intermediate health: 0~149 min/week moderate intensity or 0~74 min/week vigorous intensity; ideal health: >=150 moderate intensity or >=75 vigorous intensity or combination). Participants who had still currently smoking were defined as poor health. Former smokers but had quit within previous 12 months as intermediate level and those who had never smoked or quit more than 12 months were defined as optimal level.

We categorized poor health, intermediate health and ideal health in 3 cardiovascular health metric including total cholesterol(poor health: <200 mg/dL; intermediate health: 200-240 mg/dL ; ideal health: >240 mg/dL), blood pressure (poor health: systolic blood pressure(sbp) ≥140mm Hg or diastolic blood pressure (dbp)≥ 90 mm Hg ; intermediate health: sbp: 120-139mm Hg or dbp: 80-89 mm Hg ; ideal health: sbp<120mm Hg and dbp<80 mm Hg), fasting plasma glucose (poor health: <100 mg/dL; intermediate health: 100-126 mg/dL; ideal health: >126 mg/dL).

Life's Simple 7 score were summed of each health heart behavior and factors, giving 2 points for an ideal metric, 1 point for an intermediate metric and 0 points for a poor

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metric. Overall Life's Simple 7 score ranged 0 and 14 was devided into 4 categories as follows: 0-6, 7-9, 10-12, 13-14.

2.7 Measurements of blood pressure, weight and height measurement

According to American Heart Association recommendation, the measurement of blood pressure was obtained twice by certified interviewers. After the participants seated at rest for 5-10 min without walking, running or lifting heavy objects, the blood pressure was measured twice with arm raised to the same height as the heart using of a calibrated mercury sphygmomanometer and cuffs of the appropriate size. If the difference between twice was more than 10 mmHg, a third time of blood pressure measurement was taken and the average of blood pressure between two closet measurement were used in our study. Body mass index was calculated from weight and height measures obtained at clinical examination using a calibrate stadiometer.

2.8 Measurement of biochemistry markers

We performed the biochemical measurements once in the baseline 2002. The procedures involved in blood sample collection were previously reported. (citation. Uric acid concentration as a risk marker for blood pressure progression and incident hypertension: A Chinese cohort study) Briefly, after a 9-12 hour overnight fast, all

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venous blood samples were drawn into an EDTA anticoagulant tube, immediately refrigerated, and transported within 4 hours to central laboratory with an automatic multichannel chemical analyzer (TBA-200FR, Toshiba Corporation, Tokyo, Japan). Serum samples were stored at -20℃before conducting batch assays to determine the levels of total cholesterol, triglycerides, and high density lipoprotein cholesterol (HDL-C) with blinded quality control specimens. Serum cholesterol and triglycerides were analyzed by the standard enzymatic methods. Both high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were performed by electrophoresis. Hexokinase glucose-6 phosphate dehydrogenase procedure was used for the measurement of plasma glucose and high-performance liquid chromatographic (HPLC) method was for the determination of HbA1c. Non-high-density lipoprotein cholesterol level was derived from the simplified equation as (total cholesterol in mg/dL) - (high-density lipoprotein cholesterol in mg/dL). The inter- and intra-assay coefficients of variation of these measurements were approximately 5%.

2.9 Important covariates

At baseline, participants reported on socio-demographic factors and medical history including educational level, monthly income, marital status, menopause status, history

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of estrogen exposure and parental history of cardiovascular disease (table 12). Educational level was classified as compulsory school education (<=9 years) and 12-year school, university or college (> 9 years). The systolic blood pressure and diastolic blood pressure were obtained twice after 5 min of rest and the mean of the two measurements at clinical examinations. The value of fasting glucose, hemoglobin A1c, triglyceride, total cholesterol and non-high-density lipoprotein were measured by blood samples drawing in the morning after overnight fasting and serum level were analyzed using enzymatic methods.

Diabetes at baseline was defined as a fasting serum glucose >= 126 mg/dL and hemoglobin A1c >= 6.5 mg/dL or records with twice diagnosis of diabetes by ICD-9 or prescription of anti-diabetes drugs more than 12 weeks from NHIRD prior to enrolled date. Hypertension was defined as systolic blood pressure >= 140 mmHg or diastolic >= 90 mmHg or records with twice diagnosis of hypertension or prescription of anti-hypertensive drugs more than 12 weeks from NHIRD prior to enrolled date. Data on the use of lipid-lowering agent and aspirin were obtained from drug register and defined as yes while prescriptions were more than 12 weeks prior to the enrolled date. Abdominal obesity was indicated as waist circumflex $\geqq$ 80 cm in women and >= 90 cm in men.

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2.10 Outcome ascertainment and prospective follow-up

Follow-up information was from the national health insurance research database and the Taiwan Cause of Death Register for fatal outcomes by record linkage using the personal identification numbers assigned to every citizen on Taiwan. The International Classification of Disease 9(ICD-9) codes were used to identify coronary artery disease or ischemic stroke in the above-mentioned. (Table 13) Coronary artery disease was defined as ICD-9 codes 410-411, 414 and V45.81-82. Ischemic stroke was defined as ICD-9 codes 434-436, 4371, 4379. We ascertained incident cast of coronary artery disease and ischemic stroke using National Health Insurance Research Database with the first hospitalization with the diagnosis of above interest events and the event date defined as the first date of hospitalization. We ascertained the coronary artery disease and stroke related death using death certificate registration. All participants were flagged for death at the department of Household Registration, and coded death certificates using the international classification of disease (ICD), revision 9. The diagnoses of coronary artery disease and ischemic stroke were made by the treating physicians, based on a clinical assessment and examinations as considered relevant by the clinician in charge of treatment.

2.11 Statistical Analyses

Person-years at risk were calculated from the baseline date to the diagnosis of a CVD

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event, date of death, loss to follow-up, or end of follow-up (December 31, 2015), whichever occurred first.

Participants were categorized into 4 group among each healthy lifestyle scores, based on the numbers of adherence to Mediterranean diet related healthy lifestyle score, Taiwan healthy lifestyle score, WCRF/AICR healthy lifestyle score and Life's Simple 7 score. The continuous variables are presented by mean, standard deviation, or median levels; categorical data are presented in contingency table with ANOVA to test for differences among quintiles. Relationships between individually healthy lifestyle factor and 4 combined healthy lifestyle scores were examined by the age- and gender-adjusted Spearman's partial correlation coefficients.

We used Cox proportional hazards models to determine the hazard ratio (HR) and 95% confidence interval (CI) of the association between health lifestyle factors, either individually or as their combined health lifestyle score, and the risk of coronary artery disease and ischemic stroke during the follow-up. Multivariate Cox regression models were constructed for combined health lifestyle scores with the lowest score category as the reference category with age as the underlying time scale, and stratified jointly by age at baseline in 20 -year intervals and sex.

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We made multivariate adjustments to examine how far the effect of combined health lifestyle score might be explained by known cardiovascular factors. We adjusted for age and sex in model A; age, sex, educational level, monthly income, marital status, menopause, estrogen exposure, and parental history of cardiovascular disease in model B; And as for model B with the addition of history of hypertension, diabetes, the, lower lipid agent use and aspirin used, fasting glucose, hemoglobin A1c, systolic blood pressure, diastolic blood pressure, triglyceride and non- high density lipoprotein-cholesterol in model C.

The linear trend test for individual factors was performed by the specific median to each category and then modeling this as a continuous variable in a separate model; for combined lifestyle factors, the test was performed by treating the number of low-risk factors as a continuous variable. Proportional hazard assumption was note rejected in these Cox models by plotting the log(-log(survival time)) versus log of survival time and including time dependent covariates.

The population attributable risk (PAR), proportion of CVD hypothetically prevented if whole population with the highest number of healthy lifestyle factors, was

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estimated using hazard ratio (HRs) obtained from the different Cox regression models in our cohort. The Wacholder et al. method was performed to generate 95% confidence intervals (CI) for robust estimation according to sex, age, education years, marriage status, income level, parental histories of heart attack or stroke, menopause status, hormone replacement therapy, baseline hypertension, diabetes and hyperlipidemia, blood pressure, fasting glucose, hemoglobin A1c, triglyceride and non-HDL-C. We tested potential effect modifiers of sex and age category (20-39.9, 40-39.9, >=60) by using the likelihood ratio test comparing models with and without a cross-product term.

To further investigate the role of combined healthy lifestyle factors to predict the cardiovascular risk, we compared the 4 model with healthy lifestyle score (simple and weight Taiwan healthy lifestyle score, WCRF/AICR lifestyle score and Life's simple 7) and tested the prediction performance using calibration and discrimination ability. First, we assessed the goodness of fit of all four healthy lifestyle score by the Hosmer-Lemeshow's statistic[72] The test is aimed to exam the calibration between the predicted risks and the actual observed risk[73]. Second, we compared Harrell's C-index of survival data, the area under receiver operative characteristic curve, among 4 healthy lifestyle score to assess model discrimination. A receiver operating characteristic

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curve (ROC curve) is plotted by two parameters, true positive rate (sensitivity) versus false positive rate (1-specificity) to performance of a classification model at all classification thresholds. AUC measures the entire two dimensional area underneath the entire ROC curve from (0,0) and larger values indicate better discrimination.[74-75]. The method of Delong et al were used to compared the statistically difference in the AUCs, which is the global standardized measurement of the discrimination between prediction of positive and negative outcome.[76] In addition, calibration curve was plotted with the average predicted risk against the observed risk in decile, to conduct the 4 healthy lifestyle score calibration.

All statistical test was 2-tailed with a type I error. Statistically significant was considered as two sided and P values < 0.05. SAS version 9.4 (SAS Institute, Cary, NC, USA) and Stata version 12(Stata Corporation, College Station, Texas USA)

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Chapter Three：Result

3.1 Demographic and lifestyle characteristics among participants at baseline

The final analytic sample included During a mean follow-up of 12.5 years, 520 (8.6%) new cases of cardiovascular events and 20 confirmed CVD-deaths (3.8%) occurred in the study. Baseline characteristic of final analytic participants included 3012 men (49.8%) and 3036 women (50.2%), with a mean (SD) age of the population at baseline was 44.9 +/-SD 16 years, whereas the mean age at diagnosis of CVD was 63.0+/-SD 12.8 years. General baseline characteristics according to the number of healthy lifestyles in simple Taiwan healthy lifestyle score, weighted Taiwan healthy lifestyle score, WCRF/AICR lifestyle score and Life's Simple 7 score are presented in Table 14. Compared with participants adhering to no healthy lifestyle factors in simple Taiwan healthy lifestyle score, weighted Taiwan healthy lifestyle score and Life’s Simple 7, those adhering to highest factors tended to be women predominant and younger, with higher education level, high monthly income, low prevalence of living with spouse, parental history of CVD, menopause status, hypertension, diabetes and hyperlipidemia at baseline and hormone replacement therapy exposure. However, in contrast, compared with participants adhering to no healthy lifestyle factors in WCRF/AICR healthy lifestyle score, those adhering to highest factors tended to be

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older, with lower education level, low monthly income, high prevalence of living with spouse, parental history of CVD, menopause status, hypertension, diabetes and hyperlipidemia at baseline and hormone replacement therapy exposure.

3.2 Lifetime risk of cardiovascular disease

Overall, the lifetime risk of cardiovascular event was 0.56/ 1000 person-year at age 20~39 years old and remained constant 5.6 per 1000 person-year through age between 40~59 years old; At age more than 60 years, the lifetime risk for cardiovascular disease was 28.78 per 1000 person-year.

Lifestyle Factors and Lifetime risk of CVD

An independent inverse and graded association (table 15) among each lifestyle factor and the risk of CVD were observed after multivariable adjustment, with the strongest associations observed for BMI (risk ratio @@; 95% CI:@@), Mediterranean diet (risk ratio 0.35; 95% CI: 0.20,0.61) and alcohol consumption (risk ratio 0.5; 95% CI: 0.29,0.87) and p for linear trend 0.012, 0.006 and 0.001, respectively.

The linear relationship was noted among BMI, Mediterranean diet, alcohol and CVD and ideal weight, high score of Mediterranean diet and frequency drinking with the lowest risk. The association between the intensity of physical activity and CVD was a

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J shaped. Adequate physical activity was associated with a reduced risk of CVD with the lowest risk being among 1~49 mins per week (risk ratio 0.6; 95% CI: 0.33, 1.09). However, physical activity with more than 150 mins per week showed increasing risk of CVD (risk ration 1.08; 95% CI: 0.84,1.38). The percentage of partial population attributable fraction (95% CI) was highest for adequate alcohol consumption (41.1%, 95% CI: 18.1, 57.6), followed by ideal weight (25.7%, 95% CI: 5.6 to 41.6), Mediterranean healthy diet(23.7%, 95% CI: 6.7 to 37.6) and non-smoking status (2.4%, 95% CI: -4.7 to 8.9).

3.3 Healthy lifestyle scores and lifetime risk of CVD

When the healthy lifestyle factors were collapsed into binary categories of optimal versus not optimal, each lifestyle factor remained significantly associated with lower risk for incidental cardiovascular disease in multivariable-adjusted models including all lifestyle factors simultaneously.

Figure 1 showed the Kaplan-Meir survival curves for the probability of survival free from the risk of cardiovascular specified in the study participants among participants stratified by the numbers of healthy lifestyle factors. The highest numbers of healthy lifestyle scores had a higher survival free rate from the CVD risk in the simple and weight Taiwan healthy lifestyle scores and Life's Simple 7 with the log-rank test,

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P<0.001, <0.001 and < 0.001, inversely. (table 16)

In multivariable-adjusted analyses (table 16), healthy lifestyle scores were independently associated with reducing CVD risk, especially in simple Taiwan healthy lifestyle score, weighted Taiwan healthy lifestyle score and Life's Simple 7 (table 17) (Figure 2).

Among participants in the optimal category for all healthy lifestyle factors of ideal weight, healthy diet, achievement of physical active goal, never smoking, adequate drinking and ideal total cholesterol, blood pressure and fasting glucose, comprising approximately 7.6%, 15.2% and 17.7% of the study population in the simple and weight Taiwan healthy lifestyle score and Life's Simple 7, respectively, the HR for cardiovascular events was 0.43 (95%CI: 0.2 to 0.94), 0.44 (95%CI: 0.28 to 0.68) and 0.6 (95%CI: 0.29 to 1.24) compared to the corresponding undesirable lifestyle, comprising approximately 22.0%, 42.6% and 2.8% of the study population (table 16). There was an inverse and graded association between the number of healthy lifestyle scores and the lifetime risk of CVD with p for linear trend <0.001, <0.001 and 0.02 in simple Taiwan healthy lifestyle score, weighted Taiwan healthy lifestyle score and Life's Simple 7, respectively. However, no inverse and graded association was noted

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between WCRF/AICR lifestyle score and CVD. Furthermore, participants with increasing numbers of WCRF/AICR healthy lifestyle score had higher risk of CVD, insignificantly.

3.4 Healthy lifestyle scores and CVD risk in adult < 60 years old and ≧ 60 years old

When we stratified by age, the association between the number of different healthy lifestyle scores and CVD risk among adults <60 years old and adults ≧60 years old were demonstrated in table 17 and figure 4. Overall, we found that persistent significantly inverse association between healthy lifestyle scores and the CVD risk for a given number of lifestyle factors in all 4 healthy lifestyle scores, but among participants aging younger than 60 years with more reduction of CVD risk. In addition, age played a significant effect modifier for the association among healthy lifestyle scores and the risk of CVD, indicating the protective effect of healthy lifestyle scores on CVD incidence indeed varied by the age of adult.

3.5 Comparing different healthy lifestyle scores

Hosmer-Lemeshow test statistic indicated an acceptable goodness-of-fit of the calibration ability (table 18). Furthermore, the model was well calibrated for 12.5-year CVD risk prediction based on the calibration in four healthy lifestyle scores (figure 5).

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With regards to discriminative ability of different healthy lifestyle scores to predict the CVD risk, the Harrell's C-statistics were significantly different between the classical risk factor models with and without healthy lifestyle scores (figure 7). Specifically, when the simple and weight Taiwan healthy lifestyle score were added to the classical model, the Harrell's C-statistic increasing from 0.85 to 0.86 (95% confidence interval [CI], 0.84, 087; P_{diff}=0.048) in both lifestyle scores. Moreover, we found that the performance measures by integrated discriminative improvement (IDI) showed significant improvement with 0.38% (95% CI 0.01, 0.74; p=0.021) contained simple Taiwan healthy lifestyle score and .51% (95% CI 0.16, 0.86; p=0.002) contained Taiwan healthy lifestyle score. The net reclassification improvement was statistically significant for the information of simple and weight healthy lifestyle score (0.03; 95% CI 0.01, 0.05; p= 0.004) in and of Taiwan healthy lifestyle score. (0.04; 95% CI 0.02, 0.06; p= <0.001).

3.6 Sensitivity analysis

As a sensitivity analysis, we replaced the body mass index with waist circumflex, the HR for cardiovascular events was 0.45 (95%CI: 0.21 to 0.98) among participants in the optimal category for all 5 lifestyle factors of simple Taiwan healthy lifestyle score , comprising approximately 1% of the study population, compared with 27.4%

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of population with those adhering to none or 1 healthy lifestyles factors (table 19). The replacement of body mass index with waist circumflex among weighted Taiwan healthy lifestyle score, HR for cardiovascular events was 0.4 (95%CI: 0.25 to 0.65) among participants in participants adhering to 5 desirable lifestyle factors, comprising approximately 14.9% of the study population, compared with 26.7% of population with adhering to none or 1 healthy lifestyles factors.

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Chapter Four：Discussion

4.1 Main finding

In this represetative adult Taiwan population, 38.8% of all CVD events may have been avoided had all participant adhered to a health lifestyle of normal weight, healthy Meditereanean diet, physical activity regularly, non-smoking and adequate healthy drinking. We also noted the inverse relationship between combined healthy lifestyle score and CVD, such as simple Taiwan healthy lifestyle score, weighted Taiwan healthy lifestyle score and Life's simple 7. Furthermore, we noted age and hypertension at baseline had an modifer effect of the inverse association between combined lifestyle score and CVD. Younger and hypertension-free participants adopted optimal lifestyle had more benefit than elder population.

4.2 Comparing with previous studies

Our finding were consistent with preiouvs cohort studies in European, USA and Asia and suggested an protective effect between healthy lifestyle score and the risk of CVD in extensive Chinese population. Evidence have shown combined Mediterranean diet in healthy lifestyle score in Western with an inverse association with the CVD incidence[37, 42], adjusted HR ranging 0.22-0.43 and CVD death[77], adjusted HR ranging 0.54-0.62. In a follow-up 7.2 years cohort study in China[45], combined healthy lifestyle

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factors had decreasing the risk of CVD but diet pattern in the study defined from the habitual intake of 12 conventional food was insignificant protective effect. Our study had validate the Mediterran diet pattern had benefit in reduction of CVD events.

Previous cohort studies of lifestyle score and incident CVD are limited in the adjuted covariates. Most controlled covariates in those analyses hazard including age, sex, soci-economical status, parenal history of CVD, hypertension, diabetes, hyperlipidemia status at baseline and medication exposure, such as aspirin, hormone, anti-hypertensive, anti-diabetic or lipid-lowering agent. Several cohort studies had estimated the hazard ratio with part of additional adjuted clinical factors, like systolic blood pressure, serum level of glucose, hemoglobine A and total cholesterol[33, 36, 39-42, 46-47]. In our study, we estimated the hazard ratio after adjusted for age, sex, social-economical and healthy status at baseline and clinical factors such as blood pressure, serum level of glucose, triglyceride and non-HDL. All of those including clinical factor as adjustment covariates studies implies that combined lifestyles had additional benefit for the decreasing incidence of CVD other than the mechanism of blood pressure, glucose and lipid-controlling.

Comparison of weighted lifestyle score and simple lifestyle score to exam the

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assumption of each lifestyle factor with the same magnititude effect of the CVD risk by the area under curve, IDI nad NRI demonstrated silimar predictive performance of the incidence of CVD. The result was consistent with previous studies about healthy lifestyle and risk of heart failure[49] and as the first study of the weighted healthy lifestyle and CVD risk. The result of the simple and weighted lifesytle score with similar impact on CVD risk may imply there were no more benefits of focusing on single one or two healthy behaviors than intergration of all healthy lifestyle factors. Moreover, adapting overall healthy lifestyles rather than strong emphasis of particular lifestyle were an optimal strategy to improving cardiovascular health.

Compared with previous studies about WCRF/AICR lifestyle score

Multiple observed studies have suggested a inverse association between adherence to high numbers of WCRF/AICR lifestyle score and varitety cancer, such as colorectal cancer[78-80], breast cancer[81] (Hastert, 2013, Adherence to WCRF/AICR cancer prevention recommendations and risk of postmenopausal breast cancer), esophageal adenocarcinoma, prostate cancer[78] and total cancer incidence. Previous studies of the association between greater adherence to WCRF/AICR lifestyle score and the CVD risk factors were limited and have yielded inconsistent findings. A cross-section study reported, increasing numbers of adherence to WCRF/AICR recommendation

doi:10.6342/NTU202002676

decreased the incidence of metabolic syndrome in breast cancer patients[82]. On the contrary, a cross-sectional based study of 2267 European adults, greater adherence to WCRF/AICR lifestyle scores was observed with higher serum level of thrombomodulin and thrombopoietin which might increase the risk of CVD[83] and be explained by lower alcohol and meat consumption among persons with higher WCRF/AICR lifestyle score. To our knowledge, our study was the first prospective cohort of adherence to WCRF/AICR lifestyle score and the incidence of CVD and the association was demonstrated nonsignificantly. The result suggested that greater numbers of adherence to WCRF/AICR lifestyle score decreasing the incidence of metabolic syndrome but increasing pro-coagulative status lead to an nonsignificantly protective effect of CVD.

Compared with previous Life's Simple 7

The association between Life's Simple 7 and CVD in observational studies has been confirmed in repeated re-analyses. Most of the variables included in our model were silimar to those in previous studies[84-93]. Moreover, several clinical risk factors and biomaker, such as blood pressure, triglyceride, non- high-density lipoprotein, fasting glucose and hemoglobin A were found to be attenuated the cardiovascular protection from Life's Simple 7 in our study. The CVD preventive effect decling among Life's

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Simple 7 imply the protective benefits attributable from clinical risk factors more than lifestyle factors. When a CVD risk score both considering lifestyle factors and clinical risk factors, including blood pressure, cholesterol and glucose, which are downstream of lifestyle factors, clinical factors may mediate the lifestyle factors on CVD risk furthermore diminish the predictive value of lifestyle factors. More emphasis on clinical factors rather than lifestyle factors may drive the CVD risk score from primodrial prevention to primary prevention and identify individuals with higher short-term risk of CVD than long-term risk.

Comparion among lifestyle scores

In our study, simple Taiwan healthy lifestyle score and weighted Taiwan healthy lifestyle score had better predictive performance according to comparions of area under curve, IDI and NRI. The different components among healthy lifestyle scores includes fish, eggs, dairy diet, smoking status and optimal amount of alcohol consumption. Mediterranean diet used by Taiwan lifestyle score was defined fish as an optimal food for CVD protection but limited egg and dairy diet in daily intake. Taiwan lifestyle score defined redular adequate alcohol consumption as optimal lifestyle. However, WCRF/AICR lifestyle score considered non-alochol as and ideal lifestyle and Life's Simple 7 didn't consider the amount of alcohol consumption into

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score. Additionaly, the status of non-smoking or quit more than 12 months from smoking were suggested in Taiwan healthy lifestyle score and Life's Simple 7 score but not calculated in WCRF/AICR lifestyle score.

Simple Taiwan healthy lifestyle score, weighted Taiwan healthy lifestyle score and Life's Simple 7 score were observated the association between greater adherence to score and lower CVD incidence in model 2. However, regarding the adjustment of clinical factors, Life's Simple 7 failed to find an significant inverse association of CVD risk might explained by the different definition of healthy diet, physical activity and lack of alcohol component. Taiwan lifestyle score compared with Life's Simple 7 might be more suitable for primodrial prevention among population without no clinical risk factors.

Alcohol

However, regarding with the variations in both amount of alcohol consumed and patterns of consumption, the burden of alcohol in CVD deaths are varies in different area. (13,94) Such as in Russia and estern Europe, former soviet republics, the risk in harmaful alcohol use has led to a massive burden of CVDs due to the change of social and political situation. Alcohol drinking is not a common lifestyle culture in Taiwan

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compared with European or Russia, and the amount of alcohol consumed may less than those area. That might be the reason why the highest frequence of alcohol consumped status compared with none or less drinking with cardioprotective effect.

Physical Activity

The diverse patterns of daily activity during occupation or leisure time between countries leaded the mearsurement of physical activity as an major challenge. Further, exsiting evidence showed the inconsistent result of the association between occupational and leisure time physical activity and the risk of CVD.[94] Not like the inversely associated between leisure time physical activity and CVD risk, commuting physical activity were no statistically significat associated with CVD.[95] More and more evidence reported the association between physical activity and the risk of CVD were affected by the variate domain of physical activity, including occupational physical activity, leisure activity, active travel, household chore, family activities were an important covariates should be emphasis.

All agree physical activity reduce the incidence of CVD. However, some evidence demonstrated a U or reverse J-shaped relationship between higher physical activity dose and CVD in observational studies. Physical activity at extreme volume such as

doi:10.6342/NTU202002676

strenuous activitiy daily compared with moderate (2-3 times per week) had higher incidence of coronary artery diseases, cerebral vascular disease and venous thromboembolic events and CVD mortality rate.[96-97] The J-shaped relationship between the physical activity level and CVD were also demonstrated in our study.

4.3 Biological mechanism

Age as an effect modifier of the association between healthy lifestyle and CVD

There might 3 reasons to expline the benefit from healthy lifestyle among younger population more than elderly observed from our study. First, aging is a original strong risk factor of atherosclerosis. Research had reported even individual with ideal modifiable lifestyle and healthy status, the development of high ASCVD risk still occur among ages 65~75 years old according to different race.[98] 60% of 10-year predicted atherosclerotic CVD were attributable to age alone. Additionaly, the magnitudes of causal association between lifestyle and CVD risk might be reduced when including age as a significant covariates[99]. Second, the legacy effect of CVD from nonoptimal behavior factors had been reported.[100] Elder had longer lifestime to experience non-optimal lifestyle than younger. The legacy effect will result in the pathological change persistent even individuals have the optimal lifestyle recently. At

doi:10.6342/NTU202002676

last, people with chronic diseaese would have stronger motivation to keep healthy lifestyle. However, chronic disease may play an potential confound in the association between lifestyle and the incidence of CVD. Compared with young population, elder group may have higher prevalence of chronic disease which may reduce the protective effect of CVD from healthy lifestyle .

4.4 Clinical implication

On previous meta-analysis study, the association between healthy lifestyle scores and CVD risk was mediater by the population age. The present study based on primary data further demonstrated that age as effect modifier that adherence to healthy lifestyle scores reduced the CVD incidence, specifically before 60 years old. Therefore, identify unhealthy lifestyle factors among young and middle-age adult and aggressively healthy lifestyle intervention is crucial for improving population cardiovascular health (figure 8).

Additionally, among population with low short-term risk, healthy lifestyle scores in the absence of clinical risk factors provided additionly important information about long-term CVD risk and overall CVD burden independently with adjutment of biomarkers. The healthy lifestyle score might be implicated in healthy service, healthy

doi:10.6342/NTU202002676

education and healthy policy to develop different strategy separately for the primordial and primary prevention of CVD and to identify unhealthy lifestyle factors proceding the development of clinical risk factors of CVD.

Furthermore, healthy lifestyle scores without clinical measurements increase the application in community-based or primary healthy service without the clinical setting and may be an useful tool for broader public heatlh screening and motivating audience who may be lack of available laboratory-based measures.

4.5 Strengths and limitations

Our studeis had several strengths. TWsHHH as an population of middle-age adult with low prevalence of clinicla risk factors was national representative cohort with little loss to follow-up over 13.5 years. Furthermore, the cohort contained detailed assessment both of lifestyle factors and the direct measures of clinical risk factors and biomarkers. The benefit from healthy lifestyle score on CVD risk were robust after the adjustment of clinical factors. Second, the protectvion from healthy lifestyle score and Mediterranean diet pattern on CVD risk were validated in Asia population. The healthy lifestyle scores as an primodrial preventive policy to response 2025 global target of WHO amonog western countries extending to asia population. Additionally,

doi:10.6342/NTU202002676

to our knowledge, this is the first estimation of the CVD risk specifically from WCRF/AICR recommended lifestyle score. The first study compared different healthy lifestyle scores on CVD incidence and including biomakers considering in the model improved the discriminatory ability. Finally, age as effect modifier among the association among healthy lifestyle scores and the incidence of CVD were demonstrated by the primary data validation.

Nonetheless, several study limitations should be mentioned. The Taiwan healthy lifestyle score were assessed with TWsHHH cohort but lack external data validation. Further confirmation should be considered with other asia population. Additional, lifestyle factors recorded at baseline without repeated assessments had potential non-differential misclassification in the study. Nevertheless, if the association between healthy lifestyle score and the risk of CVD were significant with misclassification bias, the true relative risk between them should be more effective with respect to subsequent repeated measurements of exposure. Finally, although Mediaterranean were demonstrated reducing the incidence of CVD significantly, the western diet score might not be suitable for Asia diet pattern. Development of Asia healthy diet score improved the difference.

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Chapter Five：Conclusion

In conclusion, adherence to high numbers of combined healthy lifestyle scores plays an important role in the primary prevention of CVD, especially in younger adult with low short-term risk. Simple and weighted Taiwan healthy lifestyle scores can be more effective and predictable of CVD reduction than WCRF/AICR lifestyle score and Life's Simple 7 in adult Taiwanese population. Further investigation of the mechanism of CVD prevention from healthy lifestyle independent to clinical factors

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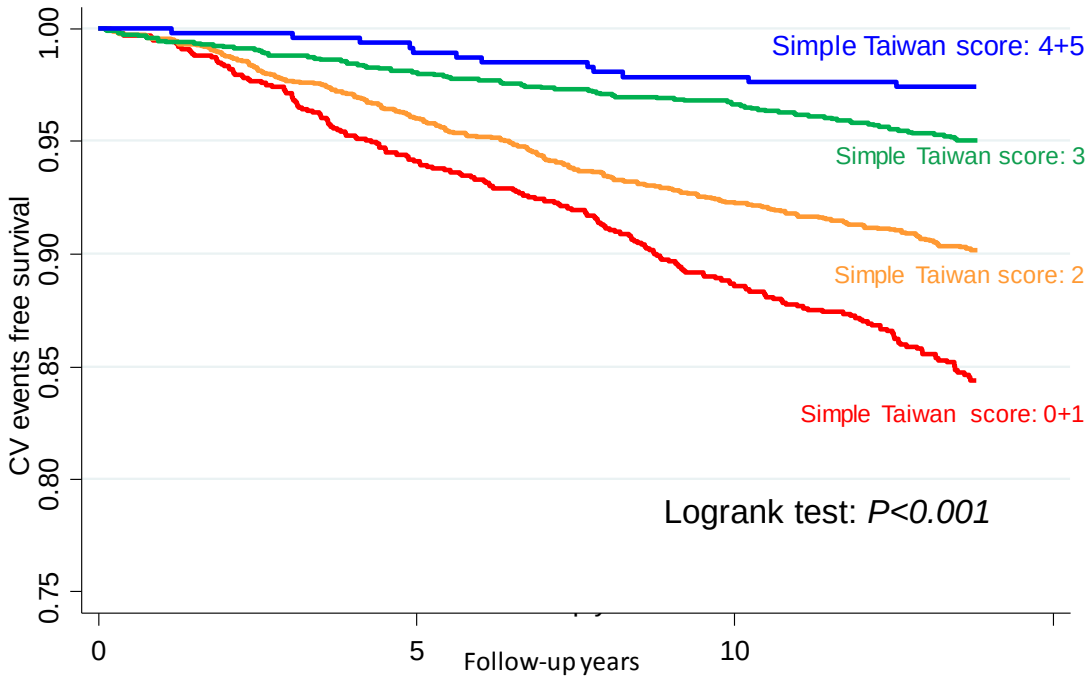
Figure

Figure 1: Kaplan-Meir survival curves for the risk of cardiovascular specified in the study participants among participants stratified by the numbers of healthy lifestyle factors by simple Taiwan healthy lifestyle score



(A) by Taiwan healthy lifestyle score

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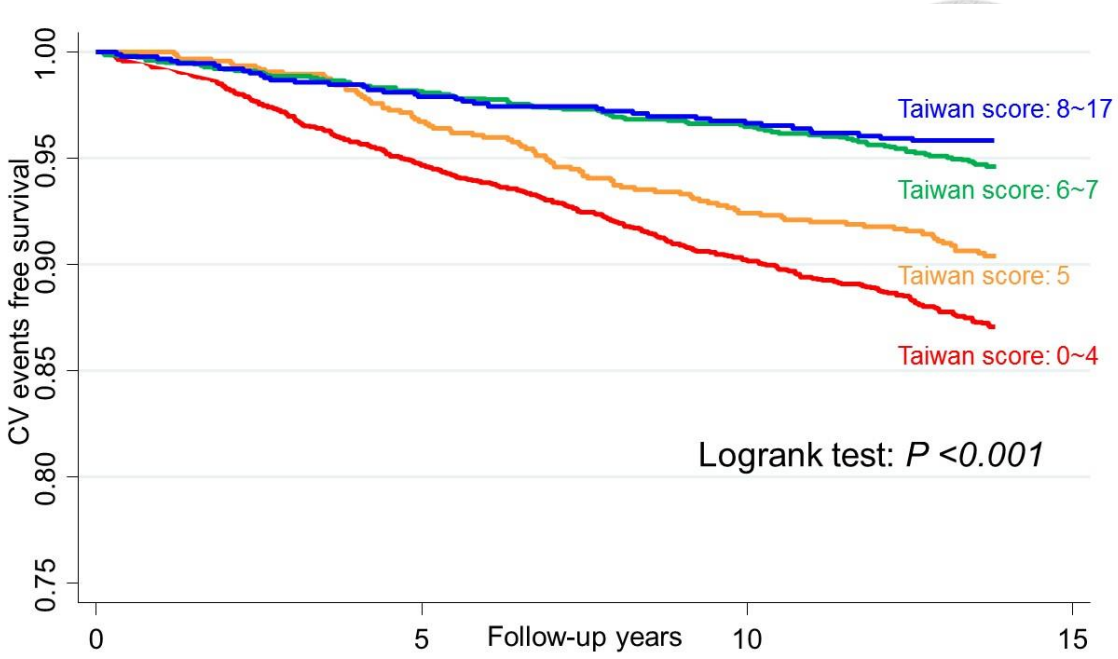
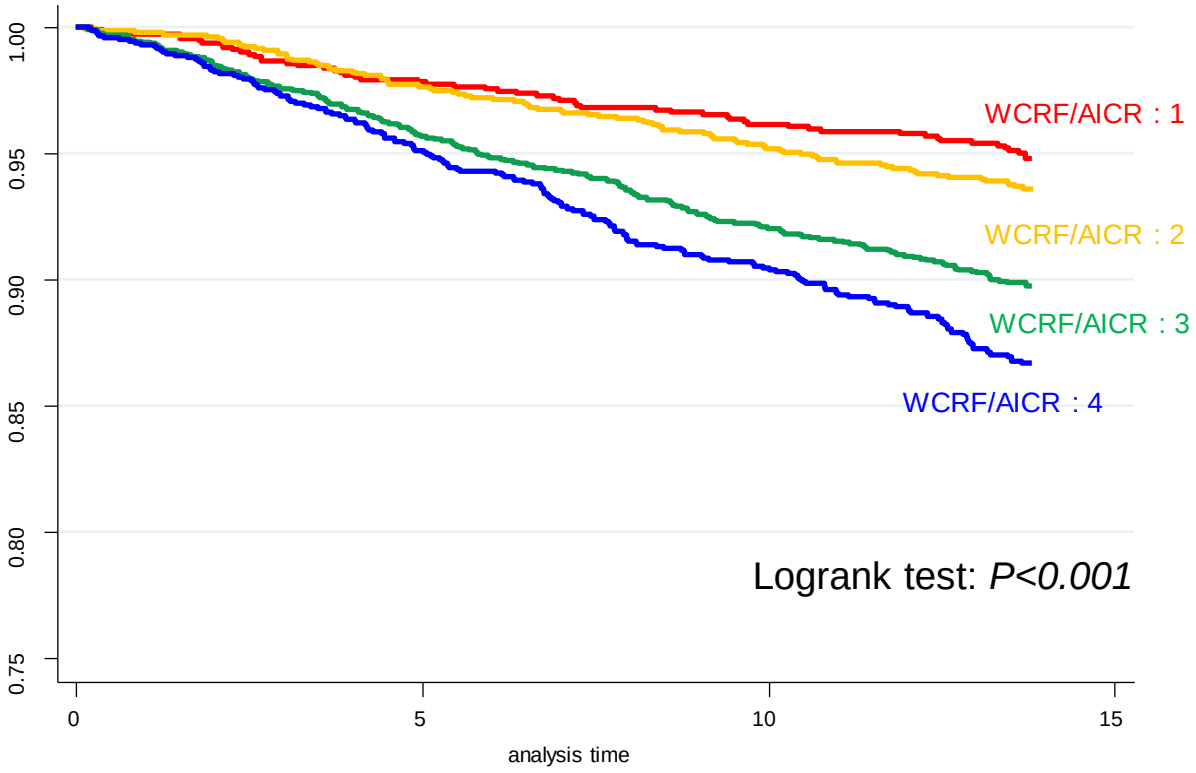


(B) by WCRF/AICR recommended lifestyle score



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(C) by Life's Simple 7

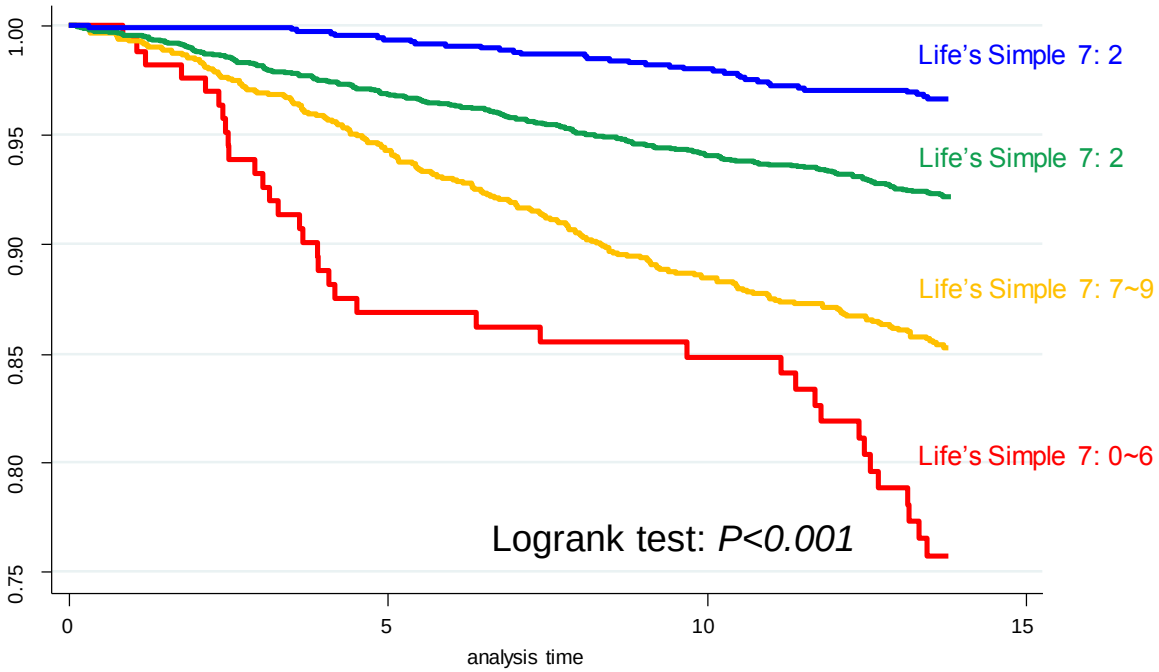

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Figure 2: Hazard ratios for cardiovascular disease specified by categories according to the numbers of healthy lifestyle factors among participants stratified by simple Taiwan healthy lifestyle score, weighted Taiwan healthy lifestyle score, WCRF/AICR recommended healthy lifestyle score and Life's Simple 7

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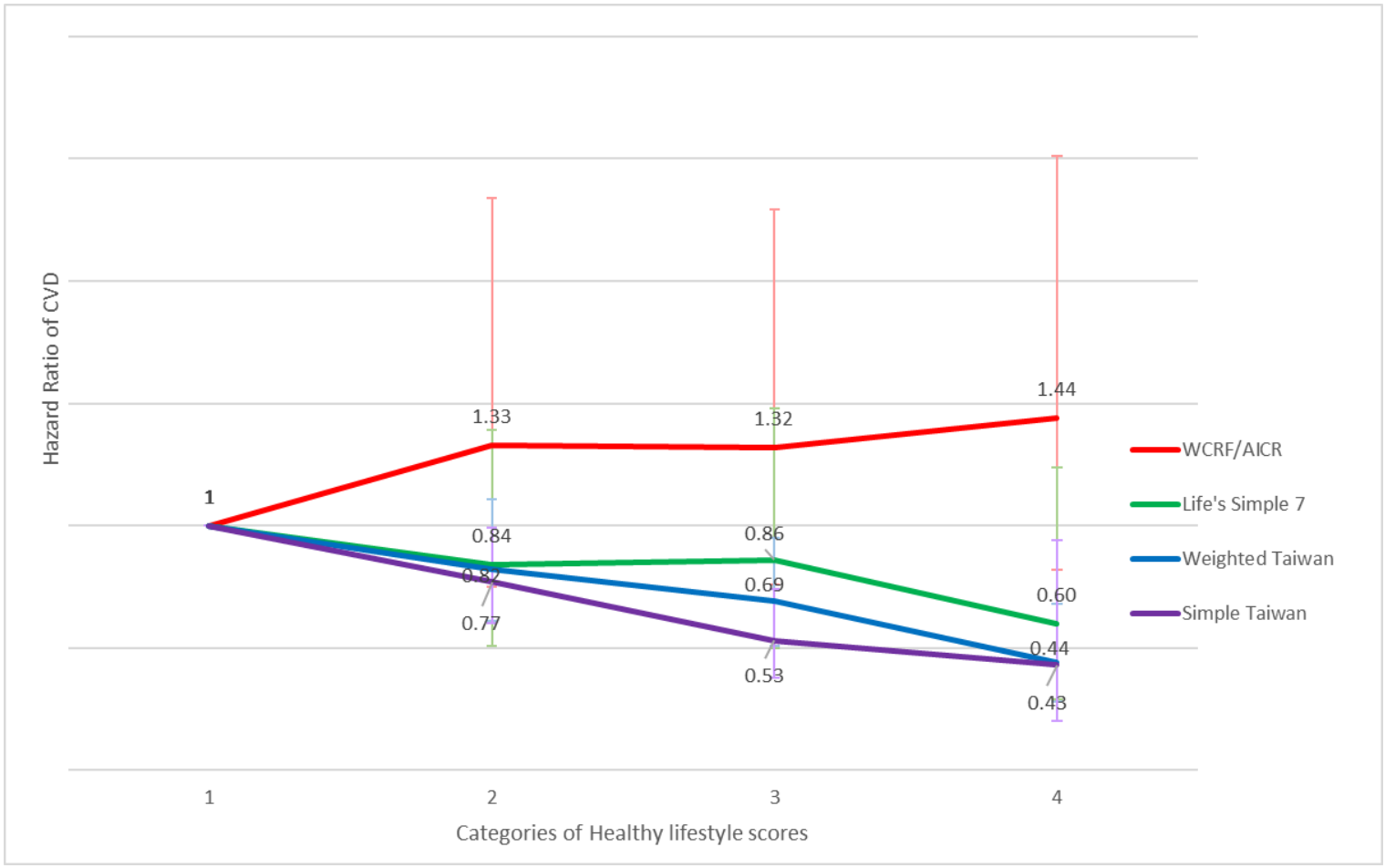

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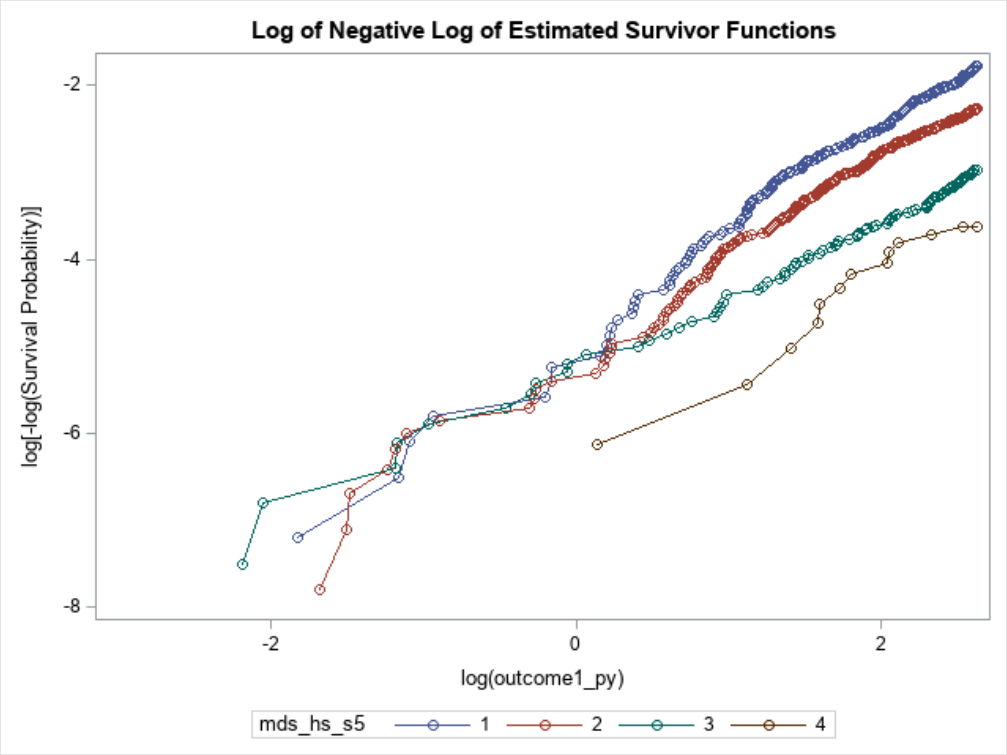
Figure 3: The log(-log(survival time)) versus log of CVD event-free survival time including time independent covariates

(A) CVD event-free survival time of simple Taiwan diet related healthy lifestyle score



(B) CVD event-free survival time of Taiwan healthy lifestyle score

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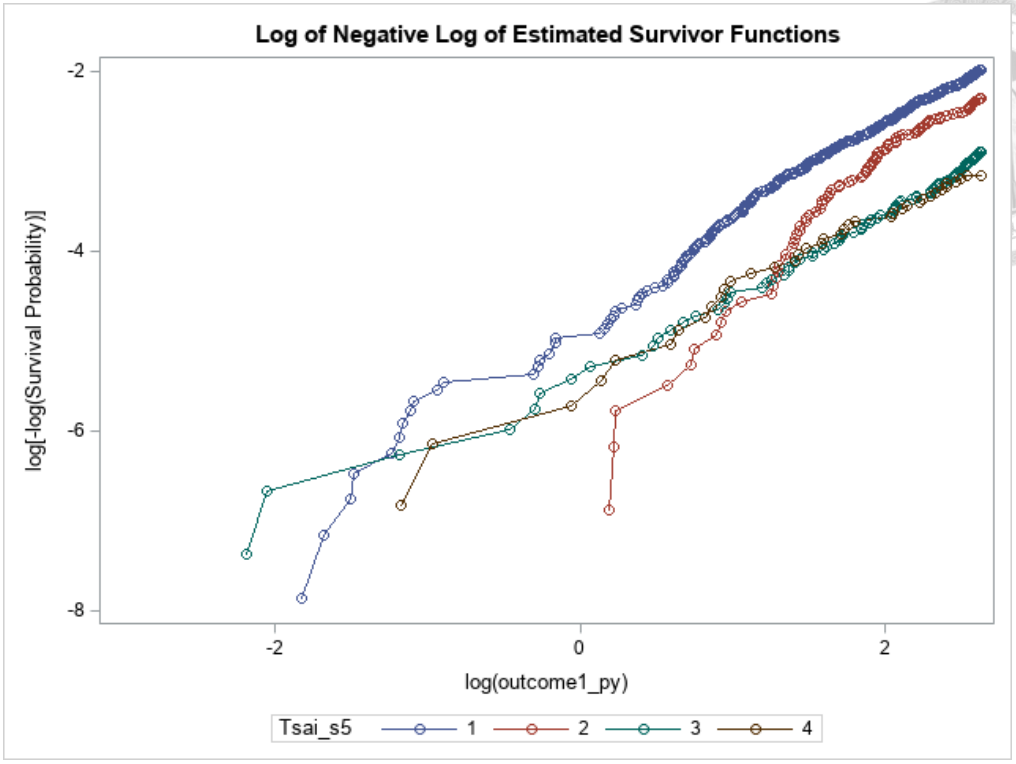
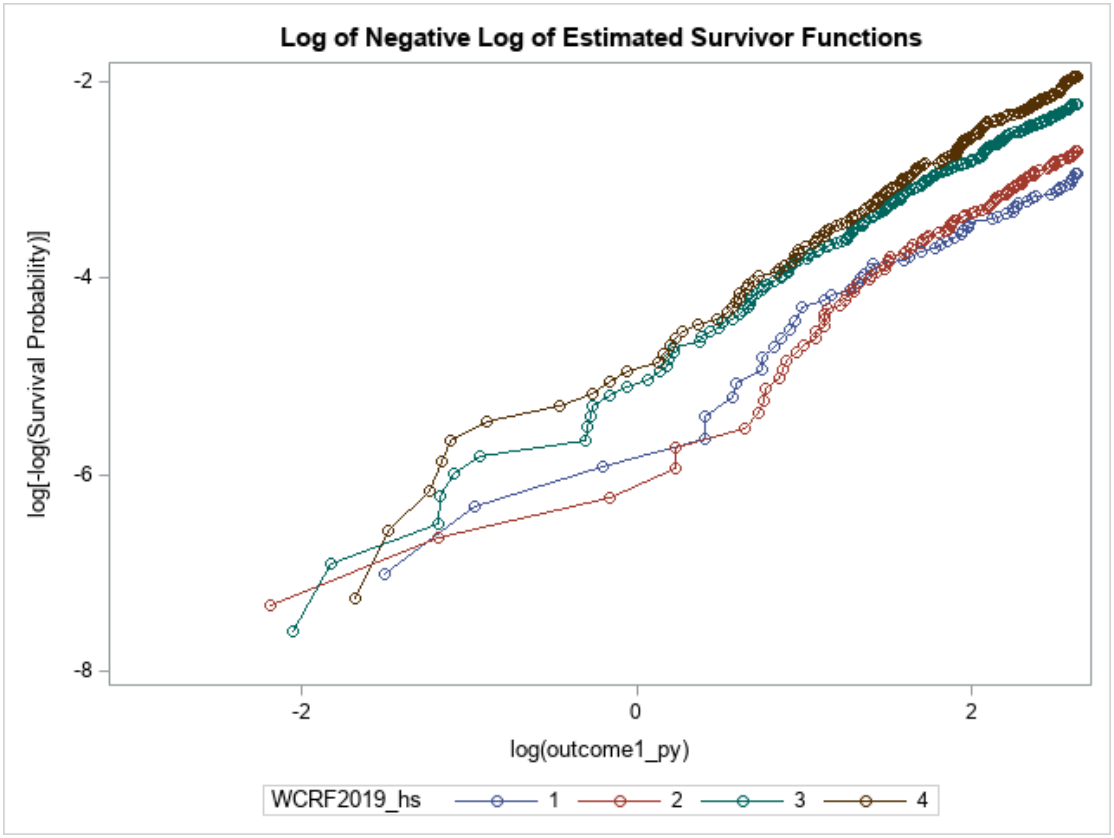


(C) CVD event-free survival time of WCRF/AICR recommended lifestyle score



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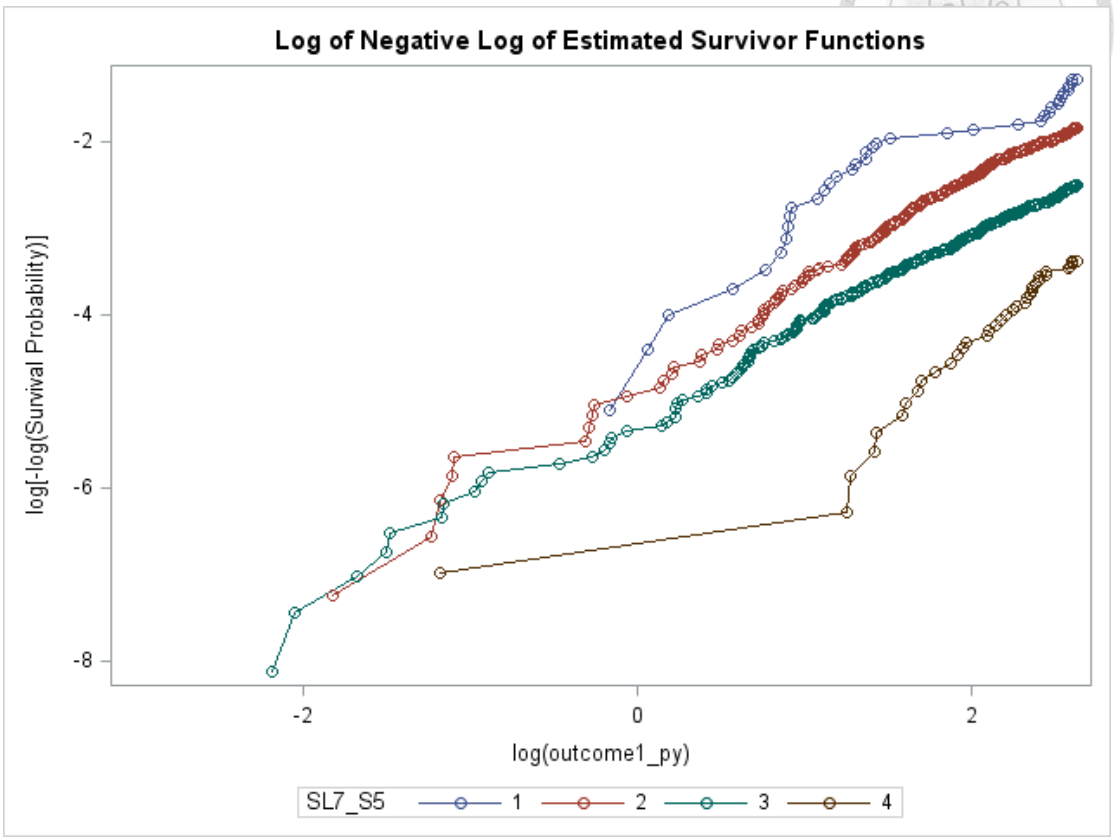
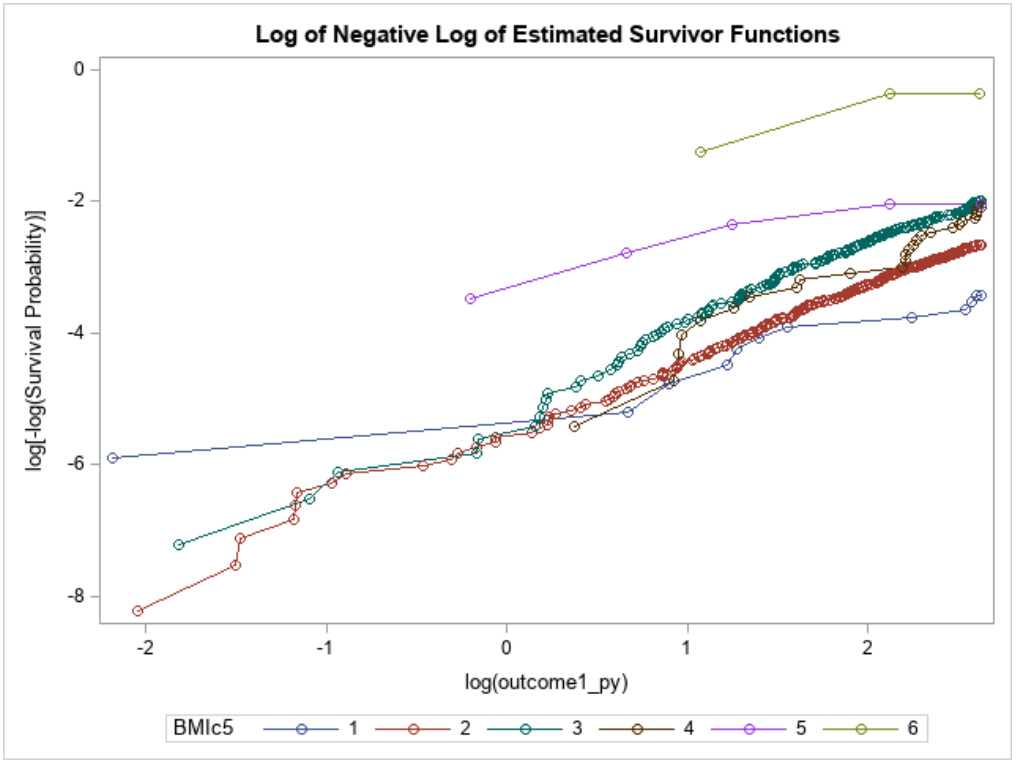
(D) CVD event-free survival time of Life's Simple 7



(E) CVD event-free survival time of body mass index



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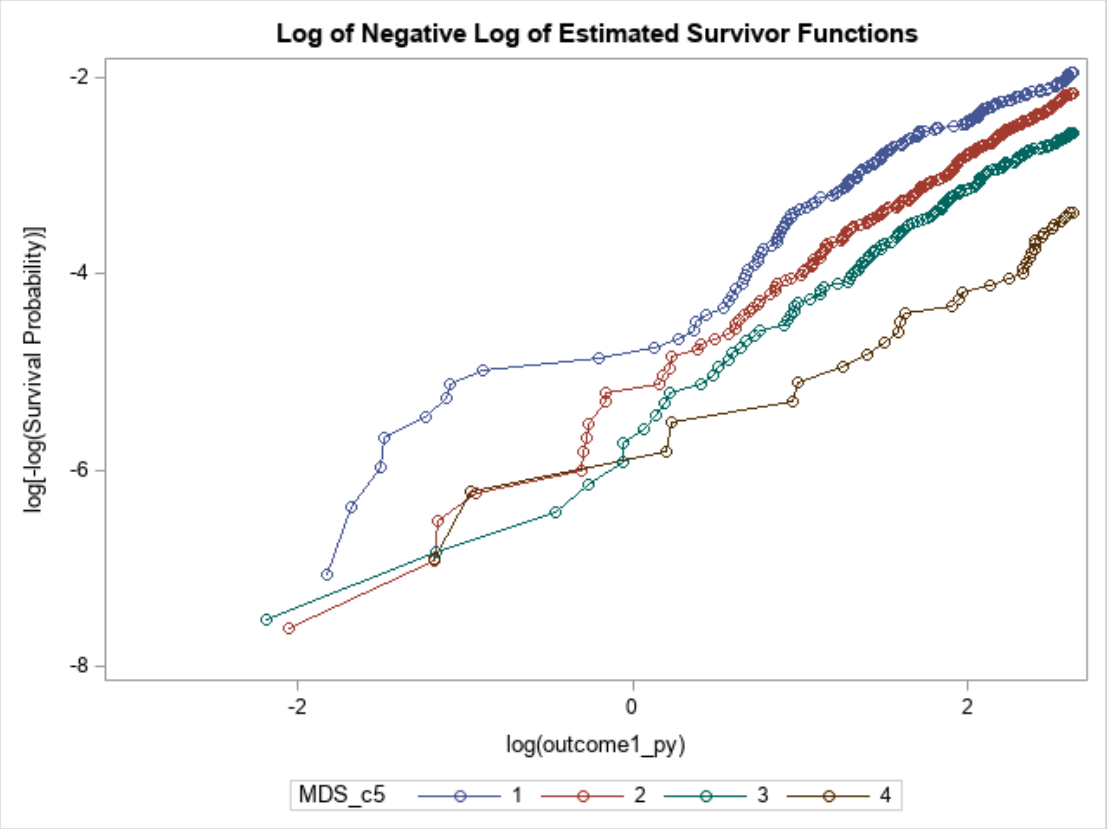
(F) CVD event-free survival time of Mediterranean diet score



(G) CVD event-free survival time of physical activity

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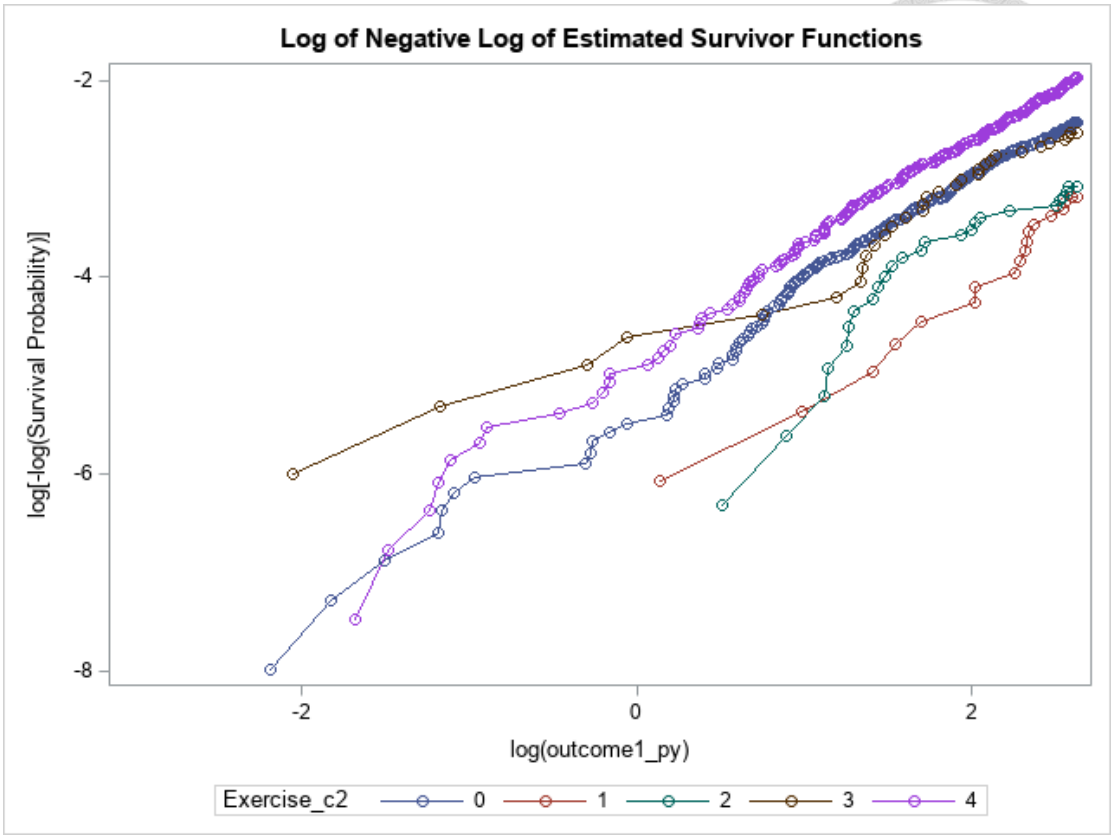
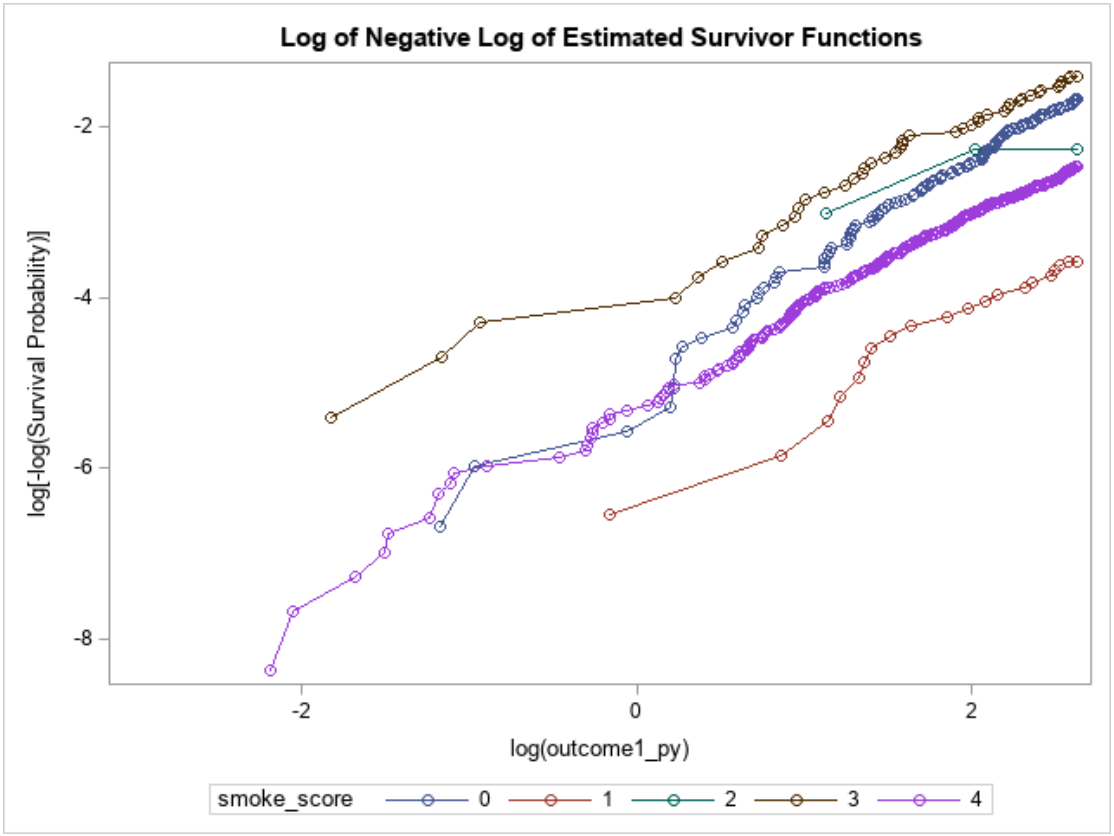


(H) CVD event-free survival time of Smoking status



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(I) CVD event-free survival time of alcohol consumption

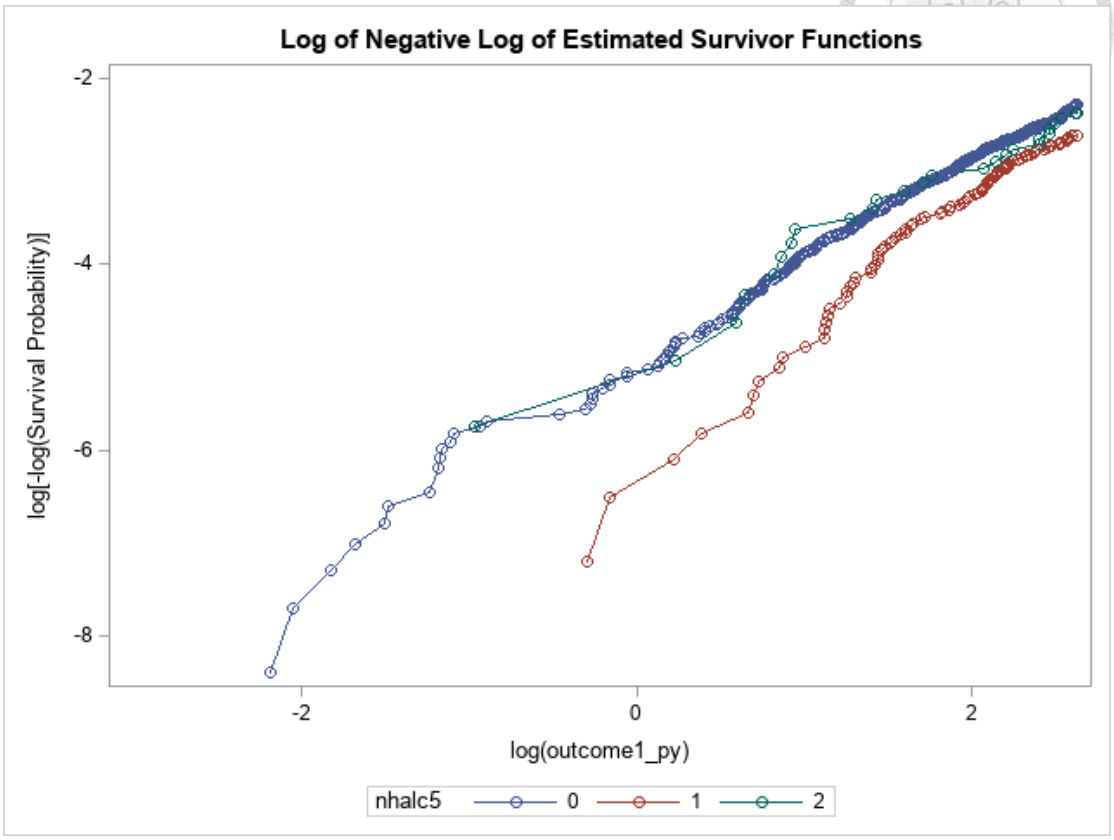

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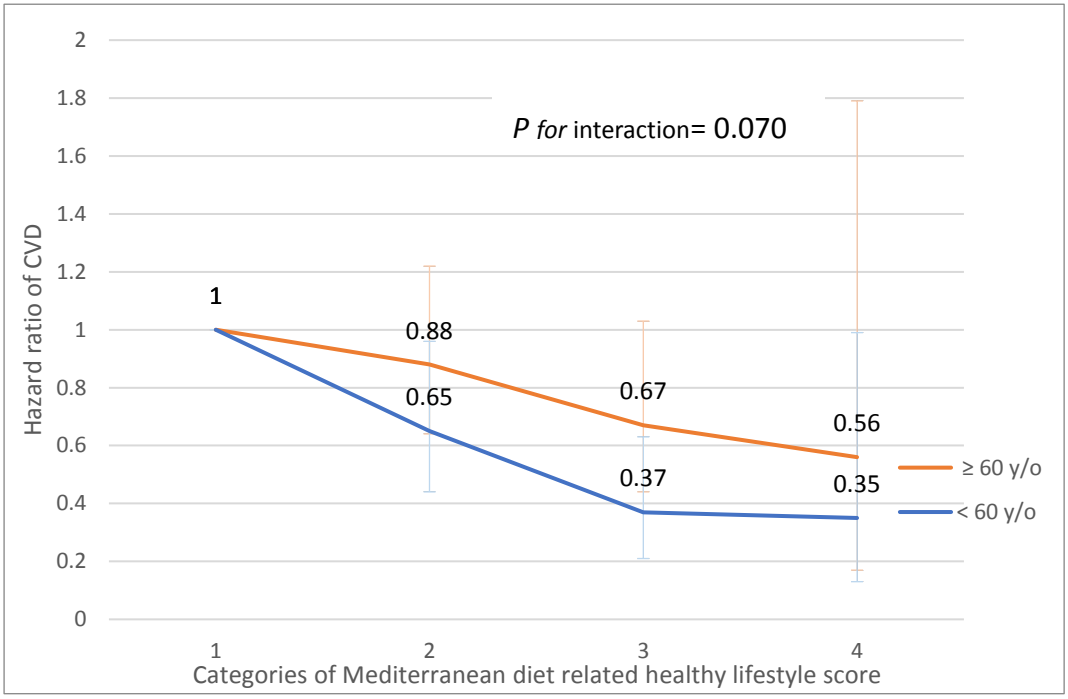
Figure 4: Hazard ratios for cardiovascular disease with categories according to the numbers of healthy lifestyle factors among participants stratified by age < 60 y/o and ≥ 60 y/o

(A) Simple Taiwan healthy lifestyle score



(B) Weighted Taiwan healthy lifestyle score

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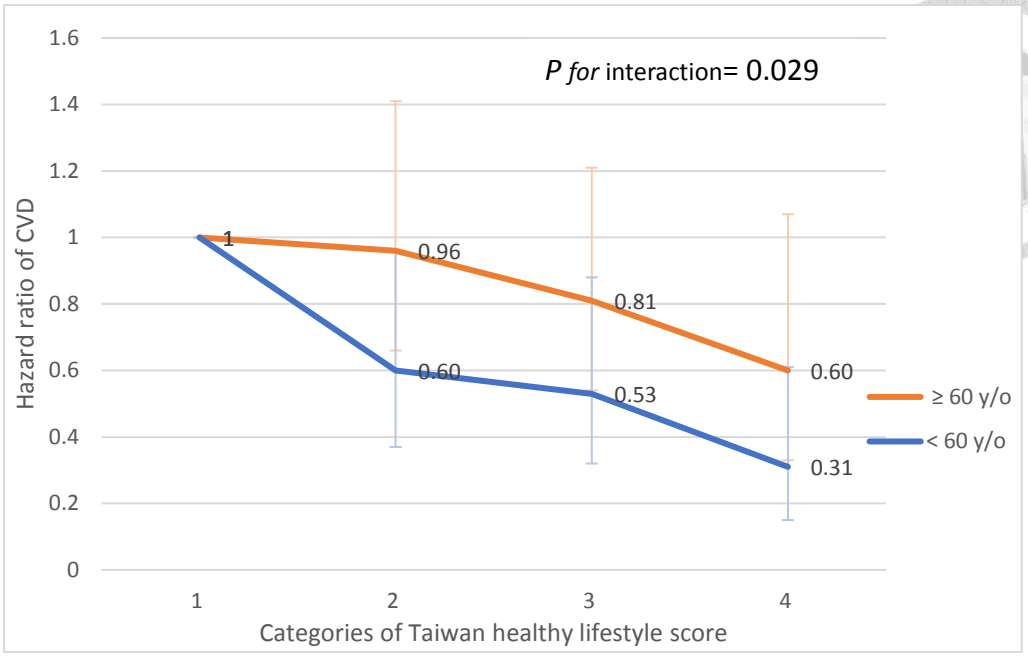
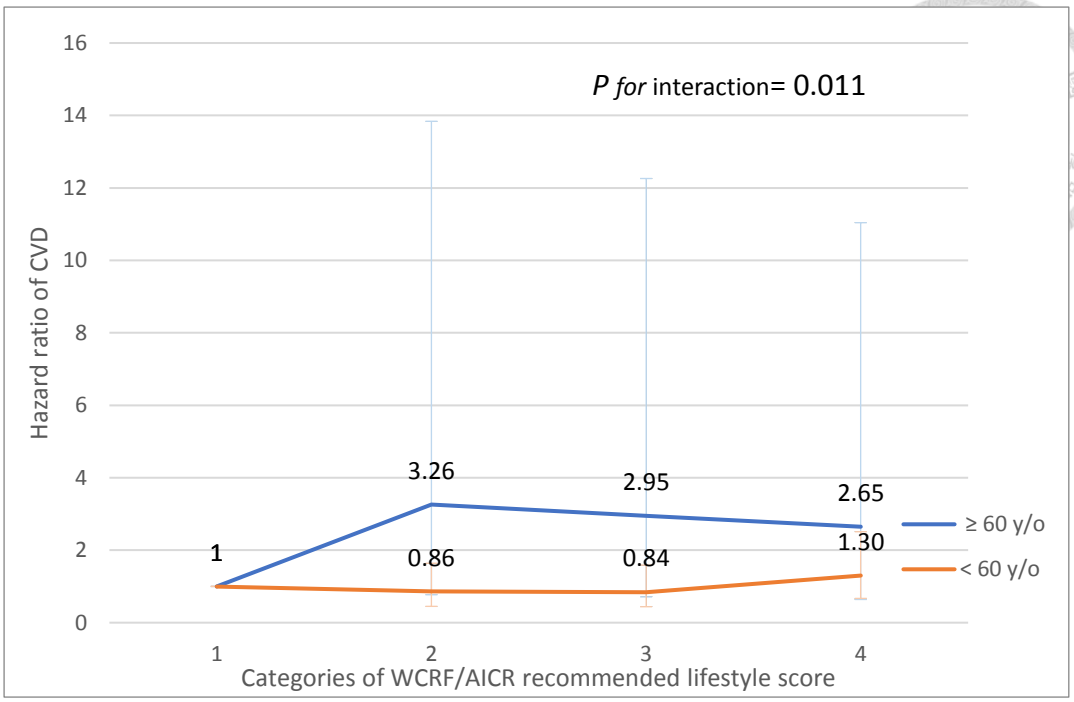


(C) WCRF/AICR recommended healthy lifestyle score

doi:10.6342/NTU202002676

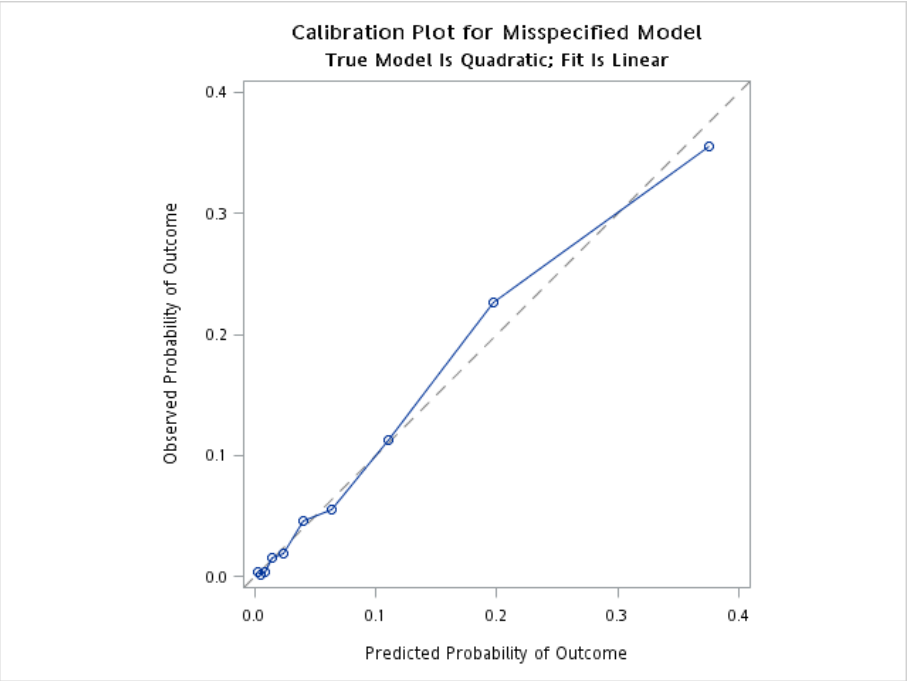


(D) Life's Simple 7 score

doi:10.6342/NTU202002676

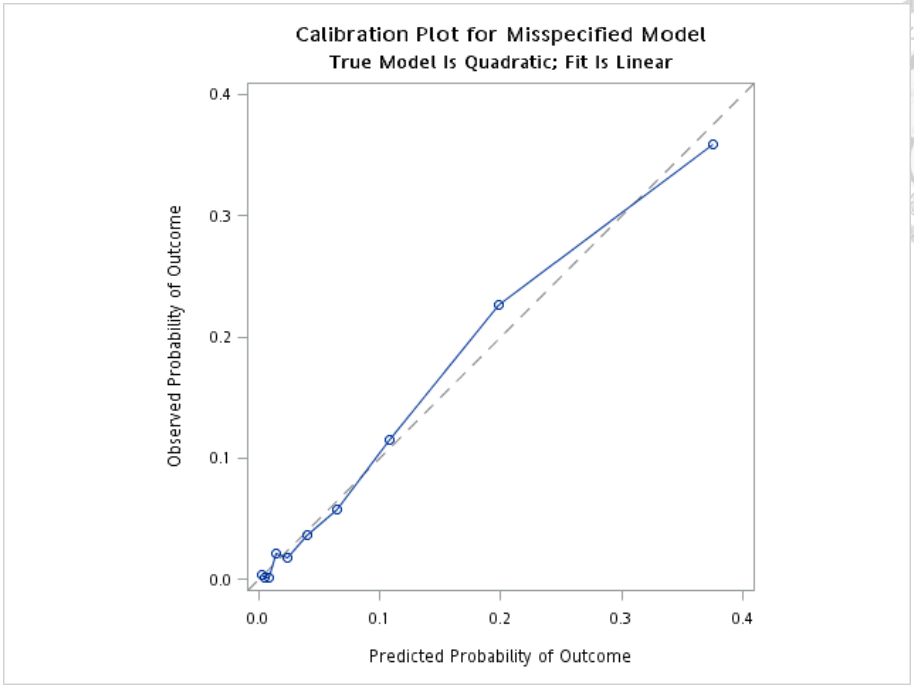
Figure 5: Calibration plot of predicted mean 12.5.following-up years cardiovascular disease (CVD) risk within deciles against the observed 12.5 following-up years CVD risk in the TWsHHH data (N=6048). Data are plotted among participants stratified by lifestyle scores

(A) Simple Taiwan healthy lifestyle score



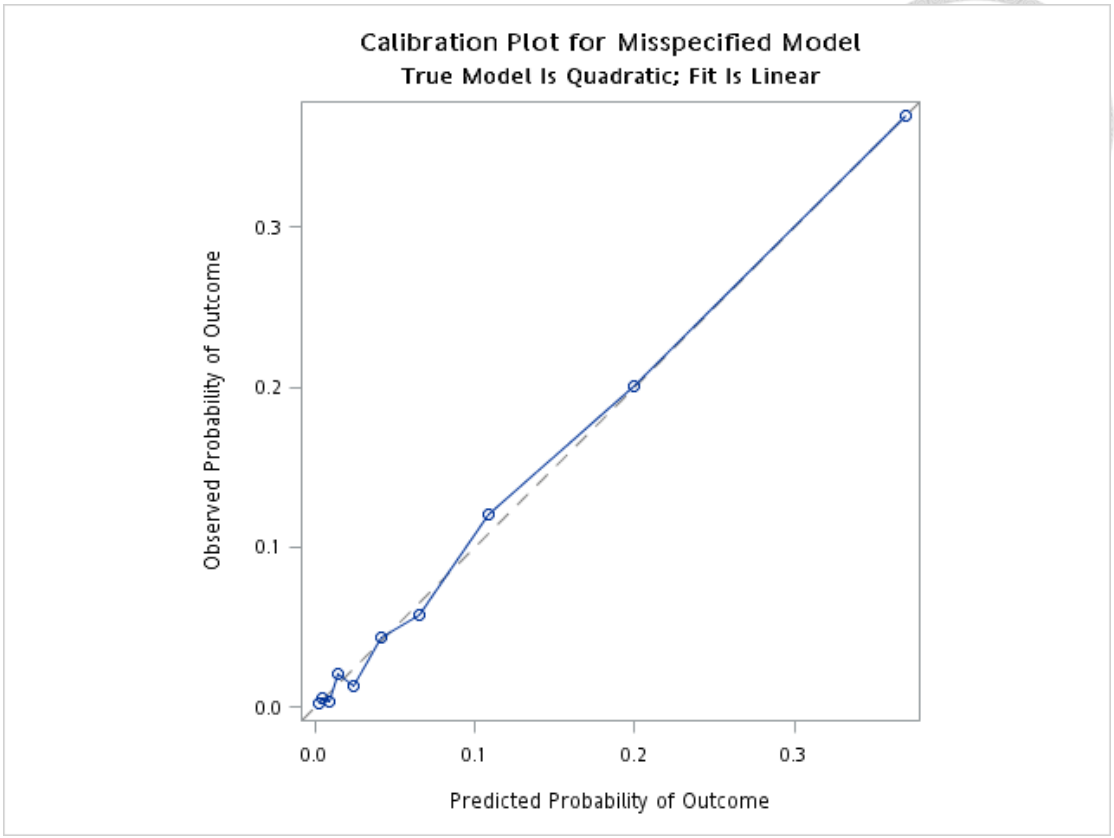
(B) Of Taiwan Healthy lifestyle score

doi:10.6342/NTU202002676

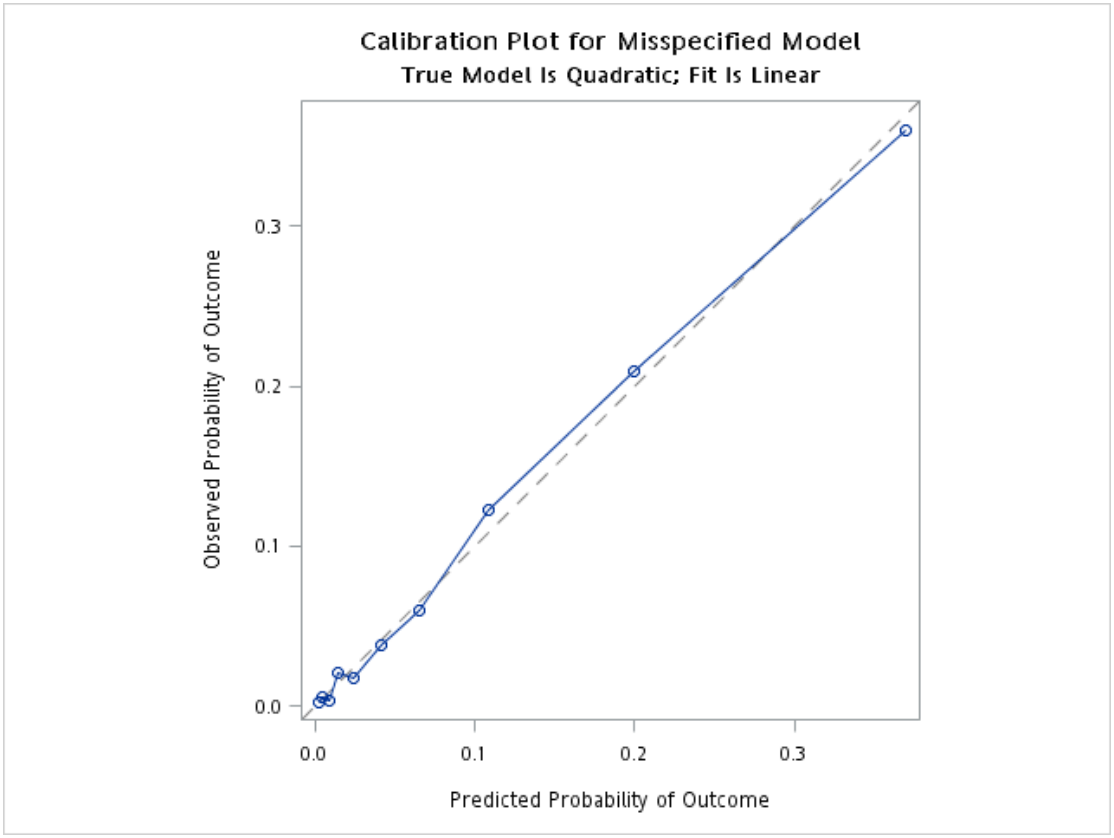


(C) Of WCRF/AICR recommended healthy lifestyle score

doi:10.6342/NTU202002676

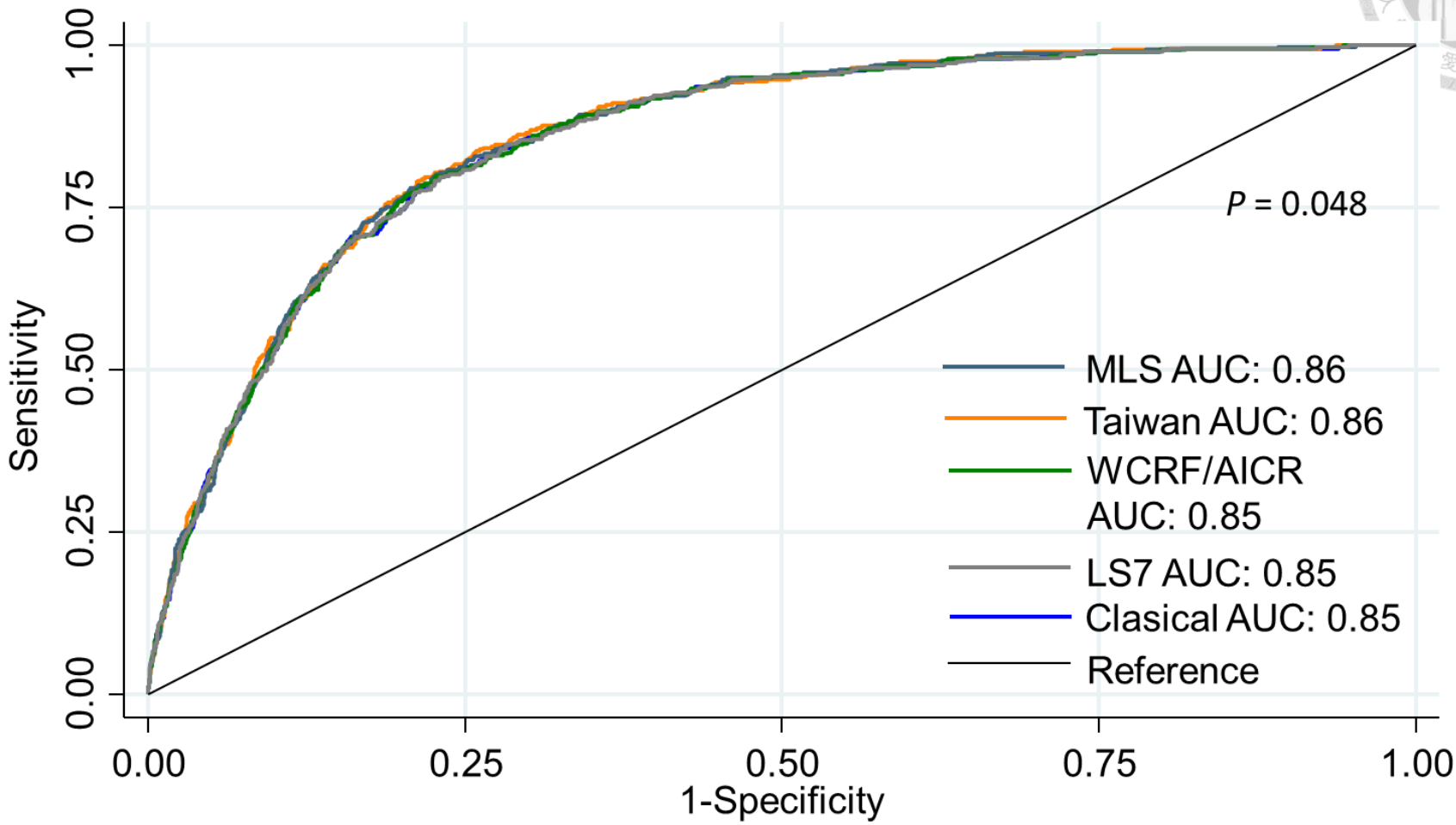


(D) Of Life's Simple 7



doi:10.6342/NTU202002676

Figure 6 : Receiver-operating characteristic curves for various models applied to the study population



doi:10.6342/NTU202002676

Figure 7: The relationship between the healthy lifestyle score and CVD

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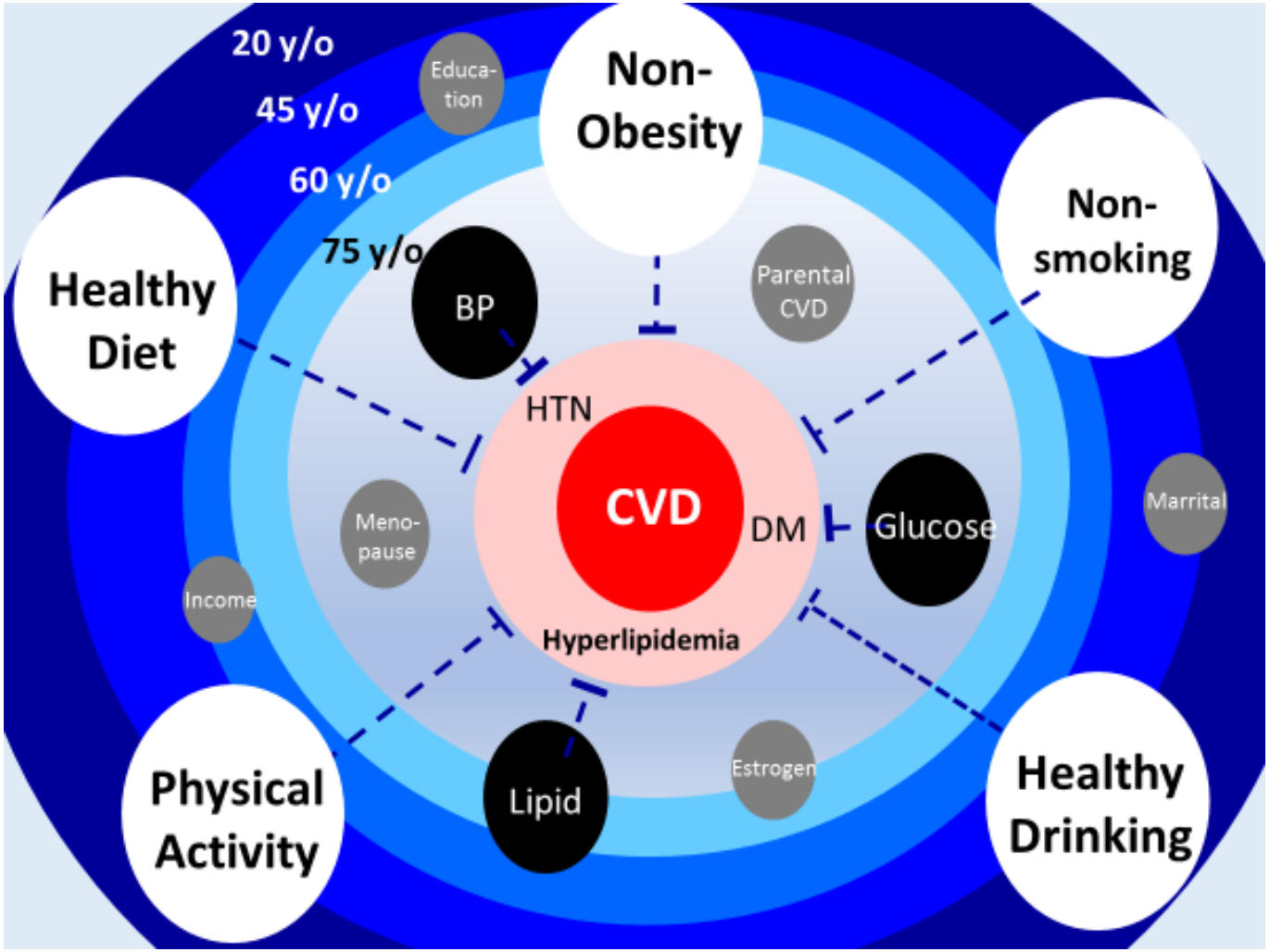

doi:10.6342/NTU202002676

Figure 8

Figure 9: Infographic about the Taiwan healthy lifestyle scores and the reduction of CVD incidence

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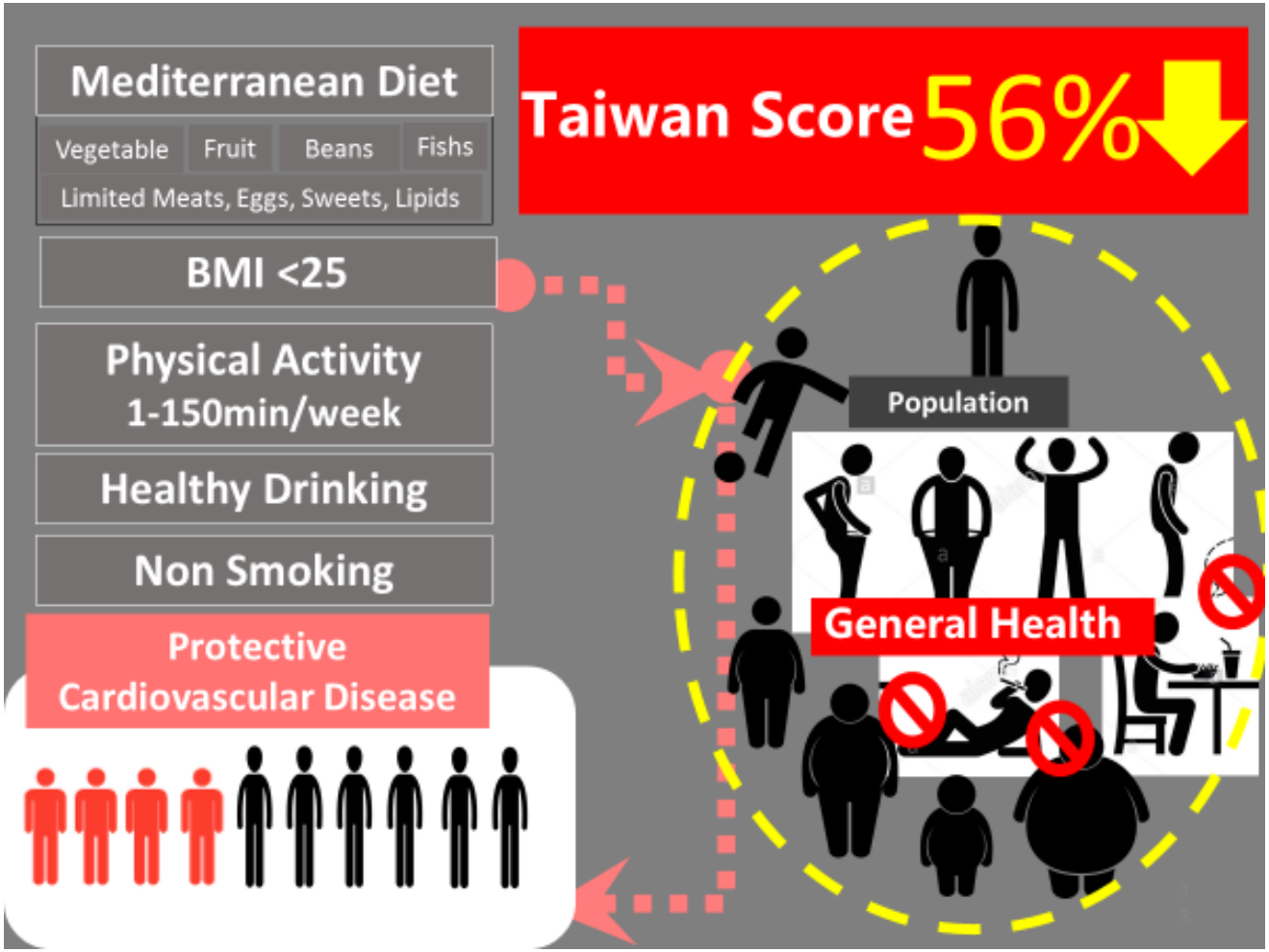

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Table 1 Characteristic of participants in 20 cohort studies

Reference	Cohort name (Country), follow-up years	Study population: participants (women proportion); age at baseline (mean age); DM prevalence	Components of the lifestyle score	Events, outcome measurement,	Adjustment factors
Stampfer, 2000	Nurses' Health Study (U.S.), mean follow-up: 14 years	84129 women; age: 30~55 years; 0% DM	Smoking habit, physical activity, alcohol intake, diet (trans fat, glycemic load, fiber, unsaturated to saturated fat)	1128, Fatal myocardial infarction, non-fatal myocardial infarction	Age, time period (seven time periods), parental history of myocardial infarction before the age of 60 years, menopausal status, postmenopausal hormones,

doi:10.6342/NTU202002676

					hypertension, TC
Akesson, 2007	Swedish Mammography Cohort (Sweden), mean follow-up: 6.2 years	24444 women, age: 48-83 years (mean:59.2); 0% DM	Diet (healthy dietary pattern score), alcohol	308, Myocardial infarction, Death	Age, educational, family history of myocardial infarction, TC, hypertension, hormone therapy, aspirin, total energy intake
Myint, 2009	Norfolk cohort of European Prospective Investigation of Cancer (EPIC Norfolk), mean follow-up: 11.5 years	20040 men and women (55.3%); age: 40-79 years, (mean:58.3); 1.9% DM	Smoking habit, physical activity, alcohol intake, diet (fruit and vegetable intake)	599, Stroke	Age, sex, BMI, systolic blood pressure, TC, diabetes, aspirin, and social class

doi:10.6342/NTU202002676

Table 1. (continued)

Ford, 2009	European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam study (German), mean follow-up: 7.8 years	23,153 women; age: 35-65 years, men: 40 - 65 years; women: 35 - 65 years (mean:49.3); 0% DM	Smoking, BMI, physical activity, diet (consumption of fruits and vegetables, whole grain bread, red meat)	214, Myocardial infarction	Age, sex, education, family history of stroke, diabetes, systolic BP, TC
Zhang, 2011	FINRISK (Finland)	36,686 men and women (53% women); age: 25-	Smoking, BMI, physical activity, diet (vegetable	1167, Ischemic stroke	age, sex, education, family history of stroke, diabete, systolic BP, TC

doi:10.6342/NTU202002676

	, mean follow-up: 13.7 years	74years (mean: 45.8); 2.2% DM	consumption), alcohol consumption		
Carlsson, 2013	Population-based prospective cohort study in Stockholm (Sweden), mean follow-up: 10.85 years	4232 men and women (51.8%); (mean age: 60 years old); 6.8% DM	Smoking, alcohol intake, leisure time physical activity, diet (consumption of fish, processed meats, fruits, vegetables)	375, Ischemic cardiovascular diseases	Sex, educational level, BMI
Hoevenaar-Blom, 2014	Monitoring Project on Risk Factors for Chronic Diseases	14,639 men and women (54.42 %); age: 20-65 years (mean:41.5); 0%	Physical activity, diet (MDS), alcohol consumption, smoking,	607, Fatal and non-fatal cardiovascular diseases	Age, sex, educational level, BMI, systolic blood pressure, and TC/HDL ratio

doi:10.6342/NTU202002676

	(MORGEN)	DM	sleep duration		
	(Netherlands), mean				
	follow-up: 12 years				

Table 1. (Continued)

Ahmed,	Multi-Ethnic Study of	6229 men and women	Diet (Mediterranean-style	655, Coronary	Hypertension, hypertension
2013	Atherosclerosis	(53%); age: 44-84 years	versus unhealthy diet),	cardiovascular events	medication, diabetes medication,
	(MESA)(U.S.), mean	(mean:10); 10% DM	BMI, smoking status,		lipid-lowering medications, fasting
	follow-up: 10 years		physical activity		plasma glucose, HDL, non–HDL,
					TG, CRP

doi:10.6342/NTU202002676

Paynter, 2014	Women's Health Initiative Observational Study (WHI-OS) (U.S.), mean follow-up: 10 years	60890 women, Age: 50-79 years (mean:10); 3.5% DM	BMI or WC, physical activity, alcohol smoking (all participants by inclusion criteria), Diet (AHEI),	1808, Major cardiovascular disease	Age, smoking status, family history of a premature MI, hemoglobin A (if participants had a history of diabetes mellitus), high sensitivity CRP, systolic blood pressure, total and HDL cholesterol, race
Larsson, 2014	Swedish Mammography Cohort (Sweden), mean follow-up: 10.4 years	31696 women; age: 49-83 years (mean:10.4); 3.38% DM	alcohol smoking, physical activity, BMI Diet (RFS),	1155, Ischemic stroke	age, education, aspirin use, diabetes, family with atrial fibrillation and myocardial infarction before 60 years of age,

doi:10.6342/NTU202002676

					total energy intake, and Non-Recommended Food Score.
Akesson, 2014	Cohort of Swedish Men (Sweden), mean follow-up: 11 years	20721 men; age: 45-79 years old, (mean: 58.6); 0% DM	Alcohol smoking, physical activity, abdominal adiposity (WC) diet (RFS),	1361, Myocardial infarction	Age, educational level, family with myocardial infarction, aspirin, marital status, non-Recommended Food Score, and total energy intake
Chomistek, 2015	Nurses' Health Study II cohort (U.S.), mean follow-up: 20 years	88940 women; age: 27-44 years (mean:20); 0% DM	Smoking, physical activity, TV watching, BMI, alcohol, diet (AHEI-	456, Coronary heart disease	Age, time period, parental history of MI before 60 years of age, aspirin, menopausal status,

doi:10.6342/NTU202002676

			2010),		postmenopausal hormone, parity, and oral contraceptive
Lv, 2017	Kadoori Biobank cohort (China), mean follow-up: 7.2 years	461,211 men and women (59%); age: 30-79 years (mean:50.7); 0% DM	Smoking, alcohol, physical activity, diet (fruits, vegetables, meat consumption), BMI, WHR	3331, Major coronary events death and nonfatal myocardial infarction and ischemic stroke	age, sex, education, marital status, and family histories of heart attack or stroke
Díaz-Gutiérrez, 2017	Seguimiento Universidad de Navarra (SUN) cohort (Spain), mean follow-up: 10.4 years	19,336 men and women (61.4%); age: ≧18 years (mean:37.3); 1.7% DM	Smoking, physical activity, BMI, alcohol, diet (Mediterranean diet), TV watching, binge drinking, having short	140, cardiovascular disease	Age, sex, year questionnaire completion, diabetes, cardiovascular disease (other than acute coronary syndrome and stroke), hypertension, hypercholesterolemia,

doi:10.6342/NTU202002676

			afternoon nap, time with friends, time working		hypertriglyceridemia
Dimovski, 2019	Malmö Diet and Cancer study (MDCS) (Sweden), mean follow-up: 18 years	26,323 men and women (61.9%); age: 43-73 years (mean: 57.6); 4.0% DM	Smoking, BMI, physical activity, healthy diet	3417, Coronary artery disease, death due to ischemic heart disease, percutaneous coronary intervention, or coronary artery bypass grafting	Age, sex, educational level and parental history of MI

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Table 2: The definition of body mass index

	BMI Categories	Healthy lifestyle scoring
BMI <18.5	Under weight	1
BMI>=18.5 and <25	Normal weight	1
BMI>=25 and <30	Obesity I	0
BMI>=30 and <35	Obesity II	0
BMI>=35 and <40	Obesity III	0
BMI>=40	Obesity IV	0

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Table 3: The official and our study definition of alternative Mediterranean Diet

Primary diet metric	Mediterranean Definition			Our Definition	
	0 point	1 point		0 point	1 point
	The amount of intake			The frequency of intake (time/week)	
Vegetables	< Median	≥ Median	Fresh vegetables	< 7	≥ 7
Legumes	< Median	≥ Median	Legumes	< 1.5	≥ 1.5
Fruits and nuts	< Median	≥ Median	Fresh fruits	< 7	≥ 7
Dairy products	≥ Median	< Median	Milk, goat's milk, fermented milk, cheese, yogurt, Yakult	≥ 1.5	< 1.5
Cereals	< Median	≥ Median	Rice or Noodles every day	< 2 (cup/day)	≥ 2 (cup/day)
Meat	≥ Median	< Median	Beef, pork, goat, chicken	≥ 4	< 4

doi:10.6342/NTU202002676

Fish	≥ Median	< Median	Fish	< 4	≥ 4
Olive oil	0	250			
Potatoes	≥ Median	< Median			
Eggs	≥ Median	< Median	Eggs	≧ 4	< 4
Sweets	≥ Median	< Median	Cookies, candies, chocolate, cakes, bread, ice cream, milkshake	Cookies, candies, chocolate, ice cream, milkshake≧0.5 cake, bread ≧1.5	Cookies, candies, chocolate, ice cream, milkshake < 0.5 cake, bread < 1.5
Nonalcoholic beverages	≥ Median	< Median	Cola, soda or sweet-beverage	≥ 0.5	< 0.5
Monounsaturated lipids	< Median	≥ Median			
Saturated lipids	≥ Median	< Median	Burger, French frizzed, pizza	> 0	= 0

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Table 3. (Continued)

Polyunsaturated lipids	≥ Median	< Median
Percentage energy from saturated lipids	≥ Median	< Median
Ratio of monounsaturated lipids to saturated lipids	< Median	≥ Median
Energy intake	≥ Median	< Median

doi:10.6342/NTU202002676

Table 4: The category and definition of physical activity

Total time (mins/week)	Categories	Healthy lifestyle scoring
0	Inactive	0
1~50	Somewhat active	1
51~100	Intermittent active	1
101~150	Active	1
> 150	Over active	0

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Table 5: The category and definition of smoking status

Smoking status	Healthy lifestyle scoring
Current smoking ≧20 years	0
Current smoking < 20 years	0
Quit smoking < 1 year	0
Quit smoking ≧1 year	0
Never or smoking less than 100 cigarettes	1

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Table 6: Healthy alcohol consumption

	The frequency of drinking				
	Once / day	Once / 2-3 days	Once / week	1-2 times / month	< 1/month
Light	Frequency	Few	Few	Few	Few
Semi-drunk	Frequency	Frequency	Few	Few	Few
Drunk	Frequency	Frequency	Frequency	Few	Few

Note.

Few = 0 point; Frequency=1 points

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Table 7: Simple Taiwan healthy lifestyle score

	BMI (Kg/m^2)	Mediterranean diet	Physical activity (min/week)	Non-smoking status	Alcohol consumption
Unfavorable (0 point)	≧25	< 6 points	0 or > 150	Current and former	No or few
Healthy (1 point)	< 25	≧6 points	1~150	Never	Frequency

Note.

Mediterranean diet related healthy lifestyle score = BMI + Mediterranean diet + Physical activity + non-smoking status + Alcohol consumption

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Table 8: Weighted Taiwan healthy lifestyle score

	BMI (Kg/m^2)	Mediterranean diet	Physical activity (min/week)	Non-smoking status	Alcohol consumption
Unfavorable (0 point)	≧25	< 6 points	0 or > 150	Current and former	No or few
Healthy (1 point)	< 25	≧6 points	1~150	Never	Frequency
Coefficient	-0.25	-0.29	-0.28	-0.18	-0.66

Note.

Taiwan healthy lifestyle score = 2*BMI + 3*Mediterranean diet + 3*Physical activity + 2*Non-smoking status + 7*Alcohol consumption

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Table 9: The official 2018 WCRF/AICR recommended healthy lifestyle score and our study definition

2018 WCRF/AICR recommendation	Operationalization of recommendation	Our definition	points
Be a healthy weight	BMI (kg/m^2):	BMI (kg/m^2):	
	18.5–24.9	18.5–24.9	0.5
	25–29.9	25–29.9	0.25
	<18.5 or ≥30	<18.5 or ≥30	0
	Waist circumference (cm):	Waist circumference (cm):	
	Men: <94 Women: <80	Men: <94 Women: <80	0.5
	Men: 94–<102 Women: 80–<88	Men: 94–<102 Women: 80–<88	0.25
	Men: ≥102 Women: ≥88	Men: ≥102 Women: ≥88	0
Be physically active	Total moderate-vigorous physical activity	Total moderate-vigorous physical	

doi:10.6342/NTU202002676

	(mins/week)	activity (mins/week)	
	≥150	≥150	1
	75–<150	75–<150	0.5
	<75	<75	0
Eat a diet rich in wholegrains, vegetables, fruit and beans	Fruits and vegetables (g/day):	The frequency of fruits and vegetables intake	
	≥400	One of them every day	0.5
	200–<400	One of them 1~5 times/week	0.25
	<200	Both of them less than once/week	0

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Table 9. (Continued)

	Total fiber (g/day):	The frequency of bean intake	
	≥30	Everyday	0.5
	15–<30	1~5 times per week	0.25
	<15	Less than 1 time/week	0
Limit consumption of “fast foods” and other processed foods high in fat, starches or sugars	Percent of total kcal from ultra-processed foods (aUPFs)	The frequency of French fried/ pizza intake	
	Tertile 1	Tertile 1	1
	Tertile 2	Tertile 2	0.5
	Tertile 3	Tertile 3	0

doi:10.6342/NTU202002676

Limit consumption of red and processed meat	Total red meat (g/wk) and processed meat (g/wk):	The frequency of pork, beef, goat, chicken and burger intake	
	Red meat <500 and processed meat <21	Tertile 1	1
	Red meat <500 and processed meat 21–<100	Tertile 2	0.5
	Red meat >500 or processed meat ≥100	Tertile 3	0
Limit consumption of sugar-sweetened drinks	Total sugar-sweetened drinks (g/day):	The frequency of cola, soda and other sweetened drinks intake	
	0	No intake	1
	>0–≤250	Less than 3 times/week	0.5
	>250	3 times or more/week	0

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Table 9. (Continued)

Limit alcohol consumption	Total ethanol (g/day):		
	0	No drinking	1
	>0–≤28 (2 drinks) males and ≤14 (1 drink) females	Few drinking	0.5
	>28 (2 drinks) males and >14 (1 drink) females	Frequency drinking	0

Total scoring of 2018 WCRF/AICR lifestyle score: 0-7 points

WCRF/AICR Score	< 3	3~ <4	4~ <5	5~7

doi:10.6342/NTU202002676

	Unfavorable	Less healthy	Intermediate	Healthy

doi:10.6342/NTU202002676

Table 10: Life's Simple 7 criteria: reference from 2010 AHA definition of ideal Cardiovascular Health and our study definition

Metric	Recommended Optimal Level (2 points)	Intermediate Level (1 point)	Poor Level (0 point)
Body mass index	<25	25-29.9	≥30
Recommendation			
Our definition	<25	25-29.9	≥30
Healthy diet: Recommendation			
Our definition (below)	5~7	3~4	0~2
Physical activity: Recommendation (mins/week)	≧150 moderate intensity or ≧75 vigorous intensity or combination	0~149 min/week moderate intensity or 0~74 min/week vigorous intensity	0 min/week

doi:10.6342/NTU202002676

Our definition	≧150 moderate intensity or ≧75 vigorous intensity or combination	0~149 min/week moderate intensity or 0~74 min/week vigorous intensity	0 min/week
Smoking: Recommendation	Never or quit ≥12 month prior	Quit <12 month	Current smokers
Our definition	Never or quit ≥12 month prior	Quit <12 month	Current smokers
Total cholesterol Recommendation	<200 mg/dL untreated	200-240 mg/dL or <200 mg/dL treated	>240 mg/dL
Our definition	<200 mg/dL untreated	200-240 mg/dL	>240 mg/dL

doi:10.6342/NTU202002676

Table 10. (Continued)

Blood pressure Recommendation	<120/80 mm Hg untreated	<120/80 mm Hg treated or 120-139/80-89 mm Hg	≥140/90 mm Hg
Our definition	<120/80 mm Hg untreated	120-139/80-89 mm Hg	≥140/90 mm Hg
Fasting plasma glucose Recommendation	<100 mg/dL untreated	100-126 mg/dL or <100 mg/dL treated	>126 mg/dL
Our definition	<100 mg/dL untreated	100-126 mg/dL	>126 mg/dL

doi:10.6342/NTU202002676

Table 11: Life's Simple 7 healthy diet criteria: reference from 2010 AHA definition of ideal Cardiovascular Health and our study definition

Recommended		Our study definition		
Metric	Optimal amount	Metric	The frequency of intake, times / week	
			0 point	1 point
Fruits and vegetables	≧ 4.5 cups per day	Fruits or vegetables	< 7	≧ 7
Fish	≧ 2* 3.5-oz servings per week	Fish	<1	≧ 1
Fiber-rich whole grains (≧1.1 g of fiber per 10 g of carbohydrate)	≧ 3*1-oz-equivalent servings per day	Rice or noodles	< 1 (cup/day)	≧ 1 (cup/day)
Sodium	< 1500 mg per day			
Sugar-sweetened	≦ 450 kcal (36 oz) per week.	Cola, soda, sugar-sweetened	≧ 1	< 1

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beverages		neverages		
Nuts, legumes, and seeds	≧ 4 servings per week	Legumes	< 7	≧ 7
Processed meats	≦ 2 servings per week	Beef, pork, goat, chieken and burger	≧ 1	< 1
Saturated fat	< 7% of total energy intake	French fried and pizza	≧ 1	< 1

Note.

Total Life's Simple 7 healthy diet score: 0~7 points

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Table 12: The definition of important covariates

Covariates	Categories		
Sex (Questionnaire)	Women		Men
Age (Questionnaire)	20~39 (y/o)	40~59 (y/o)	≧60 (y/o)
Marital status (Questionnaire)	Married; Living with spouse		Single/divorced/separated
Education level (Questionnaire)	> 9 years		≦ 9 years
Monthly income (Questionnaire)	≥ 40000 NTD		< 4000 NTD
Parental history of CVD (Questionnaire)	Yes		No
Menopause status (Questionnaire)	Yes		No
Baseline hypertension (NHIRD, ICD-9 and drug)	ICD-9*2 times or anti-HTN drug≧28 days or mean BP ≥ 140/80 mmHg		No record of ICD-9*2 times and anti-HTN drug≧28 days and mean BP < 140/80 mmHg

doi:10.6342/NTU202002676

Baseline diabetes (NHIRD, ICD-9 and drug)	ICD-9*2 times or anti-diabetes drug≧28 days or Fasting glucose ≥ 126mg/dL or HbA1C ≥ 6.5	No record of ICD-9*2 times and anti-diabetes drug≧28 days and Fasting glucose < 126mg/dL or HbA1C < 6.5
Baseline hyperlipidemia (NHIRD, ICD-9 and drug)	ICD-9*2 times or lipid lowering agent≧28 or TC ≥ 240 mg/dL days	No record of ICD-9*2 times and lipid lowering agent≧28 days and TC < 240 mg/dL days
History of hormone use (Questionnaire)	Yes	No

NHIRD: National health insurance research database; HTN: Hypertension; HbA1c: Hemoglobin A1c; TC: total cholesterol

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Table 13: International Classification of Diseases—Clinical Modification (ICD-CM) and procedure codes used to define the metabolic syndrome and clinical outcome in the study cohort

Diagnosis	definition	ICD-9 code	ICD-10 code	Procedure code
Hypertension	≥2 Outpatient department	401-405, 437.2	I10, I11.9, I11.0, I12.9, I12.0, I13.10, I13.0, I13.11, I13.2, I15.0, I15.1, I15.2, I15.8, I15.9, N26.2, , I67.4	
Diabetes mellitus	≥2 Outpatient department	250	E08, E11, E13	
Dyslipidemia	≥2 Outpatient department	272	E78.5	
Coronary heart disease	Either discharge diagnosis of ICD-9 or ICD-10 or procedure code	410 411 414.00	I21.01, I21.02, I21.09, I21.11, I21.19, I22.0, I22.1 I20.0, I24.0, I24.1, I24.8, I24.9 I25.10, I25.750, I25.751, I25.758, I25.759, I25.760, I25.761, I25. 768, I25.769, I25. 811, I25.812	revascularization PCI (33076B, 33077B, 33078B)

doi:10.6342/NTU202002676

	414.01	I25.10, I25.110, I25.111, I25.118, I25.119, I25.750,	CABG(68023B,
		I25.751, I25.758, I25.759, I25. 811	68024B,
	414.02	I25.710, I25.711, I25.718, I25.719, I25.812,	68025B)
	414.03	I25.730, I25.731, I25.738, I25.739	N26002,
	414.04	I25.720, I25.721, I25.728, I25.729	N26003
	414.05	I25.700, I25.701, I25.708, I25.709, I25.730, I25.731,	
		I25.738, I25.739, I25.760, I25.761, I25.768, I25.769,	
		I25.790, I25.791, I25.798, I25.799, I25.810, I25.812	
	v45.81	Z95.1	
	v45.82	Z95.5, Z98.61, Z95.8,	

doi:10.6342/NTU202002676

Table 13. (Continued)

Diagnosis	Definition	ICD-9	ICD-10	Procedure code
Stroke	discharge diagnosis of ICD-9 or ICD-10	433	165.1,I63.02, I63.12, I65.21, I63.22, I65.1, I65.23, I65.29 , I63.031, I63.032, I63.039, I63.131, I63.132, I63.139, I63.231, I63.232, I63.239, I65.01, I65.02, I65.03, , I65.09, I63.011, I63.012, I63.019, I65.22, I63.111, I63.112, I63.119, I63.211, I63.212, I63.219, I65.8, 163.09, I63.19, I63.59, I65.9, I63.00, 163.10, I63.20, I63.29	
		434	I66.01, I66.02, I66.03, I66.09, I66.11, I66.12, I66.13, I66.19, I66.21, I66.22, I66.23, I66.29, I66.3, I63.30, I63.311, I63.312, I63.319, I63.321, I63.322, I63.329, I63.331, I63.332, I63.339, I63.341, I63.342, I63.349, I63.39, I63.6, I66.01, I66.02, I66.03, I66.09, I66.11, I66.12, I66.13, I66.19, I66.21, I66.22,	

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	I66.23, I66.29, I66.3, I66.9, I66.40, I66.411, I66.412, I66.419, I66.421, I66.422, I66.429, I66.431, I66.432, I66.439, I66.441, I66.442, I66.449, I66.49, I66.01, I66.02, I66.03, I66.09, I66.11, I66.12, I66.13, I66.19, I66.21, I66.22, I66.23, I66.29, I66.3, I66.8, I66.9, I63.50, I63.511, I63.512, I63.519, I63.521, I63.522, I63.529, I63.531, I63.532, I63.539, I63.541, I63.542, I63.549, I63.59, I63.8, I63.9
435	G45.0,G45.8,G45.1,G45.2,G46.0, G46.1, G46.2, G45.9, I67.841, I67.848
436	I67.89
4371	I67.81, I67.82, I67.89
4379	I67.9

CABG, Coronary artery bypass graft; PCI, *Percutaneous* coronary intervention

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Table 14: Basic characteristics of the study participants at baseline, specified by adherence numbers of healthy lifestyle scores

(A) The simple Taiwan healthy lifestyle score (0~5 points)

	Whole population	Simple Taiwan Healthy Lifestyle Score				
The numbers of score	(n= 6048)	0~1(n=1332)	2 (n=2438)	3 (n=1811)	4~5 (n=461)	*P*
			%			
Women	50.2	28.2	53.3	59.3	62	<.001
Age (years) 20-39	41.1	30.3	35.5	51.1	62.5	<.001
40-59	39.2	44.1	41.4	34.7	31	
≧60	19.7	25.6	23.2	14.2	6.5	
Body mass index (kg/m^2) < 25	73.2	31.38	75.88	94.76		<.001

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≧25	26.9	68.62	24.12		5.24	
Mediterranean diet score ≧6	47.2	12.84	33.96		81.47	<.001
< 6	52.8	87.16	66.04		18.53	
Exercise time 1~150 mins/week	23	3.2	11.4	34.5	96.1	<.001
0 or >150 mins/week	77	96.8	88.6	65.5	3.9	
Never smoking	71.3	34.2	73	89.8	97	<.001
Quit and current smoking	28.7	65.8	27	10.2	3	
Adeaute drinking	5.1	2.4	5.7	5.4	8.7	<.001
Non or few drinking	94.9	97.6	94.3	94.6	91.3	

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Marital status: Living with spouse	64.6	29.1	33.3	40.5	44.7	<.001
Single, divorced or separated	35.4	71	66.7	59.5	55.3	
Education level: ≦9 years	45.7	58.6	51	35.1	22.1	<.001
> 9 years	54.3	41.4	49	64.9	77.9	
Monthly income < 40000 NTD	79.6	79.2	81.9	78.1	74.8	0.001
≧ 40000 NTD	20.4	20.8	18.1	21.9	25.2	
Parents history of CVD	21.9	24.5	22.4	20.8	16.9	0.004
Menopause status	17.3	16	21.9	14.6	7.4	<.001
Hypertension	15.7	24.9	17.1	9.8	5.4	<.001
Diabetes Mellitus	4.4	7.4	4.6	2.8	0.7	<.001

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History of hyperlipidemia	7.2		9.3	7.6	5.9	4.3	<.001
HRT use	8		6.5	8.7	8.2	7.6	0.125

Variable	Mean	SD	Mean				*P*
Systolic BP, mmHg	116.5	18.2	122.1	118	112.6	107.7	<.001
Diastolic BP, mmHg	75.6	11.4	79.6	75.9	73.3	70.9	<.001
Total cholesterol, mg/dL	186.1	37.9	191.3	187.2	182.6	178.7	<.001
Triglyceride, mg/dL	130.1	86.6	163.6	129.5	112.8	105.2	<.001
HDL-cholesterol, mg/dL	55.5	15.3	51.3	55.9	57.5	57.9	<.001
LDL-cholesterol, mg/dL	117.1	27.2	121.2	118.4	113.9	110.6	<.001
Non-HDL-cholesterol, mg/dL	130.6	35.3	140	131.3	125.2	120.8	<.001
Fasting glucose, mg/dL	95	29.4	101.1	95.5	91.8	87.1	<.001

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Hemoglobin A1c, %	5.4	1.1	5.6	5.4	5.2	5.1	<.001

(B) The weighted Taiwan healthy lifestyle score (0~5 points)

The number of score	0~4 (n=2577)	5 (n=971)	6~7 (n=1575)	8~17 (n=919)	*P*
			%		
Women	51.7	34.1	64.6	38.6	<.001
Age (years) 20-39	31.5	40.3	51.3	51.3	<.001
40-59	42.1	40.2	34.7	37.5	
≧60	26.4	19.6	14	11.2	
Body mass index (kg/m^2) < 25	65.8	49.7	94.8	81.6	<.001
≧25	34.2	50.3	5.2	18.4	
Mediterranean diet score ≧6	6.6	77.3	73.6	83.7	<.001

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< 6	93.4	22.7	26.4	16.3	
Exercise time 1~150 mins/week	1.7	22.7	27.6	75.3	<.001
0 or >150 mins/week	98.3	77.3	72.4	24.7	
Never smoking	67.2	50.3	94.8	64.6	<.001
Quit and current smoking	32.8	49.7	5.2	35.4	
Adeaute drinking	0	0	2	30.1	<.001
Non or few drinking	100	100	98	69.9	
Marital status: Living with spouse	67.3	68.8	58	64	<.001
Single, divorced or separated	32.7	31.2	42	36	
Education level: ≦9 years	56.7	44.8	35.1	34.1	<.001
> 9 years	43.3	55.2	65	65.9	

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Table. (continued)

Monthly income < 40000 NTD		83.4	76	79.5	73	<.001
	≧ 40000 NTD	16.6	24	20.5	27	
Parents history of CVD		22.8	24.3	19.6	21.1	0.019
Menopause status		23.4	14.5	15.4	6.4	<.001
Hypertension		19.7	17.6	9.4	13.4	<.001
Diabetes Mellitus		5.9	4.5	2.7	2.8	<.001
History of hyperlipidemia		8.3	7.7	6.4	5.1	0.005
HRT use		8.8	6.7	9	5.4	0.002

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Variable	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*P*
Systolic BP, mmHg	119.0	18.8	119.1	17.7	112.1	16.7	114.3	17.6	<.001
Diastolic BP, mmHg	76.7	11.5	77.3	11.1	72.9	10.7	75.2	11.6	<.001
Total cholesterol, mg/dL	188.6	39.2	187.5	37.9	182.9	36.6	182.9	36.1	<.001
Triglyceride, mg/dL	138.7	93.1	138.6	85.6	110.7	68.6	129.6	91.2	<.001
HDL-cholesterol, mg/dL	55.0	15.9	53.9	14.7	57.8	14.4	55.0	15.4	<.001
LDL-cholesterol, mg/dL	119.0	27.3	120.3	28.4	113.9	26.4	113.7	25.9	<.001
Non-HDL-cholesterol, mg/dL	133.6	36.8	133.7	34.4	125.2	33.0	127.8	34.4	<.001
Fasting glucose, mg/dL	97.8	32.4	96.4	32.2	91.7	24.6	91.5	23.5	<.001
Hemoglobin A1c, %	5.5	1.2	5.5	1.2	5.2	1.0	5.2	0.8	<.001

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(C) WCRF/AICR recommended healthy lifestyle score

	WCRF/AICR Healthy Lifestyle Score				
The number of score	0~2 (n=1116)	3 (n=2048)	4 (n=1811)	5~6 (n=861)	*P*
	%				
Women	40.4	47.2	54.5	59.6	<.001
Age (years) 20-39	50.3	42.6	37.7	33.8	<.001
40-59	33.7	37.6	42.4	42.5	
≧60	16	19.8	20	23.7	
Body mass index (kg/m^2) 18.5~23.9	19.7	44	69.4	89	<.001

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<18.5 or ≧24	80.3	56	30.6	11	
WCRF/AICR diet score ≧3	0	53.1	93.1	100	<.001
< 3	100	46.9	6.9	0	
Physical activity					
Moderate ≧ 420 or Vigorous ≧ 210	4.7	14.7	30	66.5	<.001
Moderate: 1-419 or Vigorous : 1-209	95.3	85.3	70	33.5	
Never smoking	63.8	69.8	74.4	77.2	<.001
Non or few drinking					
Marital status: Living with spouse	39.7	35.6	32.6	35.9	0.001
Single, divorced or separated	60.3	64.4	67.4	64.1	
Education level: ≦9 years	41.9	47.6	45.9	46	0.021

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> 9 years	58.2	52.4	54.1	54	
Monthly income < 40000 NTD	77.2	78.6	80.1	84.1	0.001
≧40000 NTD	22.8	21.4	19.9	15.9	
Parents history of CVD	22	19.9	24	21.7	0.018
Menopause status	12.8	16.6	18.8	20.9	<.001
Hypertension	16.8	17.6	14	13.9	0.006
Diabetes Mellitus	5.1	4.7	4.1	3.4	0.20
History of hyperlipidemia	8	7.7	6.7	6.4	0.34
HRT use	6.7	6.9	9.3	9.1	0.009
Variable	Mean				*P*

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Systolic BP, mmHg	116.9	117.3	116	115.3	0.024
Diastolic BP, mmHg	76.8	76.3	74.9	73.9	<0.001
Total cholesterol, mg/dL	187.5	187.5	184.8	184.1	0.057
Triglyceride, mg/Dl	144.9	136.8	122.3	114.4	<0.001
HDL-cholesterol, mg/dL	53.2	55.2	56.6	56.6	<0.001
LDL-cholesterol, mg/dL	118.2	117.8	116.3	115.8	0.125
Non-HDL-cholesterol, mg/Dl	134.3	132.2	128.3	127.5	<0.001
Fasting glucose	96.6	95.6	94.3	93	0.046
Hemoglobin A1c	5.4	5.4	5.3	5.3	0.048

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(D) Life's Simple 7

	Life's Simple 7				
	N=167	N=1413	N=3395	N=1073	*P*
	%				
Women	36.53	35.74	52.31	64.49	<0.001
Age (years) 20-39	34.73	33.97	41.65	49.77	<0.001
40-59	34.73	40.2	39.2	38.4	
≧60	30.54	25.83	19.15	11.84	
Body mass index (kg/m^2) < 24	10.94	41.03	77.96	94.32	<0.001

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24~26.9	51.56	45.92	20.28	5.68	
≧27	37.5	13.05	1.76	0	
Healthy diet recommended by Life's Simple 7					
5-7 points	43.11	55.77	70.93	84.25	<0.001
3-4 points	52.1	41.33	28.01	15.75	
0-2 points	4.79	2.9	1.06	0	
Physical activity					
Moderate ≧ 150 or Vigorous ≧ 75	3.59	13.75	27.88	74.65	<0.001
Moderate: 1-149 or Vigorous : 1-74	11.98	13.96	20.69	25.35	
None	84.43	72.29	51.43	0	
Never or quit smoking ≧12 mo prior	58.08	67.23	88.31	98.88	<0.001

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Quit smoking < 12 mo	6.59	6.09	3.3	1.12	
Current smoking	35.33	26.68	8.39	0	
Marital status: Living with spouse	65.27	67.73	64.59	60.3	0.002
Single, divorced or separated	34.73	32.27	35.41	39.7	
Education level: ≦9 years	70.06	56.76	45.27	28.89	<0.001
> 9 years	29.94	43.24	54.73	71.11	
Monthly income < 40000 NTD	82.04	79.83	80.53	76.14	0.016
≧ 40000 NTD	17.96	20.17	19.47	23.86	
Parents history of CVD	31.14	22.65	22.36	18.17	<0.001
Menopause status	27.54	22.08	15.99	13.33	<0.001
Hypertension	65.27	35.24	10.13	0	<0.001

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Diabetes Mellitus	32.9	9.6	2.1	0.2	<0.001
History of hyperlipidemia	45.5	15.4	4	0.2	<0.001
HRT use	8.38	6.02	8.87	7.74	0.011
Total cholesterol <200 untreated	20.96	52.37	76.55	93.1	<0.001
200-240	33.53	32.63	19.53	6.9	
>240	45.51	15	3.92	0	
Blood pressure <120/80 untreated	6.59	26.26	61.33	90.4	<0.001
<120/80 treated or 120-130/80-89	28.74	38.92	28.63	9.6	
≧ 140/90	64.67	34.82	10.04	0	
Fasting plasma glucose <100mg/dL untreated	32.93	66.74	89.48	98.7	<0.001
Fasting plasma glucose 100-126mg/dL or <100mg/dL treated	28.74	21.73	8.39	1.3	

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	> 126mg/dL	38.32		11.54		2.12		0	

Variable	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*P*
Systolic BP, mmHg	136.7	18.4	126.9	18.7	114.2	16.6	105.5	10.5	<0.001
Diastolic BP, mmHg	88.3	11.7	82	11.5	74.1	10.4	68.9	7.3	<0.001
Triglyceride, mg/dL	245	133	166.6	106.5	118.5	71.4	95.2	46.7	<0.001
Non-HDL-cholesterol, mg/dL	183.2	56.5	147.1	38.4	125.6	29.5	112.6	21.2	<0.001
Fasting glucose, mg/dL	137.9	66.1	105.3	40.3	90.7	19.3	85.9	7.4	<0.001
Hemoglobin A1c, %	6.7	2.1	5.7	1.4	5.3	0.9	5	0.5	<0.001

Note:

Abbreviation: SD, standard deviation; BP, blood pressure; HDL, high density lipoprotein, LDL, low density lipoprotein; ANOVA and the chi-

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square tests were used to compare the means and proportions among groups

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Table 15: The incidence cases, follow-up person-years, and the rates of cardiovascular disease events and the hazard ratios and 95% confidence intervals

(A) According to the body mass index in 6048 for TWsHHH study participants

BMI	<18.5	18.5~24.9		25~29.9		30~34.9		35~39.9		≧ 40		*P* of Logrank		
Cases	10	243		165		25		5		1				
Pearson-year	4639	47799		16740.8		2876		403		38.6				
Rates/1000 py	2.2	5.1		9.9		8.7		12.4		25.9		<.001		
	HR	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	*P* of Trend Test	PAF	95% CI
Univariate	1.00	2.31	1.19 4.51	4.62	2.36 9.06	3.62	1.65 7.95	4.93	1.52 16.01	40.46	8.74 187.36	<.001		
Model 1	1.00	1.24	0.64 2.42	1.87	0.95 3.67	2.05	0.93 4.49	4.09	1.26 13.30	36.56	7.82 171.00	<.001		
Model 2	1.00	1.23	0.63 2.40	1.79	0.91 3.51	1.87	0.85 4.11	3.36	1.02 11.10	40.22	8.53 189.66	<.001		

doi:10.6342/NTU202002676

Model 3	1.00	0.79	0.40	1.55	1.03	0.52	2.05	0.93	0.41	2.12	0.96	0.20	4.59	31.17	6.54	148.58	0.012	25.7	5.6 41.6

(E) according to the Mediterranean diet score in 6048 for TWsHHH study participants

	0~3	4~5			6~7			8~11			*P* of Logrank			
Cases	145	209			133			33						
Pearson-year	13786	24958			23647			13246						
Rates/1000 py	10.52	8.37			5.62			2.49			<0.001			
	HR	HR	95% CI		HR	95% CI		HR	95% CI		*P* of Trend Test	PAF	95% CI	
Univariate	1.00	0.79	0.62	1.01	0.51	0.39	0.67	0.20	0.12	0.31	<0.001			
Model 1	1.00	0.88	0.69	1.13	0.73	0.56	0.96	0.40	0.25	0.63	<0.001			
Model 2	1.00	0.90	0.71	1.15	0.78	0.59	1.03	0.42	0.27	0.67	0.002			
Model 3	1.00	0.92	0.71	1.21	0.83	0.61	1.12	0.35	0.20	0.61	0.008	23.7	6.7	37.6

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(F) According to the time of physical activity in 6048 for TWsHHH study participants

	0	1~49			50~99			100~149			≧ 150			*P* of Logrank		
Cases	234	17			24			30			215					
Pearson-year	36254	5690			7170			5130			21393.1					
Rates/1000 py	6.45	3.0			3.35			5.85			10.1			<.001		
	HR	HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI		*P* of Trend Test	PAF	95% CI
Univariate	1	0.45	0.26	0.77	0.55	0.36	0.86	0.82	0.53	1.27	1.45	1.17	1.8	<.001		
Model 1	1	0.60	0.35	1.04	0.75	0.48	1.17	0.86	0.56	1.32	1.04	0.84	1.3	0.70		
Model 2	1	0.65	0.38	1.13	0.80	0.51	1.25	0.94	0.61	1.45	1.12	0.9	1.4	0.26		
Model 3	1	0.60	0.33	1.09	0.82	0.50	1.34	0.91	0.57	1.45	1.08	0.84	1.38	0.33	-5.3	-18 6

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(G) According to the non-smoking status in 6048 for TWsHHH study participants

	0	1			2			3			4			*P* of Logrank			
Cases	120	19			2			43			336						
Pearson-year	8998	9299.4			260.7			2397			54600.5						
Rates/1000 py	13.34	2.0			7.67			17.9			6.15			<.001			
	HR	HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI		*P* of Trend Test	PAF	95% CI	
Univariate	1	0.15	0.09	0.26	0.79	0.20	3.20	1.19	0.79	1.81	0.43	0.34	0.54	<.001			
Model 1	1	1.01	0.58	1.76	1.54	0.38	6.24	1.01	0.66	1.53	0.97	0.74	1.27	0.57			
Model 2	1	0.98	0.56	1.72	1.87	0.46	7.64	1.10	0.72	1.67	1.03	0.79	1.35	0.98			
Model 3	1	1.03	0.56	1.93	2.51	0.61	10.33	0.97	0.61	1.56	0.90	0.66	1.21	0.54	2.4	-4.7	8.9

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(H) According to the frequency of alcohol consumption in 6048 for TWsHHH study participants

	Never	Few			Frequency			*P* of Logrank			
Cases	403	92			25						
Pearson-year	54756	17146.2			3734						
Rates/1000 py	7.36	5.37			6.69			0.022			
	HR	HR	95% CI		HR	95% CI		*P* of Trend Test	PAF	95% CI	
Univariate	1	0.85	0.66	1.09	1	0.63	1.57	0.035			
Model 1	1	0.77	0.59	0.99	0.59	0.38	0.94	<.001			
Model 2	1	0.76	0.59	0.98	0.59	0.37	0.93	<.001			
Model 3	1	0.79	0.6	1.05	0.5	0.29	0.87	0.001	41.1	18.1	57.6

Note.

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Model 1: adjusted for age and sex

Model 2: Model 1 + education, average month income, marital status, parental history of CVD, menopause status and estrogen exposure

Model 3: Model 2 + baseline HTN, baseline DM, history of hyperlipidemia, sBP, dBP, triglyceride, non-HDL, fasting glucose, HbA1c; The population attributable risk is the percentage of new cases of heart failure in the population attributable to nonadherence to the low-risk lifestyle factor)

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Table 16: The incidence cases, follow-up person-years, and the rates of cardiovascular disease events and the hazard ratios and 95% confidence intervals

(A) The simple Taiwan healthy lifestyle score, according to the numbers of the score

	O~1	2			3			4~5			*P* of Logrank		
Cases	193	228			87			12					
Pearson-year	15840.3	30091.5			23459.7			6163.6					
Rates/1000 py	12.18	7.6			3.71			1.95			< 0.001		
	HR	HR	95% CI		HR	95% CI		HR	95% CI		*P* of Trend Test	PAF	95% CI
Univariate	1.00	0.56	0.45	0.69	0.26	0.20	0.35	0.14	0.07	0.27	< 0.001		
Model 1	1.00	0.72	0.58	0.90	0.48	0.35	0.64	0.37	0.19	0.72	< 0.001		
Model 2	1.00	0.75	0.60	0.94	0.53	0.39	0.71	0.42	0.21	0.82	< 0.001		

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Model 3	1.00	0.77	0.60	0.99	0.53	0.38	0.74	0.43	0.20	0.94	< 0.001	38.8	19.2	53.6

(B) The weighted Taiwan healthy lifestyle score, according to the score quartiles

	0~4	5			6~7			8~17			*P* of Logrank			
Cases	312	89			82			37						
Pearson-year	31049	12213.6			20456.2			11836.4						
Rates/1000 py	10.05	7.29			4.01			3.13			<0.001			
	HR	HR	95% CI		HR	95% CI		HR	95% CI		*P* of Trend Test	PAF	95% CI	
Univariate	1.00	0.86	0.64	1.15	0.72	0.53	0.98	0.45	0.29	0.70	<0.001			
Model 1	1.00	0.80	0.61	1.05	0.62	0.46	0.82	0.47	0.32	0.69	<0.001			
Model 2	1.00	0.82	0.63	1.08	0.67	0.51	0.90	0.49	0.34	0.73	<0.001			
Model 3	1.00	0.82	0.61	1.11	0.69	0.51	0.95	0.44	0.28	0.68	<0.001	34.3	17.8	47.4

doi:10.6342/NTU202002676

(C) The WCRF/AICR recommended healthy lifestyle score, according to the numbers of the score

	<3	3~ <4		4~ <5		5~7		*P* of Logrank		
Cases	55	94		193		178				
Pearson-year	14391	19563.7		24508.2		17174.1				
Rates/1000 py	3.82	4.8		7.87		10.36		<0.001		
	HR	HR	95% CI	HR	95% CI	HR	95% CI	*P* of Trend Test	PAF	95% CI
Univariate	1	1.21	0.84 1.75	1.97	1.41 2.74	2.52	1.8 3.53	<.001		
Model 1	1	0.99	0.69 1.44	0.88	0.63 1.23	0.89	0.63 1.26	0.38		
Model 2	1	0.94	0.65 1.36	0.83	0.59 1.17	0.88	0.62 1.24	0.49		
Model 3	1	1.33	0.75 2.34	1.32	0.76 2.29	1.44	0.82 2.51	0.30	-6.2	-19 4.9

doi:10.6342/NTU202002676

(D) Life's Simple 7, according to the numbers of score (0~14 points)

	0~6	7~9			10~12			13~14			*P* of Logrank			
Cases	36	194			255			35						
Pearson-year	1801.91	16826.4			42851.6			14157						
Rates/1000 py	20.0	11.5			6.0			2.47			<0.001			
	HR	HR	95% CI		HR	95% CI		HR	95% CI		*P* of Trend Test	PAF	95% CI	
Univariate	1	0.63	0.40	0.99	0.36	0.23	0.56	0.16	0.09	0.27	<0.001			
Model 1	1	0.54	0.35	0.85	0.37	0.24	0.58	0.21	0.12	0.37	<0.001			
Model 2	1	0.60	0.38	0.94	0.43	0.27	0.66	0.27	0.15	0.47	<0.001			
Model 3	1	0.84	0.51	1.39	0.86	0.50	1.48	0.60	0.29	1.24	0.02	24.5	3.1	41.2

doi:10.6342/NTU202002676

Note.

Model 1: adjusted for age and sex

Model 2: Model 1 + education, average month income, marital status, parental history of CVD, menopause status and estrogen exposure

Model 3: Model 2 + baseline HTN, baseline DM, history of hyperlipidemia, sBP, dBP, triglyceride, non-HDL, fasting glucose, HbA1c; The population attributable risk is the percentage of new cases of heart failure in the population attributable to nonadherence to the low-risk lifestyle factor)

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Table 17: Hazard ratios for cardiovascular disease among participants stratified by different covariates, specified by simple Taiwan healthy lifestyle score, weighted Taiwan healthy lifestyle score, WCRF/AICR recommended healthy lifestyle and Life's Simple 7 according to the numbers of healthy lifestyle factors

(A) Stratified by age < 60 y/o and ≥ 60 y/o

		Group 1	Group 2			Group 3			Group 4			
		HR	HR	95% CI		HR	95% CI		HR	95% CI		$P_{interaction}$
MDS	age < 60	1	0.65	0.44	0.96	0.37	0.21	0.63	0.35	0.13	0.99	0.070
	age ≥ 60	1	0.88	0.64	1.22	0.67	0.44	1.03	0.56	0.17	1.79	
Taiwan	age < 60	1	0.60	0.37	0.96	0.53	0.32	0.88	0.31	0.15	0.61	0.029
	age ≥ 60	1	0.96	0.66	1.41	0.81	0.54	1.21	0.60	0.33	1.07	
WCRF	age < 60	1	0.86	0.45	1.64	0.84	0.44	1.59	1.30	0.67	2.51	0.011

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	age ≥ 60	1	3.26	0.77	13.84	2.95	0.71	12.26	2.65	0.64	11.04	
LS7	age < 60	1	1.25	0.59	2.63	0.61	1.24	0.54	0.97	0.32	2.98	0.234
	age ≥ 60	1	0.62	0.31	1.23	0.26	0.66	0.32	0.45	0.17	1.18	

Note.

Group1 as those with lowest number of healthy lifestyle score, Group 2 and Group 4 as those with increasing the numbers of healthy lifestyle score.

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Table 18: Improvement in discrimination performance and calibration for risk prediction of cardiovascular events in the multivariate-adjusted model after including simple Taiwan healthy lifestyle score, Taiwan healthy lifestyle score, WCRF/AICR recommendation lifestyle and Life's Simple 7

	AUC	95% CI		P	P for HL test	IDI (%)	95% CI		P	NRI (%)	95% CI		P
Clssical model	0.85	0.837	0.870				Reference						
Simple Taiwan	0.86	0.842	0.874	0.02	0.34	0.38	0.01	0.74	0.021	0.03	0.01	0.05	0.004
Weighted Taiwan	0.86	0.840	0.873	0.003	0.25	0.51	0.16	0.86	0.002	0.04	0.02	0.06	<.001
WCRF/AICR	0.85	0.838	0.870	0.49	0.49	0.10	-0.03	0.24	0.07	0.07	-1.15	1.29	0.91
Life's Simple 7	0.85	0.837	0.870	0.80	0.73	0.09	-0.06	0.24	0.11	0.95	-0.37	2.28	0.16

Note.

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Abbreviations: IDI: integrated discriminative improvement; NRI: net reclassification improvement.

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Table 19: Sensitivity test of the incidence cases, follow-up person-years, and the rates of cardiovascular disease events and the hazard ratios and 95% confidence intervals

(A) The simple Taiwan healthy lifestyle score, substitute of body mass index by waist circumflex

	O~1	2			3			4~5			*P* of Logrank		
Cases	249	205			56			10					
Pearson-year	19303	28771.5			21790.6			5689.7					
Rates/1000 py	12.9	7.1			2.57			1.76			< 0.001		
	HR	HR	95% CI		HR	95% CI		HR	95% CI		*P* of Trend Test	PAF	95% CI
Univariate	1.00	0.55	0.45	0.68	0.21	0.16	0.29	0.13	0.07	0.27	< 0.001		
Model 1	1.00	0.78	0.63	0.97	0.44	0.32	0.60	0.36	0.18	0.73	< 0.001		
Model 2	1.00	0.81	0.65	1.00	0.48	0.35	0.67	0.41	0.20	0.83	< 0.001		

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Model 3	1.00	0.86	0.68	1.10	0.54	0.38	0.77	0.45	0.21	0.98	< 0.001

(B) The weighted Taiwan healthy lifestyle score, substitute of body mass index by waist circumflex

	0~4	5			6~7			8~17			*P* of Logrank		
Cases	241	194			52			33					
Pearson-year	18822.4	26477.9			18515.8			11739					
Rates/1000 py	12.8	7.33			2.81			2.81			< 0.001		
	HR	HR	95% CI		HR	95% CI		HR	95% CI		*P* of Trend Test	PAF	95% CI
Univariate	1.00	0.57	0.46	0.71	0.25	0.18	0.34	0.22	0.15	0.33	< 0.001		
Model 1	1.00	0.81	0.65	1.01	0.51	0.37	0.71	0.41	0.27	0.62	< 0.001		
Model 2	1.00	0.85	0.68	1.06	0.57	0.41	0.80	0.44	0.29	0.66	< 0.001		
Model 3	1.00	0.92	0.72	1.18	0.67	0.47	0.95	0.40	0.25	0.65	< 0.001		

doi:10.6342/NTU202002676

Note.

Model 1: adjusted for age and sex

Model 2: Model 1 + education, average month income, marital status, parental history of CVD, menopause status and estrogen exposure

Model 3: Model 2 + baseline HTN, baseline DM, history of hyperlipidemia, sBP, dBP, triglyceride, non-HDL, fasting glucose, HbA1c; The population attributable risk is the percentage of new cases of heart failure in the population attributable to nonadherence to the low-risk lifestyle factor

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Appendix

Committee Question and Reply

Question 1. The predictive model was close validated. Predictive model should be established by training data and validation by validation data.

Reply:

We analysis again according to TwsHHH cohort diving to training data and validation data. For each cohort, randomly four fifth of the study participants to a derivation cohort, and the remaining one fifth of the participants were reserved as a validation cohort.

Appendix Table 1: The incidence cases, follow-up person-years, and the rates of cardiovascular disease events according to lifestyle factors among the derivation cohort and the hazard ratios and 95% confidence intervals

(Model 1: adjusted for age and sex; Model 2: Model 1 + education, average month income, marital status, parental history of CVD, menopause

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status and estrogen exposure; Model 3: Model 2 + baseline HTN, baseline DM, history of hyperlipidemia, sBP, dBP, triglyceride, non-HDL, fasting glucose, HbA1c; The population attributable risk is the percentage of new cases of heart failure in the population attributable to nonadherence to the low-risk lifestyle factor.)

(A) According to the body mass index in derivation cohort of TWsHHH study participants

BMI	≧ 40	<18.5			18.5~24.9			25~29.9			30~34.9			35~39.9			*P* of Logrank		
Cases	10	243			165			25			5			1					
Pearson-year	4639	47799			16740.8			2876			403			38.6					
Rates/1000 py	2.2	5.1			9.9			8.7			12.4			25.9			<.001		
	HR	HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI		*P* of Trend Test	PAF	95% CI
Univariate	1	0.02	0.003	0.19	0.07	0.01	0.49	0.15	0.02	1.06	0.12	0.02	0.90	0.19	0.02	1.66	<0.001		

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Model 1	1	0.02	0.002	0.18	0.04	0.01	0.28	0.06	0.01	0.46	0.07	0.01	0.53	0.18	0.02	1.63	<0.001			
Model 2	1	0.02	0.002	0.15	0.03	0.00	0.22	0.05	0.01	0.35	0.05	0.01	0.40	0.13	0.01	1.26	<0.001			
Model 3	1	0.02	0.002	0.20	0.03	0.003	0.20	0.04	0.01	0.29	0.03	0.004	0.27	0.05	0.004	0.58	0.002	12.73	4.45	20.29

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(B) According to the Mediterranean diet score in derivation cohort of TWsHHH study part

	0~3	4~5			6~7			8~11			*P* of Logrank			
Cases	145	209			133			33						
Pearson-year	13786	24958			23647			13246						
Rates/1000 py	10.52	8.37			5.62			2.49			<0.001			
	HR	HR	95% CI		HR	95% CI		HR	95% CI		*P* of Trend Test	PAF	95% CI	
Univariate	1	0.75	0.57	1.00	0.55	0.41	0.75	0.23	0.14	0.37	<0.001			
Model 1	1	0.85	0.64	1.13	0.79	0.58	1.08	0.46	0.28	0.77	0.017			
Model 2	1	0.87	0.65	1.16	0.84	0.61	1.16	0.51	0.30	0.84	0.07			
Model 3	1	0.91	0.66	1.26	0.91	0.64	1.29	0.46	0.25	0.84	0.16	14.77	-6.53	31.82

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(C) According to the time of physical activity in derivation cohort of TWsHHH study participants

Physical activity Mins/week	0	1~49		50~99		100~149		>= 150		*P* of Logrank		
Cases	234	17		24		30		215				
Pearson-year	36254	5690		7170		5130		21393.1				
Rates/1000 py	6.45	3		3.35		5.85		10.1		<.001		
	HR	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	*P* of Trend Test	PAF	95% CI
Univariate	1	0.40	0.20 0.78	0.59	0.36 0.98	0.77	0.46 1.28	1.50	1.17 1.92	<.001		
Model 1	1	0.56	0.29 1.10	0.85	0.51 1.41	0.80	0.48 1.34	1.07	0.84 1.38	0.69		
Model 2	1	0.60	0.31 1.18	0.91	0.55 1.50	0.89	0.53 1.49	1.16	0.90 1.49	0.34		
Model 3	1	0.50	0.23 1.07	0.89	0.50 1.59	0.91	0.52 1.59	1.10	0.83 1.47	0.35	-0.15	-0.54 0.24

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(D) According to the smoking status in derivation cohort of TWsHHH study participants

Divided groups	0	1st group			2nd group			3rd group			4th group			*P* of Logrank			
Cases	120	19			2			43			336						
Pearson-year	8998	9299.4			260.7			2397			54600.5						
Rates/1000 py	13.34	2			7.67			17.9			6.15			<.001			
	HR	HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI		*P* of Trend Test	PAF	95% CI	
Univariate	1	0.18	0.10	0.32	0.49	0.07	3.51	1.30	0.79	2.15	0.51	0.38	0.67	0.023			
Model 1	1	1.13	0.61	2.12	0.98	0.14	7.04	1.10	0.67	1.83	1.22	0.89	1.66	0.83			
Model 2	1	1.13	0.60	2.13	1.20	0.17	8.70	1.22	0.74	2.03	1.30	0.95	1.78	0.47			
Model 3	1	1.29	0.65	2.56	1.75	0.24	12.79	1.15	0.65	2.02	1.15	0.81	1.64	0.88	-0.57	-8.75	6.99

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Note: 0 group: current smoking >=20 years; 1st group: current smoking < 20 years; 2ne group: quit smoking < 1 year; 3rd group: quit smoking >= 1 year; 4th group: never or smoking less than 100 cigarettes

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(E) According to the frequency of alcohol consumption in derivation cohort of TWsHHH study participants

	Never	Few			Frequency			*P* of Logrank			
Cases	403	92			25						
Pearson-year	54756	17146.2			3734						
Rates/1000 py	7.36	5.37			6.69			0.022			
	HR	HR	95% CI		HR	95% CI		*P* of Trend Test	PAF	95% CI	
Univariate	1	0.88	0.67	1.17	0.79	0.44	1.41	0.027			
Model 1	1	0.79	0.59	1.06	0.48	0.27	0.87	0.002			
Model 2	1	0.79	0.59	1.06	0.48	0.27	0.87	0.002			
Model 3	1	0.81	0.59	1.12	0.28	0.12	0.64	0.001	48.61	24.52	65.01

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Appendix Table 2: The incidence cases, follow-up person-years, and the rates of cardiovascular disease events according to lifestyle factors and the hazard ratios and 95% confidence intervals

(Model 1: adjusted for age and sex; Model 2: Model 1 + education, average month income, marital status, parental history of CVD, menopause status and estrogen exposure; Model 3: Model 2 + baseline HTN, baseline DM, history of hyperlipidemia, sBP, dBP, triglyceride, non-HDL, fasting glucose, HbA1c; The population attributable risk is the percentage of new cases of heart failure in the population attributable to nonadherence to the low-risk lifestyle factor.)

(A) The simple Taiwan healthy lifestyle score, according to the numbers of the score

	O~1	2	3	4~5	*P* of Logrank
Cases	193	228	87	12	

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Pearson-year	15840	30092			23460			6164						
Rates/1000 py	12.18	7.6			3.71			1.95			< 0.001			
	HR	HR	95% CI		HR	95% CI		HR	95% CI		*P* of Trend Test	PAF	95% CI	
Univariate	1	0.58	0.45	0.75	0.28	0.20	0.39	0.15	0.07	0.32	<0.001			
Model 1	1	0.76	0.58	0.98	0.52	0.37	0.72	0.40	0.18	0.86	<0.001			
Model 2	1	0.79	0.61	1.03	0.57	0.40	0.80	0.45	0.21	0.97	<0.001			
Model 3	1	0.80	0.60	1.06	0.55	0.38	0.82	0.42	0.17	1.05	0.004	35.87	11.97	53.28

doi:10.6342/NTU202002676

(B) The weighted Taiwan healthy lifestyle score, according to the score quartiles

	0~4	5			6~7			8~17			*P* of Logrank			
Cases	312	89			82			37						
Pearson-year	31049	12214			20456			11836						
Rates/1000 py	10.05	7.29			4.01			3.13			<0.001			
	HR	HR	95% CI		HR	95% CI		HR	95% CI		*P* of Trend Test	PAF	95% CI	
Univariate	1	0.77	0.57	1.04	0.37	0.27	0.52	0.29	0.19	0.46	<0.001			
Model 1	1	0.87	0.64	1.18	0.64	0.46	0.89	0.45	0.28	0.70	<0.001			
Model 2	1	0.91	0.67	1.24	0.70	0.50	0.98	0.47	0.30	0.74	<0.001			
Model 3	1	0.95	0.68	1.32	0.70	0.49	1.02	0.35	0.20	0.62	<0.001	35.7	16.75	50.4

doi:10.6342/NTU202002676

(C) The WCRF/AICR recommended healthy lifestyle score, according to the numbers of the score

	<3	3~ <4			4~ <5			5~7			*P* of Logrank			
Cases	55	94			193			178						
Pearson-year	14391	19564			24508			17174						
Rates/1000 py	3.82	4.8			7.87			10.36			<0.001			
	HR	HR	95% CI		HR	95% CI		HR	95% CI		*P* of Trend Test	PAF	95% CI	
Univariate	1	1.11	0.74	1.69	1.85	1.27	2.68	2.28	1.55	3.34	<0.001			
Model 1	1	0.93	0.61	1.40	0.80	0.55	1.17	0.81	0.54	1.20	0.1			
Model 2	1	0.86	0.57	1.31	0.74	0.50	1.09	0.77	0.51	1.14	0.09			
Model 3	1	1.10	0.58	2.08	1.06	0.57	1.98	1.16	0.61	2.18	0.98	0.10	-13.5	12.08

doi:10.6342/NTU202002676

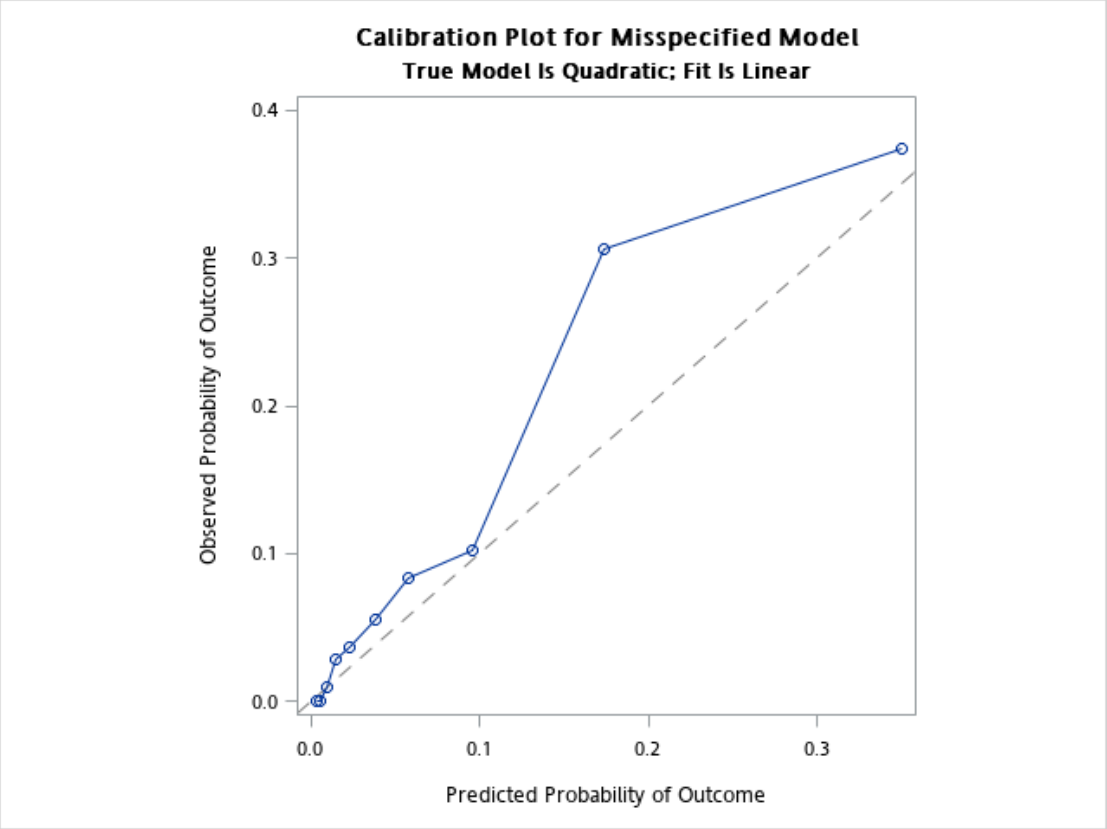
(D) Life's Simple 7, according to the numbers of score (0~14 points)

	0~6	7~9			10~12			13~14			*P* of Logrank			
Cases	36	194			255			35						
Pearson-year	1802	16826			42852			14157						
Rates/1000 py	20	11.5			6			2.47			<0.001			
	HR	HR	95% CI		HR	95% CI		HR	95% CI		*P* of Trend Test	PAF	95% CI	
Univariate	1	0.49	0.31	0.80	0.31	0.19	0.49	0.13	0.07	0.24	<0.001			
Model 1	1	0.42	0.26	0.67	0.30	0.19	0.48	0.17	0.09	0.31	<0.001			
Model 2	1	0.46	0.28	0.74	0.34	0.21	0.54	0.21	0.11	0.39	<0.001			
Model 3	1	0.71	0.41	1.23	0.74	0.40	1.34	0.49	0.21	1.14	0.018	29.23	5.32	47.1

doi:10.6342/NTU202002676

Appendix Figure 1: Validation our predictive model according to validation cohort. Calibration plot of predicted mean 12.5.following-up years cardiovascular disease (CVD) risk within deciles against the observed 12.5 following-up years CVD risk in the TWsHHH data (N=6048). Data are plotted among participants stratified by lifestyle scores

(E) Simple Taiwan healthy lifestyle score



(F) Of weighted Taiwan Healthy lifestyle score

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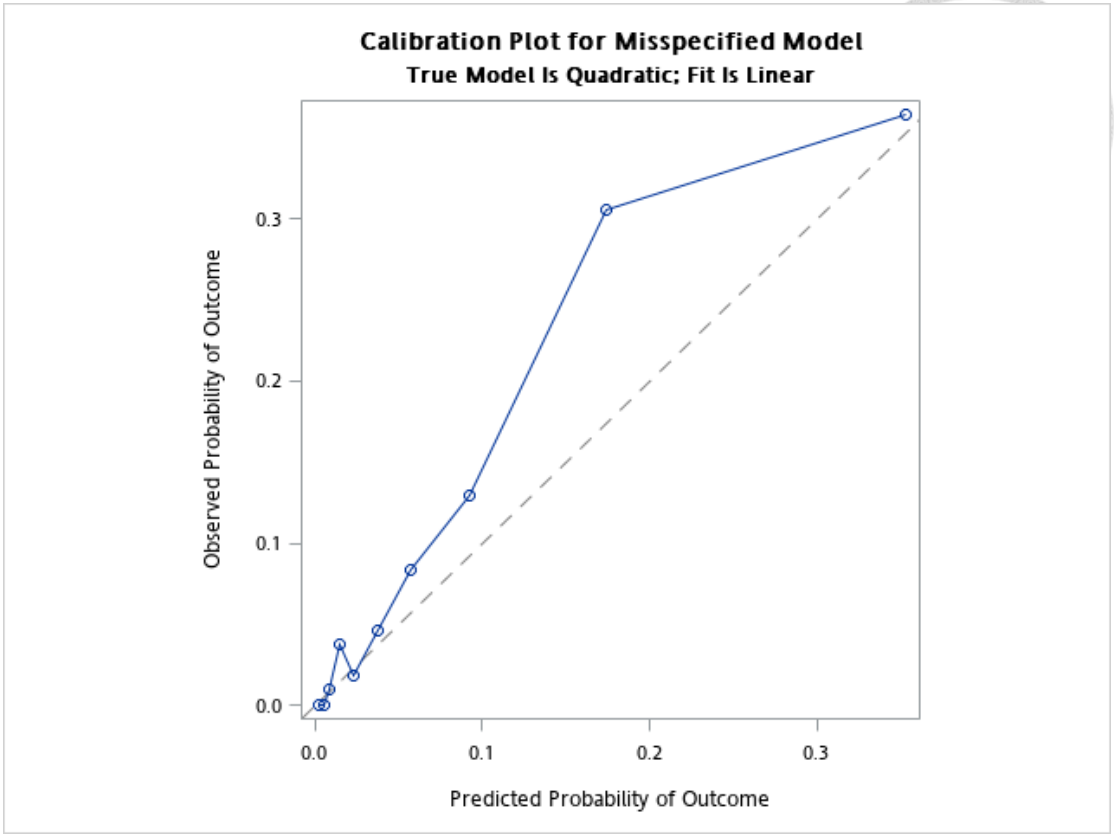
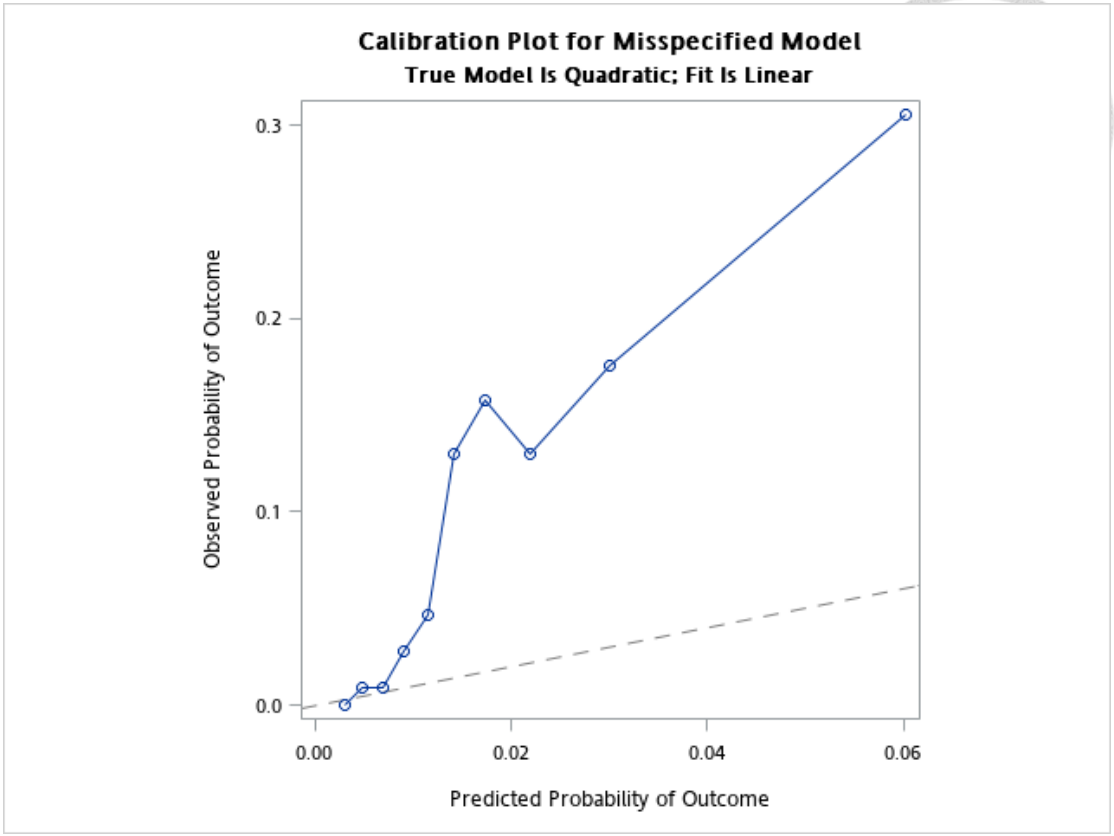
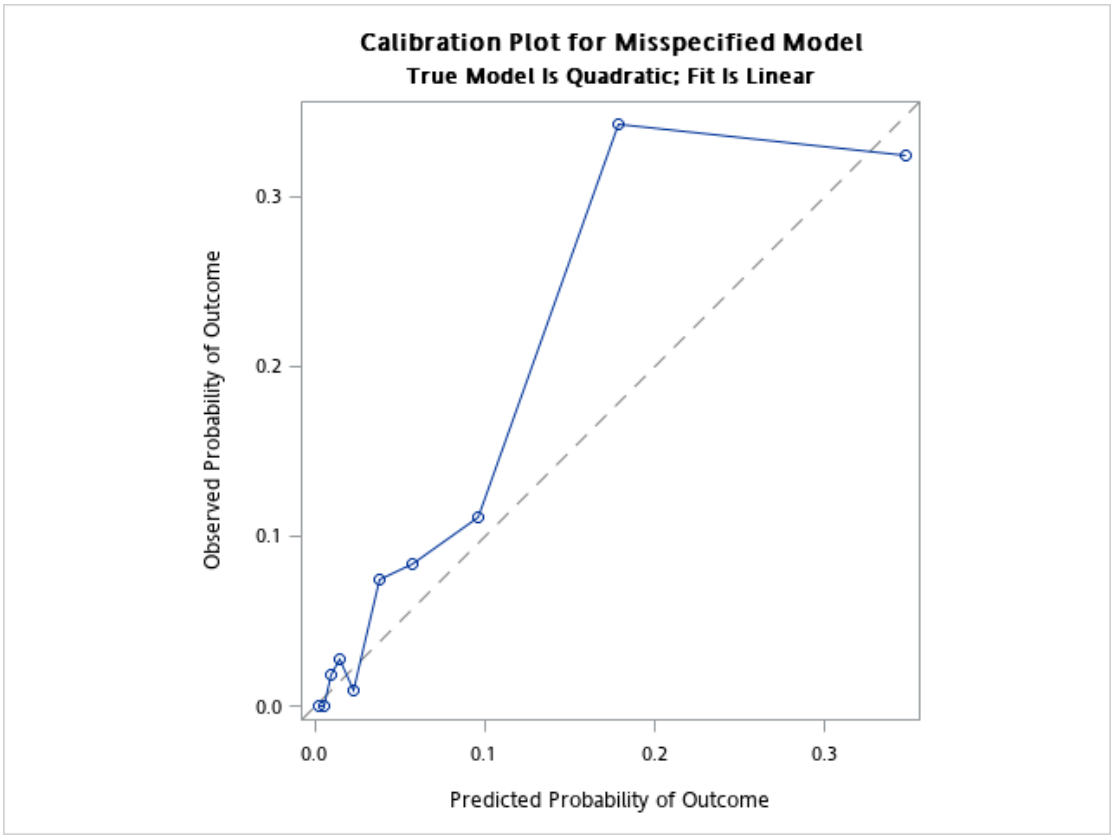


(G) Of WCRF/AICR recommended healthy lifestyle score

doi:10.6342/NTU202002676

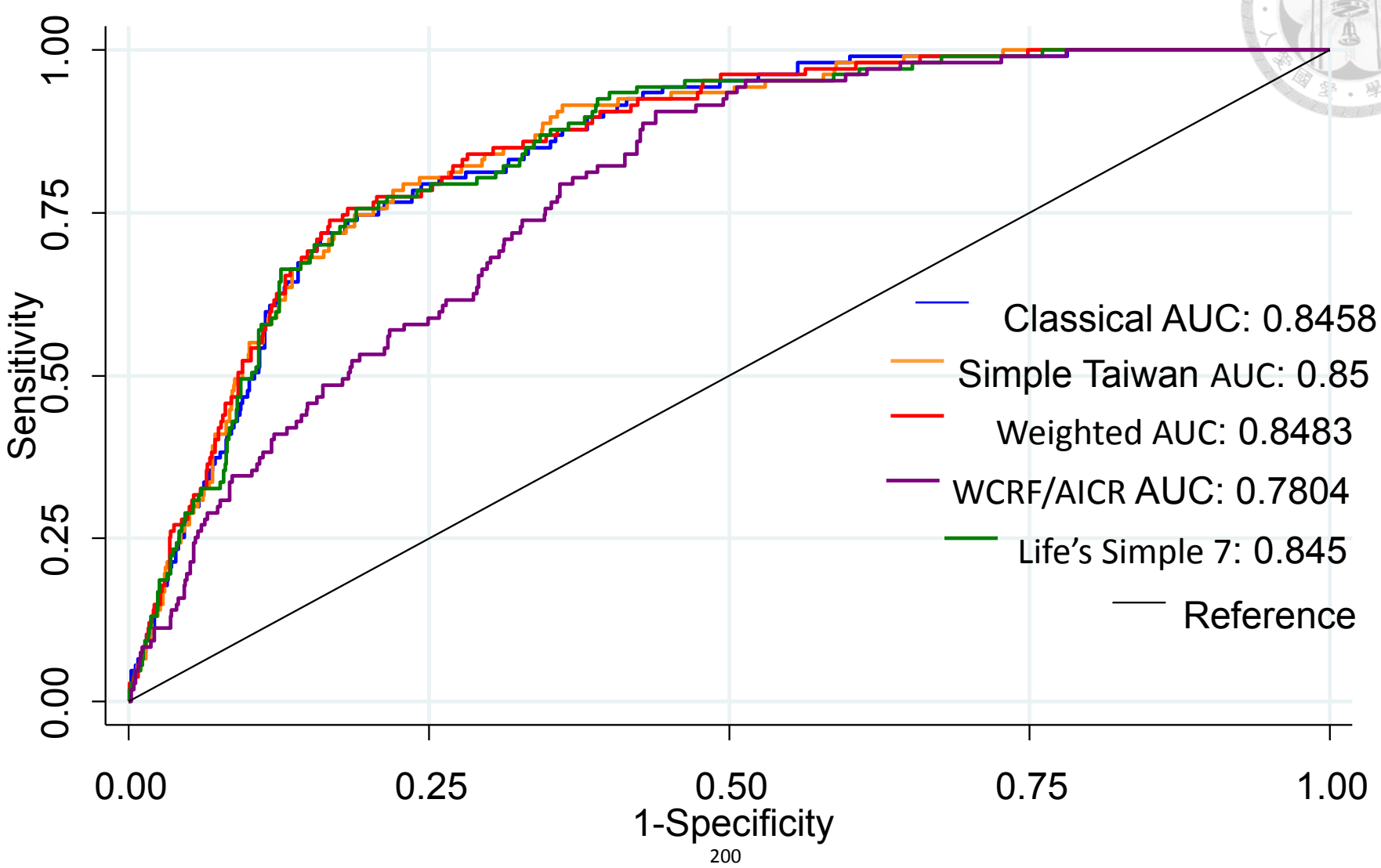


(H) Of Life's Simple 7

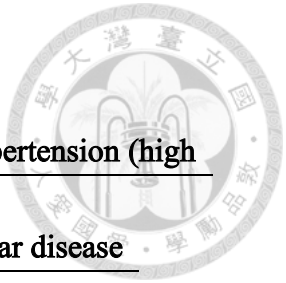


doi:10.6342/NTU202002676

Figure 6 : Receiver-operating characteristic curves for various models applied to the validation cohort



doi:10.6342/NTU202002676



Question 2:

The definition of CVD from World health organization includes hypertension (high blood pressure), coronary heart disease (heart attack), cerebrovascular disease (stroke), peripheral vascular disease, heart failure, rheumatic heart disease, congenital heart disease and cardiomyopathies. Why did the endpoint of study include coronary heart disease (heart attack) and cerebrovascular disease (stroke) only?

Reply:

Thanks for expertise suggestion. Our study focused on the atherosclerosis cardiovascular disease but excluded peripheral artery disease due to high disease burden focusing on coronary heart disease (heart attack) and cerebrovascular disease (stroke). We sill revised our manuscripts.

Question 3:

The simple Taiwan health lifestyle score was really simple and individuals could be self-evaluated the risk of CVD at home without any medical support. How do your further explore the strength of your study?

Reply:

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Thanks for expertise suggestion. We revised our manuscript in application like below: Clinical implications includes identification of unhealthy lifestyle factors among young and middle-age adult and aggressively healthy lifestyle intervention which is crucial for improving population cardiovascular health. Additionally, among population with low short-term risk, healthy lifestyle scores in the absence of clinical risk factors provided additionly important information about long-term CVD risk and overall CVD burden independently. Further, simple Taiwan healthy lifestyle as well as weighted form was an useful tool applicated in community-based, primary healthy service even individuals at home without the clinical setting and may broad public heatlh screening, motivat audience who may be lack of available laboratory-based measures or implicated in healthy education and healthy policy to develop different strategy separately for the primordial and primary prevention of CVD.

Question 4: Why WCRF/ACIR healthy lifestyle score could significantly predictive the incidence of cancer but no-significantly predictive the incidence of CVD?

Reply:

Thanks for expertise suggestion. We added further explain in our draft like below: Compared with different healthy lifestyle scores, Taiwan lifestyle score might be

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more suitable for primodrial prevention among population without no clinical risk factors. The different CVD risk performance might explained by the different definition of healthy diet, physical activity and lack of alcohol or smoking component. Mediterranean diet used by Taiwan lifestyle score was defined fish as an optimal food for CVD protection but limited egg and dairy diet in daily intake. Taiwan lifestyle scores defined regular adequate alcohol consumption as optimal lifestyle. However, WCRF/AICR lifestyle score considered non-alochol as an ideal lifestyle and Life's Simple 7 didn't consider the amount of alcohol consumption into score. Additionaly, the status of non- or quit from smoking were suggested in Taiwan healthy lifestyle score and Life's Simple 7 but not calculated in WCRF/AICR lifestyle score.

Question 5: The blood pressure, glucose and lipid was managed as confounding factor, but why not considered as mediation factors?

Reply:

Thanks for expertise suggestion. The limitation of our study was not analyzed the factor of biomarker by mediation analysis but used COX regression to adjusted. The mediation analysis should be first considered in our next evaluation the association between healthy lifestyle scores and cardiovascular disease.

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Question 6: The four healthy lifestyle score were all divided into 4 group. However, different cut-point and numbers in the fourth group among 4 healthy lifestyle scores. How do you assure that the comparison of hazard ratio was robust when the different numbers of each group among 4 healthy lifestyle scores .

Reply:

Thanks for expertise suggestion. We further used kappa analysis to evaluation the association among 4 healthy lifestyle scores.

Appendix Table 3. Agreement among 4 healthy lifestyle scores for the 4 group categories.

Kappa/ *p* value	Simple Taiwan	Weighted Taiwan	WCRF/AICR	Life's Simple 7
Simple Taiwan		0.60 / < 0.001	-0.047 / 1	0.07 / <0.001
Weighted Taiwan			-0.05 / 1	0.06 / <0.001
WCRF/AICR				0.07 / < 0.001

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Appendix Table 4: Agreement among f healthy lifestyle scores for the 4 group categories.

	Kappa	P value
4 healthy lifestyle scores	0.1	< 0.001
3 healthy lifestyle scores without simple Taiwan	0.15	< 0.001
3 healthy lifestyle scores without weighted Taiwan	0.21	< 0.001
3 healthy lifestyle scores without WCRF/AICR	0.01	0.012
3 healthy lifestyle scores without Life's Simple 7	-0.006	0.91

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