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Cardiovascular health metrics and risk of cardiovascular events and all-cause mortality among the Finnish populace

CARDIOVASCULAR HEALTH METRICS AND RISK OF CARDIOVASCULAR EVENTS AND ALL-CAUSE MORTALITY AMONG THE FINNISH POPULACE

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Author's address: School of Medicine
University of Eastern Finland
KUOPIO
FINLAND

Doctoral programme: Doctoral programme of Clinical Research

Supervisors: Professor Jari A. Laukkanen, M.D., Ph.D.
Institute of Clinical Medicine
University of Eastern Finland
KUOPIO
FINLAND

Dr. Setor K. Kunutsor, M.D., Ph.D.
Translational Health Sciences
Bristol Medical School
University of Bristol
BRISTOL
UNITED KINGDOM

Reviewers: Professor Markus Juonala, M.D., Ph.D.
Department of Medicine
University of Turku
TURKU
FINLAND

Professor Isabela M. Bensenor, M.D., Ph.D.
Department of Internal Medicine
University of São Paulo
SÃO PAULO
BRAZIL

Opponent: Professor Veikko Salomaa, M.D., Ph.D.
National Institute for Health and Welfare (THL)
HELSINKI
FINLAND

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ABSTRACT

Cardiovascular disease (CVD) remains a leading cause of mortality worldwide, with its burden persisting despite the development of several preventive strategies. Thus, the American Heart Association (AHA) was prompted to use some CVD risk factors to develop cardiovascular health (CVH) metrics as a measure to assess the CVH status of the US population and mitigate CVD challenges. Evidence in some population groups reveal the cardiovascular benefits of the CVH metrics; however, studies on CVH metrics and its applicability among Northern European populations are limited. Therefore, prospective studies that combine risk factors to evaluate future risks of CVD events and all-cause mortality in the region warrant exploration.

The aim of this thesis was to characterize in detail the associations of CVH metrics, as defined by AHA, and the risks of cardiovascular outcomes and all-cause mortality among a general population in Finland. The specific objectives are to: 1) investigate the association of ideal CVH with acute myocardial infarction (AMI) risk (Study I); 2) assess the nature and magnitude of the association of CVH metrics with CVD mortality (Study II); 3) investigate the nature and magnitude of the association of CVH metrics with sudden cardiac death (SCD) and all-cause mortality (Study III);

and 4) examine the relationship of Life's Simple 7 (LS7) with the future risk of stroke (Study IV).

We used the prospective population-based Kuopio Ischaemic Heart Disease (KIHD) cohort study, which consists of randomly selected 2682 men from eastern Finland who were between 42 and 60 years of age at baseline (1984 – 1989). The CVH metrics was computed using seven risk factors including healthy diet score (HDS), blood pressure, physical activity, body mass index (BMI), smoking status, plasma total cholesterol, and fasting blood glucose. These seven factors are categorised into ideal, intermediate and poor. The seven ideal factors, dubbed the LS7, are:
a) An HDS of 4 -5 (i.e. four to five components of: at least 4.5 cups/day of fruits and vegetables; at least two 3.5-ounce servings/week of fish; ≤36 ounces/week of sweets/sugars; and at least three 1-ounce servings/day of wholegrains; ≤2 servings/week of processed meat);
b) physical activity of ≥150 minutes/week moderate intensity physical activity (MET 3–6) or ≥75 minutes/week of vigorous intensity aerobic physical activity (MET >6), or an equivalent combination;
c) smoking status of never smoked;
d) BMI <25 kg/m^2;
e) blood pressure <120/<80 mmHg;
f) fasting blood glucose <5.55 mmol/l; and
g) total cholesterol <5.18 mmol/l.

The composite CVH score or LS7 score ranged from 0 to 7 and was categorised as poor (0 – 2), intermediate (3-4) and ideal (5 – 7). In Study II, the composite score ranged from 0 to 14 and was classified as optimum (0 – 4), average (5 – 9), and inadequate (10 – 14). Lower values represented a better composite score. Multivariable Cox regression models were used to estimate the hazard ratios (HR) and 95% confidence intervals (CIs) of CVH metrics for all outcomes.

In Study I, men with ideal CVH metrics had a HR (95% CI) for AMI of 0.28 (CI 0.15–0.55, p < 0.001) compared to those with poor CVH metrics. A restricted cubic spline curve showed that the risk of AMI decreased continuously with increasing CVH metrics across the range 2–7 (*p*-value for nonlinearity=0.07). In Study II, men with optimum CVH score had a HR (95%

CI) for CVD mortality of 0.30 (CI 0.21 – 0.42, p < .0001) compared to those with inadequate CVH score. The risk of CVD mortality increased gradually with increasing CVH score across the range 3–14 (*p*-value for non-linearity =0.77). In Study III, men with an ideal CVH score had an 85% reduced risk of SCD compared with men with a poor CVH score (HR 0.15; 95% CI 0.05–0.48; *p* = 0.001). There was a 67% lower all-cause mortality risk among men with an ideal CVH score compared with those with a poor CVH score (HR 0.33; 95% CI 0.23–0.49; p <0.001). The risks of SCD and all-cause mortality decreased continuously with increasing number of CVH metrics across the range 2–7 (*p*-value for non-linearity for all >0.05). In Study IV, the risk of both stroke outcomes decreased continuously with increasing LS7 scores across the range 2 to 6. Men with optimal LS7 had 48% (HR: 0.52; 95%CI: 0.32–0.86) lower risk of total stroke when compared with those with inadequate LS7. The association was similar for the risk of ischaemic stroke, with 50% (HR: 0.50; 95%CI: 0.29–0.87) lower risk among men with an optimal LS7 compared with those with inadequate LS7.

In conclusion, ideal and optimum CVH and LS7 scores are associated with lower risks of CVD outcomes and all-cause mortality among middle-aged Finnish men. The dose-response relationships revealed that achieving more ideal CVH factors reduces the risk of AMI, CVD mortality, SCD, stroke and all-cause mortality in a graded manner. The CVH metrics may be a potential tool for CVD and stroke risk classification as well as monitoring and measuring progress for a healthier lifestyle.

Keywords: Cardiovascular Diseases/prevention & control; Cardiovascular Health Metrics; Male; Mortality; Risk Factors; Risk Assessment; Death, Sudden; Acute Coronary Syndrome; Myocardial Infarction; Stroke; Cohort Studies

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TIIVISTELMÄ

Sydän- ja verisuonisairaudet ovat maailmanlaajuisesti johtava kuolinsyy, ja sydän- ja verenkiertoelinten sairauksista johtuva terveydenhuollon kuormitus on edelleen suuri. Tehokkaan ennaltaehkäisyn tukena Yhdysvaltojen sydänyhdistys (American Heart Association, AHA) on suositellut useiden tärkeiden riskitekijöiden huomiointia sydän- ja verisuonisairauksien ennaltaehkäisyn edistämisessä. Aiemmat tutkimukset osoittavat kokonaisarvion hyödyt riskin arvioinnissa; mutta kyseisen AHA:n menetelmän soveltuvuus Pohjois-Eurooppalaisissa väestöissä vaatii kuitenkin tutkimuksia. Tarvitaankin kattavia prospektiivisia tutkimuksia, joissa huomioidaan useita riskitekijöitä samanaikaisesti, jotta voidaan arvioida mahdollisimman tarkasti sydän- ja verisuonitautitapahtumien vaaraa ja kuolleisuutta.

Tämän väitöskirjatutkimuksen tarkoituksena oli selvittää AHA:n sydänterveyden kokonaismittareiden yhteyttä sydän- ja verisuonitautien ja kuolleisuuden vaaraan Itä-suomalaisessa väestössä. Osatöiden tavoitteina oli: 1) tutkia ihanteellisen sydänterveyden yhteyttä akuutin sydäninfarktin vaaraan (tutkimus I); 2) arvioida sydänterveyden mittareiden ja sydän- ja verisuonitaudeista johtuvan kuolleisuuden välistä yhteyttä (tutkimus II); 3) tutkia sydänterveyden-mittareiden yhdistämisen vaikutusta äkillisen

sydänkuoleman vaaraan ja kokonaiskuolleisuuteen (tutkimus III); ja 4) edelleen selvittää 'Life's Simple 7 (LS7)'- mittarin yhteyttä aivohalvauksen vaaraan (tutkimus IV).

Tutkimus perustuu Kuopion alueelta koottuun sydän- ja verisuonisairauksien kohorttitutkimukseen, johon on otettu mukaan 2682 satunnaisesti valittua miestä. Miehet olivat lähtötilanteessa 42–60-vuotiaita (1984 -89). Sydänterveyden kokonaisarviointiin kuuluivat terveellisen ruokavalion pistemäärää, verenpaine, fyysinen aktiivisuus, kehon painoindeksi, tupakointi, kokonaiskolesterolia ja veren paastosokeri. Sydänterveyden mittareiden ja keskeisten päätetapahtumien välistä yhteyttä tutkittiin Cox-regressiomallien avulla.

Tutkimuksessa I sydäninfarktin vaara oli 0,28 (95 % luottamusväli 0,15 – 0,55, p <0,001) miehillä, joilla oli ihanteellinen sydänterveys verrattuna miehiin, joilla oli matalat sydänterveyden pisteet. Sydäninfarktin vaara väheni lineaarisesti, kun sydänterveyden pisteet nousivat. Tutkimuksessa II korkeimmat sydänterveyden pisteet omaavilla miehillä sydän- ja verisuonitautikuolleisuuden vaara oli pieni (riskisuhde 0,31; 95 % luottamusväli 0,21 - 0,42, p <0,0001) Tutkimuksessa III sydänperäisen äkkikuoleman vaara 85% pienempi ihanteellisen sydänterveyden omaavilla miehillä kun heitä verrattiin miehiin, joilla oli alhaiset sydänterveyden pisteet (riskisuhde 0,15; 95% luottamusväli 0,05 – 0,48; p = 0,001). Ihanteellinen sydänterveys oli yhteydessä 67 % (riskisuhde 0,33; 95% luottamusväli 0,23 – 0,49; p <0,001) pienempään kokonaiskuolleisuuteen.

Tutkimuksessa IV aivohalvauksen vaara väheni LS7 -pisteiden kasvaessa kahdesta kuuteen. Miehillä joilla oli optimaalinen LS7, aivohalvauksen riski oli 48% (riskisuhde 0,52; 95% luottamusväli 0,32-0,86) pienempi verrattuna niihin, joiden LS7 on matalin. Yhteys oli samanlainen iskeemisen aivohalvauksen osalta: 50% (riskisuhde 0,50; 95% luottamusväli 0,29 – 0,87) pienempi riski miehillä, joilla oli korkea LS7, verrattuna niihin, joilla oli matala LS7 pistemäärä.

Yhteenvetona voidaan todeta, että ihanteellinen sydänterveys ja optimaaliset AHA LS7 -pisteet liittyvät keski-ikäisten miesten pienempään

sydän- ja verisuonitautien vaaraan ja kuolleisuuteen. Annos-vastesuhteet osoittivat, että rikistekijöiden avulla arvioitu ihanteellinen sydänterveys on vahvasti yhteydessä pienempään sydäninfarktin, sydän- ja verisuonitautikuolleisuuden, äkkikuoleman, aivohalvauksen ja kokonaiskuolleisuuden vaaraa. Sydänterveyden kokonaisarvion mittarit ovat käyttökelpoinen menetelmä sydän- ja verisuonitautien ja aivohalvauksen vaaran arviointiin sekä terveellisempien elämäntapojen edistämiseen.

Avainsanat: Sydän- ja verisuonitaudit; ennaltaehkäisy; ihanteellisen sydänterveyden; miehet; mittaus; riskitekijät; riskinarviointi; aivohalvaus; kuolleisuus; sydäninfarkti; äkkikuolema; kohorttitutkimus

"Above all else, guard your heart,
for everything you do flows from it."

Proverbs 4:23 (NIV)

DEDICATION

In loving memory of my Dad

To my lovely Mum

And to all who may be at risk of cardiovascular disease

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Kuopio, December 2021
Isiozor, Nzechukwu Michael

LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications:

I. **Isiozor N M**, Kunutsor S K, Voutilainen A, Kurl S, Kauhanen J and Laukkanen J A. Ideal cardiovascular health and risk of acute myocardial infarction among Finnish men. Atherosclerosis 289: 126–131, 2019.

II. **Isiozor N M**, Kunutsor S K, Voutilainen A, Kurl S, Kauhanen J and Laukkanen J A. American heart association's cardiovascular health metrics and risk of cardiovascular disease mortality among a middle-aged male Scandinavian population. Annals of Medicine 51(5-6): 306-313, 2019.

III. **Isiozor N M**, Kunutsor S K, Voutilainen A, Kurl S, Kauhanen J and Laukkanen J A. Association between ideal cardiovascular health and risk of sudden cardiac death and all-cause mortality among middle-aged men in Finland. European Journal of Preventive Cardiology 28(3): 294-300, 2021. DOI: 10.1177/2047487320915338

IV. **Isiozor N M**, Kunutsor S K, Voutilainen A, Kauhanen J and Laukkanen J A. Life's simple 7 and the risk of stroke in Finnish men: A Prospective Cohort Study. Preventive Medicine 153: 106858, 2021. DOI:https://doi.org/10.1016/j.ypmed.2021.106858

CONTENTS

ABBREVIATIONS

AHA	American Heart Association
AMI	Acute myocardial infarction
Apo-A	Apolipoprotein-A
Apo-B	Apolipoprotein-B
ARIC	Atherosclerosis Risk in Communities
ASCVD	Atherosclerotic cardiovascular disease
BMI	Body mass index
BP	Blood pressure
CAD	Coronary artery disease
CCR	C-C chemokine receptor
CHD	Coronary heart disease
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
CVH	Cardiovascular health metrics
eNOS	Endothelial nitric oxide synthase
HDL-c	High-density lipoprotein cholesterol
HDS	Healthy diet score
ICD	International Classification of Diseases
KIHD	Kuopio Ischaemic Heart Disease
LDL(-c)	Low density lipoprotein (cholesterol)
LMIC	Low- and middle-income countries
LS7	Life's Simple 7
MCP-1	Monocyte Chemoattractant Protein-1
NCD	Noncommunicable disease

NHANES	National Health and Nutrition Examination Survey
NO	Nitric Oxide
PA	Physical activity
PAD	Peripheral arterial disease
ROS	Reactive oxygen species
SBP	Systolic blood pressure
SCD	Sudden cardiac death
SDG	Sustainable development goal
SES	Socioeconomic status
SOD	Superoxide dismutase
Th-1	T helper 1 cells
T-reg	Regulatory T cells
UN	United Nations
US	United States (of America)
VLDL	Very low-density lipoprotein
WHO	World Health Organization

1 INTRODUCTION

Cardiovascular diseases (CVDs) involve a group of disorders affecting the heart and blood vessels. These include for example coronary heart disease (CHD), cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary embolism (World Health Organization, 2017). Atherosclerotic CVDs constitute majority of the CVDs. Globally, CVD is among the leading causes of mortality, accounting for over 17 million deaths annually (World Health Organization, 2017). Although several efforts have been made to reduce the associated burden of CVDs over the years, the challenges persist.

The United States (US) is facing significant challenges from CVDs. Thus, the American Heart Association (AHA) developed a metric to tackle the burden of CVD among the US population while improving their cardiovascular health (CVH) status. The AHA's CVH metrics was based on four health behaviours (smoking, body mass index (BMI), physical activity and diet) and three health factors (blood pressure (BP), fasting blood glucose and total cholesterol levels) (Lloyd-Jones, Donald M. et al., 2010). These seven factors were categorised into ideal, intermediate and poor. At ideal levels of these factors, healthier lifestyles can be achieved leading to the possibility of living free of CVD and stroke.

Despite the evidence of research on the benefits of ideal CVH and some cardiovascular outcomes in other countries (Han et al., 2018, Lachman et al., 2016, Ommerborn et al., 2016, Fang, Jiang & Fan, 2016, Dong, Y. et al., 2019, Gaye, Canonico et al., 2017), there are limited studies on the applicability and relationship of AHA's CVH metrics and risks of different cardiovascular events in Northern Europe. Cardiovascular disease is a major health concern in Finland, accounting for approximately 36% of all deaths across ages and sex (World Health Organization, 2018). The decline in CVD mortality in Finland, from 40% in 2014 to 36% in 2018, could be attributed to various efforts made over the years to curtail the menace. Despite the decline, there are still challenges. Men are at higher risk of CVD

and premature death in Finland, and the additional economic burden associated with the middle-aged men, which is attributable to CVDs makes it imperative for a CVD preventive approach to be embraced. The assessment of AHA's CVH among the Finnish population is still limited, particularly among the middle-aged populace. Since the middle-aged group make a significant proportion of the working population of the country, their quality of life needs to be improved with an effective intervention towards CVD prevention for both economic and health benefits in Finland. Thus, following a middle-aged cohort for years can reveal the impact modifiable lifestyle factors can have on future risk of CVD. Possibly, the AHA's CVH metrics can be considered as a health promotion tool for CVD prevention among the middle-aged Finnish population. However, limited evidence is available on the association between AHA's CVH metrics and the risk of CVD mortality, acute myocardial infarction (AMI), sudden cardiac death (SCD) and stroke among the aging Finnish population. Therefore, a detailed assessment, distribution, and applicability of CVH metrics and the risk of CVDs among a northern European population is a major step towards reducing the associated CVD burden in the region, and globally.

2 REVIEW OF THE LITERATURE

2.1 CARDIOVASCULAR DISEASE

Cardiovascular diseases can refer to many disease conditions affecting the heart and blood vessels. These include:

- coronary heart disease- affects the blood vessels for the myocardium
- cerebrovascular disease- affects the blood vessels for the brain
- peripheral arterial disease (PAD)- affects blood vessels for the arms and legs
- rheumatic heart disease- affects the myocardium and heart valves resulting from rheumatic fever
- congenital heart disease- heart structure malformations present at birth
- deep vein thrombosis and pulmonary embolism- heart and lungs disorder from dislodged thrombus from the leg veins (World Health Organization, 2017).

Most of the CVD deaths are caused by CHD and strokes (World Health Organization, 2017), and atherosclerosis plays an underlying role in their pathogenesis.

2.1.1 Burden of cardiovascular disease

Coronary heart disease is the major manifestation of CVD. Mortality from CVD has been on the rise globally, from 12.6 million deaths in 1990 to 17.8 million in 2017 (Roth et al., 2017, Roth et al., 2018), and the figure is expected to increase to 24 million by 2030 if no adequate preventative measures are adopted. In Western Europe, it was estimated that about 1.5 million deaths were caused by CVD in 2015 despite the decline in CVD prevalence during the last decades in the region (Roth et al., 2017), age-standardized prevalence of 7.82% and 6.76% in 1990 and 2017, respectively. An approximately 10% decline in CVD deaths was observed in Western Europe across all ages from 42.98% in 1990 to 32.58% in 2017

(Table 1; Figure 1). In low- and middle-income countries (LMIC), the rates of CVD mortality are increasing with about 300 to 600 deaths per 100,000 population linked to CVD. This may be attributed to socioeconomic and modifiable traditional risk factors (Cappuccio, Miller, 2016). For example, the highest prevalence of hypertension is seen in Africa at 46% in adults above 25 years (Seedat, 2004); and this is expected to increase in the future (Cappuccio, Miller, 2016).

Burden of CVD in Finland

In Finland, the rise in CHD mortality began in the 1950s to become the highest in the world by late 1960s. It was linked to the improving standard of living, dietary and lifestyle changes in the country. The high mortality was more among working class middle-aged men, about 700 per 100 000, in the eastern part of Finland (Jousilahti, Laatikainen et al., 2016a, Puska, Jaini, 2020), thus, leading to the development of the North Karelia Project in the early 70s (Vartiainen, 2018). Currently, according to the Global Burden of Disease, the age-standardized prevalence of CVD has decreased from 7.74% in 1990 to 6.79% in 2017. Furthermore, CVD deaths which accounts for 38% of all mortality across all ages and sex in the country has also been on the decline in the past three decades - from 48.03% in 1990 to 38.79% in 2017 (Institute for Health Metrics and Evaluation, 2020).

The overall decline in CVD prevalence could be because of interventions made to reduce the burden of noncommunicable diseases (NCDs), particularly those focusing on CVDs, over the years in different countries. For example, the North Karelia Project in Finland aimed to prevent CVD by improving healthy lifestyles in the 70s (Vartiainen, 2018, Jousilahti, Laatikainen et al., 2016b). The emerging increase in some crucial CVD risk factors, such as obesity and type 2 diabetes will pose a huge challenge in tackling CHD-related mortality in the future if no proper interventional measures are taken. The WHO, however, continues to contribute its quota to reducing CVD prevalence and has not relented in its efforts to curb the present challenges of CVD. Thus, CVD is included in the WHO's 25x25 Global Action Plan aimed to reduce NCD-related premature deaths by 25% by 2025 (World Health Organization, 2013). Additionally, the

United Nations (UN) through its sustainable development goal 3 (SDG 3) has recognized the need to reduce premature deaths from NCDs, including CVD, by 2030 (United Nations, 2015). These show the prospective global focus on reducing CVD burden even beyond this decade.

Table 1. Prevalence of cardiovascular disease in general population. (Institute for Health Metrics and Evaluation, 2020)

Year	Age-standardized prevalence (% of total prevalent cases) of CVD both Male/Female			
	Global	Western Europe[a]	Nordic Region[b]	Finland
1990	6.50	7.82	7.86	7.74
1995	6.40	7.39	7.66	7.32
2000	6.34	7.15	7.40	7.23
2005	6.30	6.96	7.22	7.15
2010	6.29	6.87	7.04	7.04
2015	6.31	6.79	6.89	6.88
2017	6.32	6.76	6.83	6.79

[a] 'Western European countries' are Finland, Austria, Belgium, Denmark, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, The Netherlands, Norway, Portugal, Spain, Sweden, Switzerland and the United Kingdom.

[b] Nordic region consists of Finland, Denmark, Iceland, Norway, and Sweden, and three smaller autonomous areas of two of the countries: Greenland and Faroe Islands (Denmark), and Åland Islands (Finland).

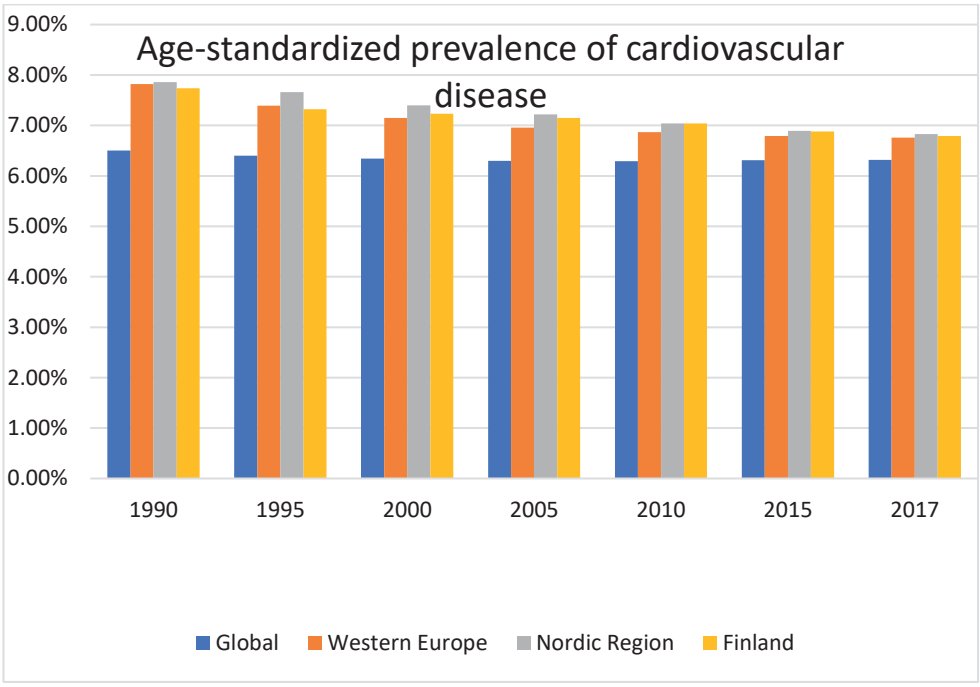

Figure 1. Prevalence of cardiovascular disease in general population (Institute for Health Metrics and Evaluation, 2020)

2.1.2 Aetiology of cardiovascular disease

Cardiovascular diseases are most often caused by atherosclerosis of the blood vessels. Atherosclerosis, a chronic vascular disease which is also related to ageing, contributes largely to vascular pathologies. It usually starts with fatty streaks in the arterial walls that slowly progress to atheroma and plaques (Kumar, Clark, 2009, Kasper et al., 2015). The vascular changes are similar in the aorta, coronary and carotid arteries. Individual variations can occur as the process of lipid accumulation and inflammation continues. Early fatty streak can commence development as early as in childhood or adolescence to form foam cells. Fibroatheroma starts at about 15 to 30 years when there is accumulation of many macrophage foam cells and activated inflammatory cells. At the age of 55 and above, advancing atheroma ensues, and the thin-cap fibroatheroma developed may rupture (Insull, 2009). Inflammation may play a role in the endothelial desquamation by causing endothelial cell death through local inflammatory mediators or cytolytic action of activated killer T cells (Libby,

2002). Following an abrupt rupture of these atheromatous plaques, thrombosis can ensue leading to an occlusion of an affected artery. The resultant clinical manifestation of this effect, which could take years, is dependent on the degree and suddenness of the occlusion as well as the circulatory bed affected. The most common circulations affected are that of the heart causing ischaemic heart disease and the central nervous system leading to ischaemic stroke. Atherosclerosis can also manifest as PAD affecting the arteries of the lower extremity to cause gangrene and intermittent claudication; the kidneys causing renal artery stenosis; and the splanchnic circulation causing mesenteric ischaemia (Kumar, Clark, 2009, Kasper et al., 2015).

People with CVD usually have an array of presentations and the degree of severity varies among individuals. The clinical presentation can be chronic, as seen in demand-induced angina pectoris; or acute, seen in stroke and SCD where it can be the first manifestation of an atherosclerosis. The common cardiac symptoms are chest pain, difficulty in breathing/dyspnoea, fatigue, syncope, palpitations and peripheral oedema (Kumar, Clark, 2009, Kasper et al., 2015). There are persons, however, that will remain asymptomatic, and the degree of atherosclerosis is only recognized post-mortem. In some asymptomatic patients, high blood pressure, cardiac murmurs or an unusual finding on electrocardiography or imaging investigation abnormality can be the first indication of a heart disease.

It is therefore necessary to use a wholistic approach while assessing individuals at risk of CVD. This can initiate further investigations and the commencement of preventive measures to reduce the associated mortality and morbidity of CVD. For instance, SCD and stroke which can be fatal, may be the first clinical manifestation in a previously asymptomatic patient.

2.2 RISK FACTORS FOR CARDIOVASCULAR DISEASES

Risk factors for atherosclerosis, and apparently atherosclerotic CVD (the major focus in this research), derive their evidence-base from a variety of studies ranging from experimental to observational studies. These risk

factors can be grouped into two: modifiable and non-modifiable risk factors. The modifiable being those factors which can be altered by appropriate lifestyles and/or medications, while the non-modifiable factors ideally cannot be changed, for example, age and sex (Kasper et al., 2015). Another group, the non-traditional risk factors, have been considered, but their impact on CVD risk remains debatable, e.g., homocysteine, lipoprotein(a) and infection. The roles of genetics, psychological and environmental factors in CVD events have also been reported (Allen, 2000, Cohen, B. E., Edmondson & Kronish, 2015, Cosselman, Navas-Acien & Kaufman, 2015).

However, from the WHO perspective, some risk factors for CVD can be classified into behavioural factors (tobacco use, an unhealthy diet, harmful alcohol use and inadequate physical activity) and physiological factors (high blood pressure (hypertension), high blood cholesterol, and elevated blood glucose levels). These factors are associated with some social determinants as well as drivers, for example, income, ageing, and urbanization (World Health Organization, 2020a).

This research will be focusing on the modifiable risk factors; and those to be discussed include blood pressure, smoking status, cholesterol level, diet and alcohol use, obesity, diabetes mellitus and physical activity. Supporting studies shall be highlighted as well as underlying possible mechanisms in the development of atherosclerosis or CVD events.

Hypertension: Mean arterial blood pressure is the product of cardiac output and total peripheral vascular resistance (Foëx, Sear, 2004). Persistent elevation in blood pressure results in hypertension- a systolic BP ≥140mmHg and/or diastolic BP ≥90mmHg according to the WHO (World Health Organization, 2019b) and the European Guidelines (Williams et al., 2018); and by the American Guidelines (Whelton et al., 2018), systolic BP >130mmHg or diastolic BP >80mmHg (de la Sierra, 2019). So basically, hypertension results from an increase in cardiac output or peripheral resistance or both. Whereas elevated cardiac output plays a major role in hypertension among the younger age groups, increased vascular resistance is mostly linked to the elderly. The vascular changes could be as a result of increased stimulation of the alpha- adrenoceptors or release of

angiotensin or endothelins (Foëx, Sear, 2004). The prevalence of hypertension among European countries varies between 30 to 45% in the general population and increases with ageing (Pereira et al., 2009). The established link between hypertension and CVD has been reported in numerous studies from mid 1920s till present (Joint Committee on Mortality of the Association of Life Insurance Medical Directors and the Actuarial Society of America., 1925). Some of them have aggregated large cohort studies to further support the association, such as with the overview of 9 large prospective cohort studies in 1990 involving 420,000 participants (MacMahon et al., 1990), and a 2002 meta-analysis from the Prospective Collaboration, involving 1 million participants from 61 studies, which reported that an average increase of systolic BP and diastolic BP by 20mmHg and 10mmHg respectively was associated with an increased risk of vascular disease (Lewington et al., 2002). The systolic BP is considered a stronger predictor of CVDs than the diastolic BP for people above 50 years of age, however, the pulse pressure provides more information on prognosis among the elderly (Kjeldsen, 2018).

Smoking: In 2016, over 6 million deaths were attributed to smoking, which is also a major risk factor for CVDs (Drope et al., 2018). Worldwide, approximately 1 billion adults smoke, accounting for a global prevalence of 21% with the WHO European region having the highest prevalence (>28%) of tobacco smoking among adults (World Health Organization, 2020c, Drope et al., 2018). To reduce premature mortality, tobacco control was targeted by the World Health Assembly as an entry point towards the reduction of premature deaths from NCDs by 2025 (World Health Organization, 2019a, World Health Organization, 2020). The rate of people that smoke across Europe vary across countries, with Finland having 20% of the population as current smokers (TNS, European Commission, 2017), below the 51% prevalence among male smokers in the 1970s (Heloma, Puska, 2016). The decline can be attributed to the Finnish Tobacco Act in the 1970s restricting smoking in public places, sales to underage and ban on advertisement; currently, the country is pioneering e-cigarette regulations (World Health Organization, 2020b).

Research has shown tobacco products as a major contributor to diseases and mortality, Specifically, the link between smoking and CVD in cohort studies has been revealed (Hackshaw et al., 2018), including lower risk of CVD mortality following smoking cessation (Honjo et al., 2010). Active smoking as well as passive or environmental exposure to cigarette smoke are shown to lead to cardiovascular dysfunction. Although the specific mechanism is not perfectly understood, it is assumed that the oxidative stress, the inflammation, and the thrombosis associated with cigarette smoke exposure underlies the pathophysiology of CVD development (Ambrose, Barua, 2004). Moreover, in an analyses of different individual adult studies, smoking was shown to favour atherosclerosis by revealing a dose dependent relationship with higher levels of serum total cholesterol, triglycerides and low-density lipoprotein (LDL) cholesterol, and lower concentrations of high-density lipoprotein (HDL) cholesterol and apolipoprotein A1 (Apo A-1) (Craig, Palomaki & Haddow, 1989).

Cholesterol level: Cholesterol was discovered to be a major component of atherosclerotic plaque in the early 20th century (Goldstein, Brown, 2015). The two major types of cholesterol - HDL and LDL, have been reported to have an association with CVD events (Ference et al., 2017, Klag et al., 1993, Povey, 2016).

In the Johns Hopkins Precursors Study (Klag et al., 1993), a strong graded relationship was established between serum cholesterol in early adult life and CVD events (particularly for CHD) and mortality in midlife, independent of other risk factors. Similar findings were noted in the Cooper Center Longitudinal Study (CCLS) where non-HDL cholesterol (total cholesterol minus HDL cholesterol (HDL-c)) was associated with increased risk of CVD and CHD mortality (Abdullah et al., 2018). Considering that LDL cholesterol (LDL-c)/HDL-c ratio can give better assessment for CVD risk, the KIHD study (Kunutsor et al., 2017) evaluated the prospective relationship with this indicator and sudden cardiac death (SCD) and demonstrated a significant association between high LDL-c/HDL-c ratio and increased risk of SCD. Populations in countries with higher blood cholesterol levels (for example Finland, USA and Norway) recorded higher CHD mortality than populations in countries with lower blood cholesterol levels in southern

Europe and Japan (Keys et al., 1986). In general, predictors of CVD events include Apo B/Apo A-1, Apo-B, non-HDL cholesterol, LDL/HDL cholesterol and Total/HDL cholesterol in primary prevention populations (Perera et al., 2015).

The notable role of LDL-c in the aetiology of atherosclerosis has led to its identification as the main causal atherosclerotic lipoprotein and sometimes called the 'bad' cholesterol (Steinberg, 2009, Kannel, Wilson, 1992, Information, National Center for Biotechnology, 2017). On the other hand, the HDL-c is considered as the principal anti-atherosclerotic lipoprotein with protective effects on atherosclerotic CVD and oftentimes termed the 'good' cholesterol (Viles-Gonzalez et al., 2003, Gordon et al., 1977, Information, National Center for Biotechnology, 2017).

The enormous inflow of modified LDL coupled with the accumulation of cholesterol esters in intimal macrophages are the primary cause of foam cells generation. These foam cells are involved in all stages of atherosclerotic lesion development- from the first stage to the advanced plaque development stage, which are more likely to be formed around arterial branches or curved regions (Chistiakov et al., 2017, Linton et al., 2000). The increased nitric oxide (NO) production and superoxide dismutase (SOD) expression ensure adequate endothelial barrier integrity by maintaining effective barrier and reducing cellular oxidative stress respectively (Figure 2). Thus, reduced expression of endothelial nitric oxide synthase (eNOS) and SOD would lead to the accumulation and retention of subendothelial atherogenic apoB-containing lipoproteins i.e., LDL, VLDL and chylomicrons. The consequent of this is endothelia cell activation and increased production of reactive oxygen species. On the contrary, the HDL exhibits 'atheroprotective' function by preventing endothelial cell activation and promoting NO production to maintain the endothelial barrier integrity.

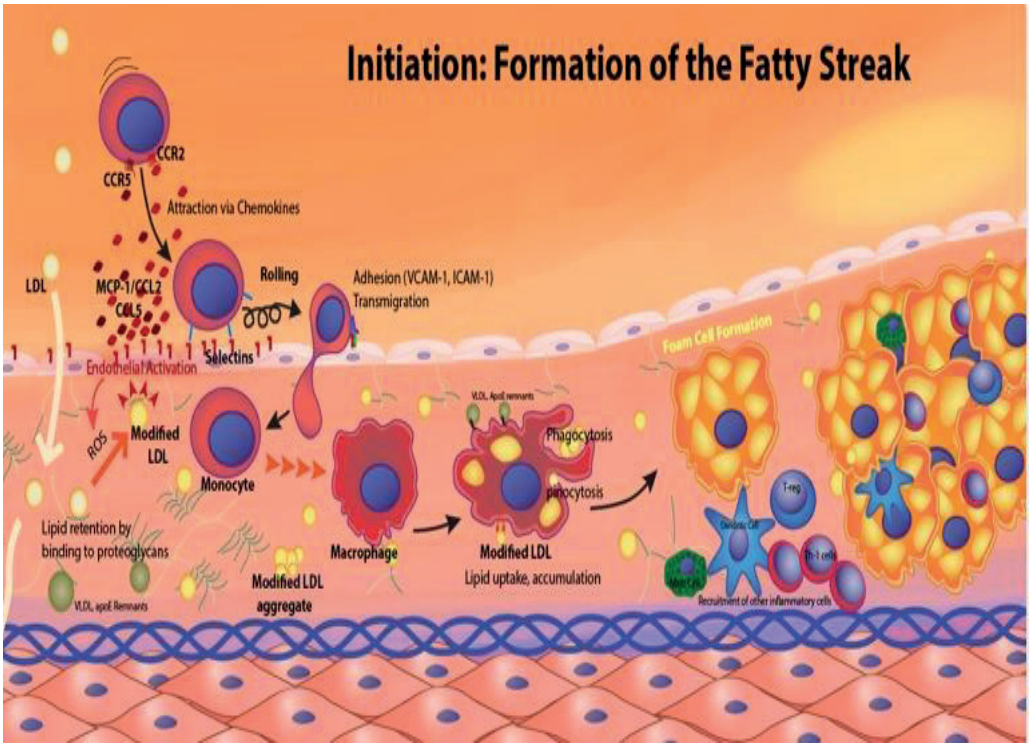

Figure 2. Formation of Fatty Streak in atherogenesis
(Adapted with permission from ENDOTEXT (Linton et al., 2000))

Diet: Many dietary measures have been studied in relation to their effects on CVD (Lanier, Bury & Richardson, 2016). However, it is challenging to recommend a particular strategy for the primary prevention of CVD. Nevertheless, dietary recommendations promote increased consumption of whole grains, pulses, fruits and vegetables, while discouraging the intake of red meat, sweets and high-sugary products, and processed foods high in salt, fat or with low fibre contents (Migliaccio et al., 2020). Different dietary strategies, such as the Mediterranean (de Lorgeril, Salen, 2007), DASH (Dietary Approaches to Stop Hypertension) (Eckel Robert et al., 2014), Swedish (Hlebowicz et al., 2013) and Vegetarian diets, take some of these into consideration.

The Mediterranean diet considers seasonality and is characterized by intake of fruits and vegetables, whole grains, olive oil, moderate intake of fish, seafood, daily and wine (Lanier, Bury & Richardson, 2016). A meta-analysis of cohort studies has shown that more adherence to this Mediterranean dietary pattern is associated with 10% reduced risk of CV

events and mortality (Sofi et al., 2010). The DASH eating plan is comprised of high consumption of fruits and vegetables, low-fat dairy products, whole grains, nuts, fish and poultry, and low intake of total and saturated fat and cholesterol. A meta-analysis of cohort studies showed that adherence to the DASH diet reduced the risk of coronary artery disease (CAD) and stroke by 21% and 19% respectively (Salehi-Abargouei et al., 2013, Lanier, Bury & Richardson, 2016). The Swedish diet, based on diet quality index of the Swedish Nutrition Recommendations includes six components: energy percentage (E%) from saturated fatty acids (SFAs), E% from polyunsaturated fatty acids (PUFAs), intake of fish and shellfish (g/week), dietary fiber (g/MJ), fruit and vegetables (g/day), and E% from sucrose. It emphasizes low intake of saturated fat and sugar, and higher intake of dietary fibre, fish, and fruits and vegetables; and prospective evidence show its relation to lower the risk of CV events (Hlebowicz et al., 2013). Vegetarian diet basically excludes or reduces animal products, with more emphasis on the consumption of fruits and vegetables, grains, pulses, and nuts (Migliaccio et al., 2020), and research has shown the associated lower risk of CVD in vegetarians as compared with nonvegetarians (Kwok et al., 2014).

Alcohol consumption: Alcohol consumption, although not part of AHA's CVH metrics, can influence other unhealthy lifestyles, such as smoking. Alcohol has been associated with CVDs including alcoholic cardiomyopathy, CAD, arrhythmias, stroke and heart failure (Klatsky, 2015), despite the controversies surrounding it. Beneficial effects are seen more in light-moderate drinkers than in heavy drinkers and reports have shown a U-curve or J-curve association between increasing alcohol consumption and CAD, when compared with abstaining (Ronksley et al., 2011). Whereas moderate drinkers show lower risk of AMI and CAD mortality compared to abstainers, heavy drinkers have higher risk of CAD and arrhythmias (Klatsky, 2015, Cohen, E. J., Klatsky & Armstrong, 1988). The mechanism underlying the development of the pathologies is not well understood. The accumulation of acetaldehyde (an alcohol metabolite) and fatty acid ethyl esters (from non-oxidative metabolic pathway for alcohol) which are toxic

to the myocardium, have been hypothesized as possible causes of alcohol cardiomyopathy (Klatsky, 2015).

Diabetes mellitus: Diabetes is a major risk factor for CHD (Leon, Maddox, 2015) and its prevalence has been on the rise in the past years probably due to increase in the ageing population, prevalence of obesity, urbanization and physical inactivity. About 90% of people with diabetes have type 2 diabetes (Zheng, Ley & Hu, 2018), and it is estimated that over 500 million people will develop diabetes by 2035 globally (Leon, Maddox, 2015). Other CVD risk factors such as obesity, hypertension and dyslipidaemia, are more common in patients with diabetes, which adds more burden to their health status (Leon, Maddox, 2015, Matheus et al., 2013). Individuals with type 2 diabetes are at more risk of CVD mortality compared with those without diabetes (Gu, Cowie & Harris, 1999, Einarson et al., 2018), and similar relationship is also reported in people with type 1 diabetes, such that those with type 1 diabetes have more than 2-fold increased risk of CVD compared with those without diabetes (Juutilainen et al., 2008, Schnell et al., 2013). The higher prevalence of MI, heart failure and diabetic cardiomyopathy among patients with diabetes can be attributed to increased coagulability, reductions in systolic and diastolic functions and greater left ventricular mass compared with patients without diabetes (Santra et al., 2011, Leon, Maddox, 2015). The higher risk of CVD among patients with diabetes could be as a result of an increase in circulating free fatty acids and triglycerides, higher stimulation of apolipoprotein B and very low-density lipoprotein cholesterol (VLDL), decreased HDL levels and C-reactive protein (a biomarker of inflammation), and hyperglycaemia-induced excess superoxide production (Leon, Maddox, 2015, Schnell et al., 2013).

Obesity: The prevalence of obesity has been on the rise over the last decades, with a prevalence of 42.4% (2018) in adults, and approximately causing 4 million deaths worldwide, of which more than 60% are linked to CVD (Elagizi et al., 2020). The prevalence of obesity has also increased in Finland in the last decades (1978 to 2017), from 12.0% to 26.1% among men and 18.8% to 27.5% among women (Lundqvist et al., 2018). Obesity is strongly associated with other CVD risk factors such as

hypertension, diabetes, atherosclerosis and dyslipidaemia (Elagizi et al., 2020) and has been analysed in various studies and found to increase the risk of CVD (Katta et al., 2020). However, epidemiological data suggests central obesity (defined by the WHO (World Health Organization, 2011) as waist circumference ≥ 94 cm for men and ≥ 80 cm for women or waist-to-hip ratio ≥ 0.90 in men and ≥ 0.85 in women and a waist-to-height ratio of > 0.50) is a better predictor of CV events and mortality compared to BMI and relative body weight (Katta et al., 2020). Central obesity is generally considered a component of metabolic syndrome, in addition to hyperglycaemia, hypertension and dyslipidaemia. These components of metabolic syndrome, directly or indirectly, are involved in the initiation and progression of atherosclerosis (Qiao et al., 2007). In obesity, the mechanism underlying the development of some CVDs could partly be due to increased body mass and significant growth of different tissues and organs (Elagizi et al., 2020). Additional effects of obesity on the CV system can be seen in the hemodynamic alterations in the structure and function of the heart and blood vessels due to the need for more blood supply to the increased body mass in obesity. Thus, total blood volume, stroke volume and cardiac output are increased leading to higher cardiac filling pressure and volume. This will lead to more CV work and subsequent ventricular dilation and hypertrophy, and finally systolic and diastolic dysfunction (Lavie, Carl J. et al., 2014). Obesity being an independent risk factor for diabetes, contributes to endothelial dysfunction and dyslipidaemia thereby increasing the risk of CAD (Elagizi et al., 2020).

It is important to highlight that not all obese people have metabolic derangement, and other than increased BMI, they may not have other CVD risk factors. These individuals who are obese but do not have hypertension, dyslipidaemia, or impaired fasting glucose or diabetes mellitus are classified under the term - 'metabolically healthy obesity' (Lavie, Carl J. et al., 2014).

Physical activity (PA): The rising prevalence of physical inactivity may be attributed to the modern lifestyle changes and advancement in technology leading to reduction in active transportation, leisure time PA, or increase sedentary time. It is estimated that about 2 million people die

annually from physical inactivity worldwide (Lavie, C. J. et al., 2019, Elagizi et al., 2020, Weintraub et al., 2011). The AHA also acknowledged sedentary behaviour as one of the top preventable causes of mortality (Elagizi et al., 2020, Weintraub et al., 2011). In fact, a systematic review confirms sedentary behaviour as an independent risk for the incidence of CVD, irrespective of PA (Biswas et al., 2015).

The minimum guidelines for aerobic PA to improve CV health is set at 150 min/week of moderate or 75 min/week of vigorous PA for healthy adults; and lifestyle PA is presumed to reduce the risk of CVD or recurrent CVD related events by enhancing physical and physiological body function as well as promoting cardiorespiratory fitness (CRF), irrespective of age, sex and race (Ozemek et al., 2018). Despite the beneficial effects of PA, there may be possible potential hazards, particularly in extremes of vigorous PA in hypertensives (Wannamethee, Shaper, 2002). The mechanisms behind the relationship between PA and CVD are still unclear. The protective effect of PA may be attributed to the slowing of atherosclerotic development as well as the control of other known CVD risk factors, such as hypertension, obesity, and diabetes (Cheng et al., 2013). Thus, some mechanisms proposed are in relation to blood pressure, lipoprotein metabolism, insulin sensitivity, haemostatic function and fibrinolytic activity (Wannamethee, Shaper, 2002).

There is documented evidence that more physically people have lower blood pressure, lower serum triglyceride and higher serum HDL levels (Wannamethee, Shaper, 2002). Physical activity might reduce insulin resistance and improve insulin sensitivity, thereby reducing the risk of diabetes, which is a major risk factor for CVD (Cheng et al., 2013, Wannamethee, Shaper, 2002). Many haemostatic markers, such as fibrinogen, blood viscosity, plasminogen activator inhibitor-1, and blood coagulation factors are reduced with physical activity; thus, PA may function as an anti-thrombotic by reducing haemostasis and improving fibrinolytic activity resulting in decelerating the process of atherosclerosis (Cheng et al., 2013, Wannamethee, Shaper, 2002). The energy expenditure during PA can be beneficial in weight control, lowering the risk of obesity and CVD (Cheng et al., 2013). Regular PA can also lower the production of

reactive oxygen species in the peripheral vasculature and improve antioxidant defence proteins in the cells (Lavie et al., 2019). All these may contribute to reduce the future risk of CVD.

Genetics: Genetic factor is one of the nonmodifiable risk factors of CVD and its influences on risk factors of CVD are well documented (Banerjee, 2012, Vogler et al., 1997, Lloyd-Jones, D. M. et al., 2004, Imes, Lewis, 2014). Studies, including twin studies, have reported the positive association between family history of CVD and risk of CHD, particularly those involving first-degree relatives with history of premature CHD (Imes, Lewis, 2014, Lloyd-Jones et al., 2004, Vogler et al., 1997). This reveals the possibility that genetic factors can pose future risk of CVD. Some traditional CVD risk factors, however, do occur and accumulate in families such as, unhealthy dietary pattern and smoking. Similarly, known hereditary traits, such as familial hypercholesterolemia and familial combined hyperlipidaemia can be a predisposing factor for CVD in the family (Banerjee, 2012). Furthermore, genetic studies on CVD risk factors have identified associations with blood pressure, ApoA1, ApoB and BMI (Vogler et al., 1997).

2.3 CARDIOVASCULAR HEALTH METRICS

In 2010, AHA for its 2020 Impact Goal, developed a metric to improve the cardiovascular health of Americans by 20%, while reducing the deaths from CVD and stroke by 2020 and beyond (Lloyd-Jones et al., 2010, Roger Véronique et al., 2020). The metrics concisely defines seven components, which include three health factors (blood glucose, serum cholesterol, blood pressure) and four health behaviours (BMI, physical activity, diet and cigarette smoking) into ideal, intermediate and poor categories (Table 2); these seven factors have been dubbed the Life's Simple 7(LS7). The application of this CVH metrics among the Finnish population is limited, and awareness of its potential benefits to reduce the burden of CVD and improve cardiovascular health in Finland is low.

Table 2. Definition of cardiovascular health metrics

Cardiovascular health metrics	Poor	Intermediate	Ideal
Healthy diet score	0 – 1	2 – 3	4 – 5 components[a]
Physical activity	No physical activity	1-149 mins/week of moderate intensity physical activity or 1-74 mins/week of vigorous intensity or both	≥150minutes/week moderate intensity (MET 3-6) or ≥75 minutes/week of vigorous intensity (MET >6) or combination
Body mass index, kg/m^2	≥ 30	25 – 29.9	<25
Smoking status	Current smokers	Previous smokers ≤12 months	Never smoked >12 months
Blood pressure, mmHg	SBP ≥140 or DBP ≥90	SBP, 120–139 or DBP, 80–89	SBP <120 and DBP <80
Fasting blood glucose[b], mmol/l	≥7.00	5.55 – 6.99	<5.55
Plasma total cholesterol [c], mmol/l	≥ 6.22	5.18 -6.21	< 5.18

[a]The components are: ≥4.5 cups/day of fruits and vegetables, ≥two 3.5-ounce servings/week of fish, <1,500mg/day of sodium, ≤ 36ounces/week of sweets/sugars and ≥ three 1-ounce servings/day of whole grains; [b]mmol/l x 18 = mg/dl; [c]mmol/l x 38.6= mg/dl
DBP, diastolic blood pressure; MET, metabolic equivalent; mmHg, millimetre mercury; SBP, systolic blood pressure

Table 3 shows some studies across the globe that have examined the association of CVH metrics and risk of CVD events.

Table 3. Studies on CVH metrics and CVD events

Study, year	Country	Cohort	Age, mean	Health metrics	Outcome event	Result, risk ratios	Adjusted for	Follow-up years/ year for outcome data
Ahmed et al., 2020	United Kingdom	British Region Heart Study	50.0	Optimal (9-12) vs inadequate (0-4)	Stroke	0.39 (0.25-0.61)	Age, social class and alcohol intake at baseline	19.8
Bensenor et al., 2016	Brazil	ELSA-Brazil study	M/F: 50.9/50.7	≥5 vs 0-1	Coronary artery calcium	0.36 (0.24-0.56)*	Age and sex	2008-2010
Dong, C. et al., 2012	USA	NOMAS study	69.0	Ideal (5-6) vs poor (0-1)	Composite CVD events	0.41 (0.26-0.63)	Age, sex and race-ethnicity	8.0
					Myocardial infarction	0.16 (0.05-0.52)		
Han et al., 2018	China	China-PAR project	51.6	ideal (7) vs poor (0-2)	ASCVD events	0.24 (0.18–0.31)	Age, sex, living region, urbanization, drinking status, education level, family history of ASCVD, and cohort sources	15.0
					Stroke	0.21 (0.15–0.28		
Gaye et al., 2017	France	The Three-City Study	72.8	Ideal (≥5) vs poor (0-2)	Coronary heart disease	0.27 (0.13-0.57)	Age, sex, study site, education level, and living alone	9.0

					Stroke	0.45 (0.20-1.03)		
Lachman et al., 2016	Europe	EPIC-Norfolk Study	57.0	Healthiest (12-14) vs unhealthiest (0-2)	Composite CVD events	0.07 (0.02-0.23)	Age and sex	10.0
					Stroke	0.16 (0.02-1.37)		
Miao et al., 2015	China	Kailuan Study	79.5	Optimum (10-14) vs Inadequate (0-4)	Composite CVD events	0.29 (0.24-0.35)	Age, sex, alcohol consumption, income, education and history of CVD, heart rate, uric acid, and high-sensitivity CRP	6.8
					Myocardial infarction	0.26 (0.18-0.38)		
					Stroke	0.30 (0.24-0.37)		
Ommerborn et al., 2016	USA	Jackson Heart Study	54.5	ideal CVH metrics: ≥4 vs 0-1	Composite CVD events	0.29 (0.17–0.52)	Age, sex, income, and education	8.3
Saleem et al., 2015	USA	Cooper Center Longitudinal Study	M/F: 53.9/61.7	Favourable (≥4 ideal CVH) vs unfavourable (0-2 metrics)	Coronary artery calcification	0.41 (0.34–0.50)*	Age and sex	1997-2007

*Odds ratio; atherosclerotic CVD (ASCVD); CVH, cardiovascular health; CVD, cardiovascular disease; M/F, male/female

3 AIMS OF THE STUDY

The primary aim of this study was to characterize in detail the associations of CVH metrics (also referred to as LS7), as defined by AHA, and the risk of cardiovascular outcomes and all-cause mortality among a general population in Finland.

Specific objectives:

To assess the nature and magnitude of the association of:

i) Ideal CVH with myocardial infarction risk
ii) CVH metrics with CVD mortality
iii) CVH metrics with SCD and all-cause mortality
iv) Life's Simple 7 with the future risk of stroke.

4 SUBJECTS AND METHODS

4.1 STUDY POPULATION

This study used the ongoing population-based Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD). The KIHD was designed to investigate different risk factors for developing atherosclerotic CVD and other chronic diseases among middle-aged and aging population in Kuopio and surrounding communities in Eastern Finland (Isiozor et al., 2019, Laukkanen, J. A. et al., 2010). The study population was a random sample of men selected from the national population register, stratified and balanced for age, who were 42, 48, 54 or 60 years old at baseline examination between March 1984 and December 1989. Three thousand two hundred and thirty-five (3235) men were eligible for the study, however, 2682 (82.9% of eligible men) finally volunteered to participate in this study, 367 declined to give informed consent and 186 did not respond to the invitation at baseline (Figure 3). The description of the study population in the respective studies (I to IV) is summarized in Table 4. The Research Ethics Committee of the University of Eastern Finland, Kuopio, Finland, approved the KIHD study. Informed consent was obtained from all individual participants included in the study.

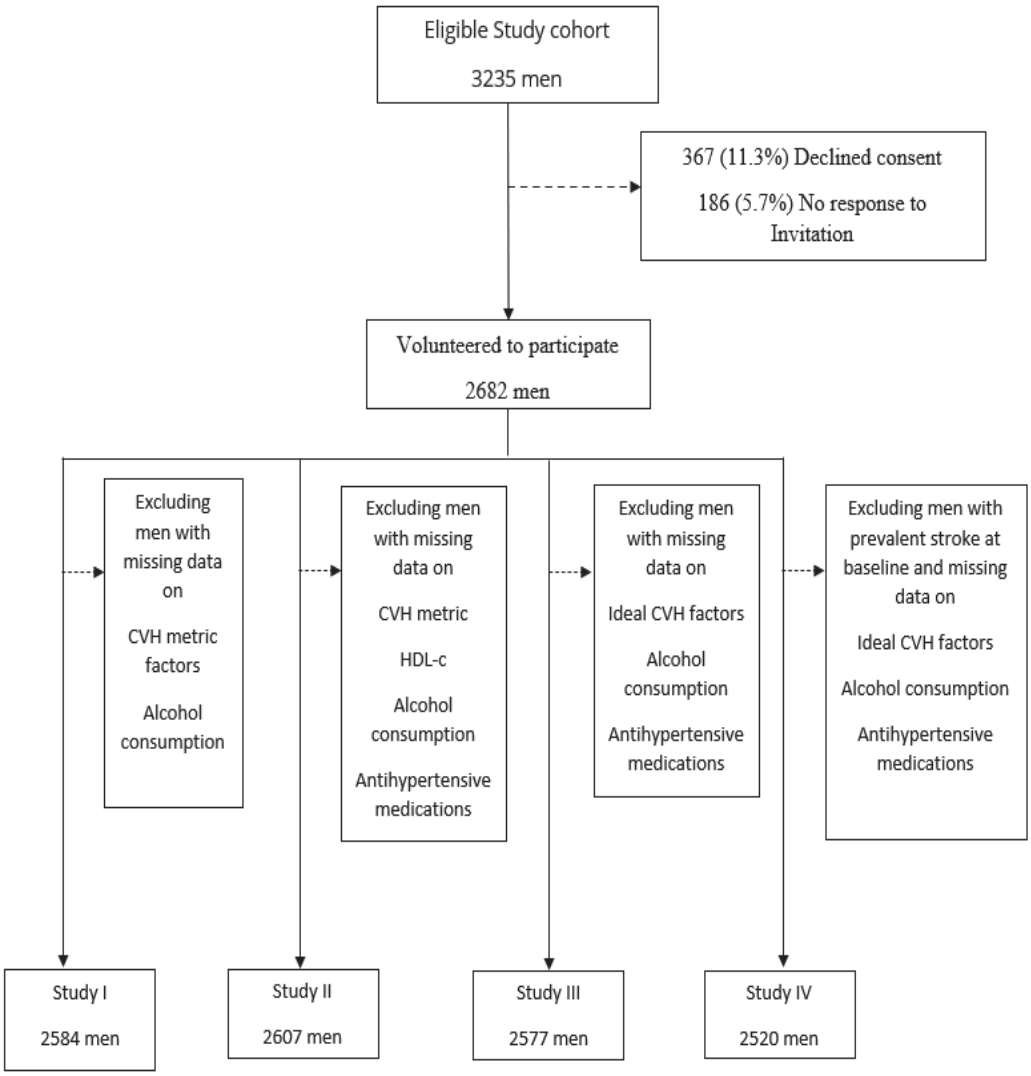

Figure 3. Flow chart of the KIHD study recruitment

Table 4. The description of the study population and main variables in study I – IV

Study	n	Population	Exposure	Healthiest metrics category*	Follow-up time	Main outcomes
I (AMI)	2584	Healthy and unhealthy (CVD and diabetes mellitus)	CVH metrics	5-7[a]	25.2 years	513 acute myocardial infarctions
II (CVD death)	2607	Healthy and unhealthy (CVD and diabetes mellitus)	CVH score	0-4[b]	25.8 years	609 CVD deaths
III (SCD and all-cause death)	2577	Healthy and unhealthy (CVD and diabetes mellitus)	CVH metrics	5-7 [a]	25.8 years	280 sudden cardiac deaths 1289 overall deaths
IV (Stroke)	2520	Healthy and unhealthy (CVD and diabetes mellitus)	Life's Simple 7	5-7 [a]	26 years	362 ischaemic stroke 428 total stroke

AMI, acute myocardial infarction; CVD, cardiovascular disease; CVH, cardiovascular health; n, number of participants; SCD, sudden cardiac death

*Healthiest score range

[a] Overall score range 0 to 7; [b] Overall score range 0 to 14

4.2 DATA COLLECTION

4.2.1 Food records (healthy diet score (HDS))

A 4-day food record diary was used to quantitatively assess the dietary intake of foods and beverages at the baseline of the study. Participants filled the food records by household measures and delivered them at study visits. The four days were to be consecutive – three workdays and one weekend day. In next study visits, food records were interview-checked. In cases of atypical day, food records were accepted if correctly filled; otherwise, they were rejected in cases of obvious scarcity of food records (Salonen et al., 1992).

Healthy diet score: The AHA has considered an "ideal" adult diet as the consumption of four or five of the following: at least 4.5 cups per day of fruits and vegetables, at least two 3.5-ounce servings a week of fish (oily is best), less than 1500 milligrams a day of sodium, fewer than 450 calories (36 ounces) a week of sweets/sugar and at least three 1-ounce servings a day of whole grains. Additional three factors, considered as secondary dietary metrics, are also considered to contribute to a healthy diet. These are: less than 7% of total calories from saturated fat, at least 4 servings a week of nuts, legumes or seeds and none or fewer than 2 servings a week of processed meats (Lloyd-Jones et al., 2010). Based on the available data in the KIHD study, the salt intake for the calculation of the HDS was substituted with the intake of processed meat (recognized by AHA as a secondary dietary metric). Processed meat has been shown to contain much salt (sodium) (Susic, Frohlich, 2012), and in the 1980s, the Finnish diet and lifestyle recommendations on the use of salt included the intake of processed meats under convenience foods to be avoided because they were among the sources of excess salt in the Finnish diet (Kuusipalo, Määttänen-Bourke, 2013). Therefore, HDS among participants with 4–5 components were considered "ideal"; 2–3 components considered "intermediate" diet; and 0–1 as "poor" adult diet.

4.2.2 Blood pressure

Resting blood pressure was measured with a random-zero sphygmomanometer (Hawskley, Lancing, UK) by two trained nurses. The measurement protocol included six measurements with five minutes' intervals in the supine, standing and sitting positions. The resting blood pressure was measured after 5 and 10 minutes of rest in a seated position between 8 a.m. and 10 a.m. (Salonen et al., 1992, Laukkanen, Jari A. et al., 2012)

According to AHA, ideal BP was defined as systolic BP<120mmHg and diastolic BP<80mmHg. Intermediate BP was considered as having systolic BP of 120–139mmHg or diastolic BP of 80–89mmHg. Poor BP was defined as a systolic BP ≥140mmHg or diastolic BP ≥90mmHg.

4.2.3 Physical activity

The KIHD 12-Month Leisure-Time Physical Activity Questionnaire (a modification of the Minnesota leisure time activity questionnaire), a 7-day leisure time activity recall, the 24-hour total activity recording, and the occupational activity interview were used to assess the physical activity of the participants (Lakka et al., 1994). The quantitative questionnaire encompasses most common physical activities of middled-aged Finnish men and allows the assessment of all components of physical activity. For every type of physical activity, the subjects were required to record the frequency (number of sessions per month), average duration (hours and minutes per session) and intensity (scored as 0 for no or recreational activity, 1 conditioning activity, 2 for brisk conditioning activity, and 3 for competitive, strenuous exercise). All metabolic indices were calculated using the product of duration of each activity and the caloric coefficient of the specific activity and intensity class. The intensity was expressed in metabolic units (MET), which is the ratio of metabolic rate during activity to the metabolic rate at rest. A trained nurse checked and completed the questionnaire in an interview.

Participants were considered to have ideal physical activity when they pursue at least 150min per week of moderate-intensity physical activity (MET 3–6) or 75min per week of vigorous intensity aerobic physical

activity (MET>6), or an equivalent combination of moderate- and vigorous-intensity aerobic activities. Intermediate physical activity was considered as having 1–149min per week of moderate intensity physical activity (MET 3–6) or 1–74min per week of vigorous intensity aerobic physical activity, or an equivalent combination of both. Poor physical activity was defined as no physical activity.

4.2.4 Body mass index

The weight and height of participants were measured at baseline. Body mass index (BMI) was calculated as the weight in kilograms divided by height in meters squared (kg/m^2) (Laukkanen, Jari A. et al., 2006). Ideal, intermediate, and poor BMI were defined as <25 kg/m^2, 25–29 kg/m^2 and ≥30 kg/m^2, respectively.

4.2.5 Smoking status and alcohol consumption

Smoking status and duration of regular smoking in years of each participant were collected through a mailed self-administered questionnaire prior to their visit to the study centre. Ideal smoking status was defined as men who never smoked, whereas previous and current smokers were considered as having intermediate and poor smoking status, respectively. Alcohol consumption was assessed with a structured quantity-frequency method using the Nordic Alcohol Consumption Inventory on drinking behaviour over the previous 12 months and from a dietary record over four days (Salonen et al., 1991).

4.2.6 Biochemical analyses

Participants provided blood samples between 8 a.m. and 10 a.m., after abstaining from - alcohol consumption for 3 days, smoking for 12 hours and eating for 12 hours. After a 30-minute rest in a supine position by the participant, blood sample was drawn from the antecubital vein with Terumo Venoject VT-100PZ vacuum (Terumo Corp., Tokyo, Japan), without the use of tourniquet. The cholesterol contents of serum lipoprotein fractions and triglycerides were measured enzymatically (Boehringer, Mannheim, Germany). Serum HDL cholesterol and its subfractions were

separated from fresh serum samples using ultracentrifugation and precipitation. The glucose dehydrogenase method was used to measure the fasting blood glucose (Merck, Darmstadt, Germany) after precipitation of proteins by trichloroacetic acid (Salonen et al., 1991, Salonen et al., 1992).

Ideal total cholesterol level was <5.18mmol/l (200mg/dl), intermediate cholesterol level was 5.18–6.21mmol/l (200–240mg/dl), and ≥6.22mmol/l (240mg/dl) was considered poor total cholesterol level. For blood glucose, fasting blood glucose <5.55mmol/l (100mg/dl) was considered as ideal, 5.55–6.99mmol/l (100–125mg/dl) considered as intermediate, and ≥7.00mmol/l (126mg/dl) considered as poor.

4.2.7 Baseline cardiovascular diseases and medications

A self-administered questionnaire was used to obtain information on the medical history, medication use and family history of diseases from participants. This information was checked during medical examination. Prevalent CHD was defined as having either a history of myocardial infarction, angina pectoris on effort or the use of nitroglycerin for chest pain once a week or more frequently. Prevalent CVD was defined as having a history of CHD, hypertension, congestive cardiac failure, cardiomyopathy, arrythmias, stroke or claudication (Laukkanen et al., 2006, Lynch et al., 1995).

A family history of CHD was defined as premature CHD in parents or in first degree relatives before 55 years in men, or 65 years in females. Diabetes was defined as fasting blood glucose ≥6.7 mmol/l or a clinical diagnosis of diabetes with either dietary, oral or insulin treatment (Laukkanen et al., 2006)

4.2.8 Assessment of education and socioeconomic status

At baseline, the KIHD participants received a self-administered questionnaire mailed to them prior to their visit to the study centre. The participants were invited to the study centre for interviews and clinical examination. A trained research nurse was responsible for interviewing the participants and checking and completing the questionnaires. Information

about education, type of occupation and past medical records was obtained using detailed questionnaires and were checked during medical examination by a physician. The adulthood socioeconomic status (SES) was generated from combined measure of current income, current and previous occupations, highest level of education, perception of financial security, housing tenure, and an index of material living conditions (from a 12-item list) (Lynch et al., 1994, Laukkanen, T. et al., 2015). The SES scale ranged from 0 through 25, with 0 indicating the highest and 25 the lowest SES.

4.3 ASSESSMENT OF CARDIOVASCULAR HEALTH METRICS

The CVH metrics adopted in this study was in conformity with AHA's developed CVH metrics, consisting of seven health behaviours and factors (also known as the LS7) including healthy diet score (HDS), BP, physical activity, BMI, smoking status, plasma total cholesterol, and fasting blood glucose (Lloyd-Jones et al., 2010). The level of each factor was classified at baseline as ideal, intermediate, or poor (Table 2). The summary score of LS7 was generated from the summation of AHA's ideal CVH metrics, ranging from 0 to 7 (a point for each AHA's ideal category and zero point for intermediate and poor categories).

4.4 ASCERTAINMENT OF FOLLOW-UP EVENTS

4.4.1 Mortality

All deaths that occurred between study entry (March 1984 to December 1989) to the end of 2014 were included and checked against hospital documents, health centre wards and death certificates. There were no losses to follow-up due to the linkage to the National Death Registry using Finnish personal identification codes. Two physicians (members of the research group) cross-checked all the documents related to mortality. Death from CVD were coded using the Ninth International Classification of Diseases (ICD) codes (390 – 459) or the Tenth ICD codes (100 – 199).

4.4.2 Cardiovascular outcomes

The data collection and the diagnostic classification of fatal and non-fatal coronary events were part of the WHO MONICA (MONItoring of Trends and Determinants in CArdiovascular Diseases) Project in which comprehensive information of all coronary events and strokes were prospectively collected (Tuomilehto et al., 1992). All the KIHD participants, at baseline, lived in Kuopio province which was one of the monitoring areas of the Finnish part of the WHO MONICA Project (FINMONICA). The National Hospital Discharge Data Register was used to obtain data and the FINMONICA regional teams collected data on coronary events from hospitals and wards of health centres and classified the events. The sources of the information were interviews, hospital documents, death certificates, autopsy reports and medico-legal reports. The diagnostic classification of events was based on symptoms, electrocardiographic (ECG) findings, cardiac enzyme elevations, autopsy findings and history of CHD, together with the clinical and ECG findings of the paramedic staff.

The ICD-9 (code numbers 410–414) or ICD-10 (code numbers 120–125) was used to code and classify each suspected coronary event by a physician using the original patient records. The corresponding ICD-9 and ICD-10 codes for definite AMI are 410 and 121 respectively. All AMI cases that occurred from the study enrolment to end of 2014 were included. If a participant had multiple events, the first was considered as the end point. Thus, censoring of AMI was done on the date of the first event; if no AMI but dead before first day of 2015, censoring was on the date of death; and if no AMI and alive to the end of 2014, censoring at the end of observation (31.12.2014).

Sudden cardiac death was determined by death that occurred within one hour of the onset of an abrupt change in symptoms or within 24 hours after the onset of symptoms when the clinical findings did not reveal a non-cardiac cause of sudden death. Deaths that occurred unwitnessed during the night, such as being found dead in bed, were classified as those whose death occurred within 24 h of the start of symptoms. Patients who were successfully resuscitated from ventricular tachycardia and/or ventricular fibrillation were also defined. The deaths

due to aortic aneurysm rupture, cardiac rupture or tamponade, and pulmonary embolism, cancer, or other non-cardiac co-morbidities were not included as SCDs. Out-of-hospital SCDs and non-SCDs were documented. The Independent Events Committee, masked to the clinical data, classified the deaths. Censoring was carried out on the date from the baseline visit to first development of SCD, death, loss to follow-up, or the end of the observation period (31.12.2014).

The diagnosis of stroke was based on sudden onset of clinical signs or focal or global disturbance of cerebral function lasting more than 24 hours (except in the case of sudden death or interruption by surgical intervention) with no apparent cause other than a vascular origin. A neurologist classified the diagnostic information from hospitals using diagnostic criteria similar to the FINMONICA criteria and complying with the ICD – 9 (codes 430–439) and ICD – 10 (codes I60–I68 and G45 – G46). Each definite stroke was classified into (1) an ischaemic stroke (ICD-9 codes 433–434; ICD-10 code I63) or (2) a haemorrhagic stroke (ICD-9 codes 430–431; ICD-10 codes I60–I61). Computed tomography (CT) was performed in 90% of the patients by 1993, and CT, MRI and autopsy reached 100% by 1997. The FINMONICA stroke register data were annually re-checked with the data obtained from the computerized national hospital discharge and death registers. The first stroke was considered as the end point if a participant had multiple non-fatal strokes during follow-up. Thus, censoring of stroke events were done on the date of the first event; loss of follow-up; if no stroke but dead before first day of 2018, censoring was on the date of death; and if no stroke and alive to the end of 2017, censoring at the end of observation.

4.5 STATISTICAL METHODS

The statistical analyses were performed using Microsoft windows software, IBM SPSS Statistics 25 (SPSS Inc., Chicago, IL, USA 9) and Stata MP version 16 (Stata Corp, College Station, TX). Descriptive statistics was used to summarize the baseline characteristics of the participants as mean (standard deviation) or median (interquartile range) values for continuous

variables, and as number (percentage) for categorical variables. Analysis of variance was used to assess the differences in baseline characteristics of continuous variables, chi-squared test for categorical variables. The shapes of the relationships between the CVH metrics (as a continuous variable) and the risk of outcomes were explored using restricted cubic splines with knots at 5^{th}, 35^{th}, 65^{th} and 95^{th} percentiles of the CVH metrics distribution in a multivariable adjusted model. The association of baseline CVH metrics with the risk of outcomes, adjusted for established risk factors and potential confounders, were analysed using multivariable Cox regression models to estimate the hazards ratios (HRs) and 95% confidence intervals (CIs), after confirmation of no major departure from the proportionality assumptions using Schoenfeld residuals (Therneau, Grambsch, 2000). A two-sided *p* value <0.05 was considered statistically significant.

4.5.1 Study I (AMI)

In this population-based cohort, following the exclusion of men with missing data on CVH factors and alcohol consumption, 2584 men from eastern Finland were followed for a median follow-up time of 25.2 years. The associations of baseline CVH metrics and the risk of AMI was examined with multivariable Cox regression models. The CVH metrics were dichotomized, with a score of 1 given for every ideal component and 0 for poor and intermediate components, generating a CVH score ranging from 0 to 7. The seven scores were categorized into three groups: poor (0 – 2), intermediate (3 – 4) and ideal (5 – 7), with the poor CVH used as the reference comparison. The HRs were calculated with adjustments in two models: 1) model 1: age, alcohol consumption and SES; 2) model 1 plus history of CHD and history of type 2 diabetes mellitus.

4.5.2 Study II (CVD mortality)

This study was based on 2607 men (after excluding men with missing data on CVH metrics, HDL cholesterol, alcohol consumption, antihypertensive medications) after a median follow-up of 25.8 years. The associations of CVH score and risk of CVD mortality were analysed using established risk factors and potential confounders (age, alcohol consumption, SES, HDL

cholesterol, use of cholesterol lowering medications, use of antihypertensives, history of CHD, and history of type 2 diabetes mellitus) adjusted Cox proportional hazards' models. A CVH score ranging from 0 to 14 was generated in consistency with the Atherosclerosis Risk in Communities (ARIC) and NHANES III (Third Report of the National Health and Nutrition Examination Survey) studies (Ahmad et al., 2019, Garg et al., 2018). Thus, the CVH score was generated by assigning the following scores to AHA's CVH metrics: 0 for every ideal level, 1 for intermediate level and 2 for poor level. Thus, the CVH score ranged from 0 to 14, with lower scores representing a better CVH score. The CVH scores were classified as optimum (0 – 4), average (5 – 9), and inadequate (10 – 14), and the inadequate was used the reference comparison.

4.5.3 Study III (SCD and all-cause mortality)

In this cohort, following the exclusion of men with missing data on ideal CVH factors, alcohol consumption and antihypertensive medications, 2577 men were followed up for a median time of 25.8 years, and the associations between CVH metrics and risk of SCD and all-cause mortality were examined using adjusted multivariable Cox regression models. The CVH metrics were classified into three groups: poor (0 – 2), intermediate (3-4) and ideal (5 – 7), with the poor CVH was used as referent. Also, health scores of 0, 1, 2, ≥3 for the behavioural factors (i.e., physical activity, smoking, BMI and HDS) and 0, 1, 2, 3 for the biological health factors (blood pressure, FBG and total cholesterol) of the CVH metrics were generated, with a 0 score as the referent. Adjustment for covariates was based on two models: model 1) age and alcohol consumption and SES and model 2) age and alcohol consumption, SES, history of CHD and a history of type 2 diabetes mellitus. A sensitivity analysis which involved excluding participants with a previous history of CHD at baseline was conducted.

4.5.4 Study IV (Stroke)

This study was based on 2520 men without stroke at baseline and non-missing data on ideal CVH factors, alcohol consumption and antihypertensive medications, with a median follow-up of 26 years. The

association of ideal CVH, otherwise called LS7, and the risk of total and ischaemic stroke were examined using adjusted Cox proportional hazards' models. The LS7 score was generated from the summation of AHA's ideal CVH metrics, ranging from 0 to 7 (a point was assigned for each AHA's ideal category and zero point for intermediate and poor categories). The LS7 score was then categorized into three groups: 0 – 2 (inadequate); 3 – 4 (average); and 5-7 (optimal); the inadequate (0 – 2) LS7 score served as the referent comparison. Two models were used to estimate the hazard ratios. The first model (model 1) adjusted for age, alcohol consumption and SES and the second model adjusted for model 1 plus a history of CHD and a history of type 2 diabetes mellitus. Sensitivity analyses excluding men with history of CHD and history of type 2 diabetes mellitus were also conducted.

5 RESULTS

The baseline characteristics of men according to cardiovascular events and all-cause mortality in the four studies are presented in Table 5.

Table 5. The baseline characteristics of the KIHD study cohort according to outcomes

Characteristics (mean [SD] or median [IQR])	**Study I**		**Study II**		**Study III**			**Study IV**		
	AMI n, 513	Without AMI n, 2071	CVD death n, 609	Without CVD death n, 1998	SCD n, 280	Without SCD n, 2297	All-cause death n, 1289	Ischaemic stroke n, 326	Total stroke n, 428	Without stroke n, 2092
Age in years	54.0 (4.5)	52.8 (5.3)	54.7 (4.2)	52.6 (5.3)	54.4 (4.2)	52.9 (5.2)	54.6 (4.3)	54.2 (4.3)	54.2 (4.4)	52.8(5.3)
Socioeconomic status	12.9 (4.8)	12.1 (5.2)	13.4 (5.0)	11.9 (5.1)	13.4 (4.8)	12.1 (5.2)	13.4 (5)	13.2 (5.1)	13.0 (5.2)	12.1 (5.1)
Alcohol (g/week)	30.8 (5.4 – 88.3)	31.9 (6.3-92.9)	34.1 (5.4–111.6)	30.5 (6.3-88.2)	39.7 (7–113)	30.7 (6.2-89.2)	38 (6.4–115.5)	27.3 (5.3–93.0)	29.8 (6.4–95.1)	32.0 (6.3-92.0)

History of coronary heart disease n(%)	184 (35.9)	463 (22.4)	246 (40.4)	412 (20.6)	128 (45.7)	518 (22.6)	420 (32.6)	121 (33.4)	129 (30.1)	493 (23.6)
History of diabetes mellitus, n(%)	62 (12.1)	91(4.4)	72 (11.8)	85 (4.3)	34 (12.1)	117 (5.1)	116 (9.0)	31 (8.6)	36 (8.4)	108 (5.2)
Systolic blood pressure (mmHg)	136.8 (17.2)	133.5 (16.9)	139.0 (18.0)	132.7 (16.5)	139.7 (17.6)	133.5 (16.9)	136.6 (18.0)	138.9 (18.4)	138.7 (18.3)	133.1 (16.6)
Smoker, n(%)	201 (39.2)	617 (29.8)	246 (40.4)	585 (29.3)	121 (43.2)	697 (30.3)	539 (41.8)	110 (30.4)	131 (30.6)	671 (32.1)
Body mass index, (kg/m^2)	27.6 (3.9)	26.7 (3.5)	27.7 (4.0)	26.6 (3.4)	28.1 (4.1)	26.8 (3.5)	27.3 (3.9)	27.4 (3.7)	27.4 ±3.7	26.8 (3.5)
Total cholesterol, (mmol/l)	6.1 (1.1)	5.9 (1.1)	6.1 (1.2)	5.8 (1.1)	6.1 (1.1)	5.9 (1.1)	6.0 (1.1)	6.0 (1.2)	6.0 ±1.2	5.9 (1.1)

AMI, acute myocardial infarction; CVD, cardiovascular disease; IQR, interquartile range; g, gram; KIHD, Kuopio Ischaemic Heart Disease; n, number of participants; n(%), number of men (percentage); mmol/l, millimole per litre; SCD, sudden cardiac death; SD, standard deviation

5.1 STUDY I: IDEAL CVH AND AMI RISK

At baseline, the mean age (SD) of the study population was 53.1 (5.1) years. The number of participants (%) in the different categories of the CVH metrics were as follows: poor, 1608 (62.2); intermediate, 859 (33.2); and ideal, 117 (4.5). During the median follow-up years of 25.2 [IQR 14.7–27.6] years, 513 cases of AMI was recorded. The distribution of the seven factors in CVH metrics and the variations in the number of CVH metrics among the KIHD study participants are shown in Table 6. Most of the participants (78.1%) were physically active, whereas HDS was the least attained ideal component (1.9%). Only one participant attained all the seven AHA ideal components (7 CVH metrics) and achieving one ideal metric was the most common among the participants.

Table 6. Distribution of cardiovascular health metrics among the KIHD Study participants based on AMI

Cardiovascular Health Metrics	All participants N=2584[a]	Without AMI N=2071[a]	AMI N=513[a]	*p* value for Trends
Physical Activity				
[b] 150mins/week of moderate-intensity or 75mins/week of vigorous intensity or both	2018 (78.1)	1625 (78.5)	393 (76.6)	0.352
[c] 1-149 mins/week of moderate intensity physical activity or 1-74 mins/week of vigorous intensity or both	21 (0.8)	18 (0.9)	3 (0.6)	0.356
[d] No physical activity	545 (21.1)	428 (20.7)	117 (22.8)	0.473
Body mass index				
[b] <25 kg/m^2	809 (31.3)	679 (32.8)	130 (25.3)	<0.001
[c] 25 – 29.9 kg/m^2	1328 (51.4)	1067 (51.5)	261 (50.9)	0.001
[d] ≥ 30 kg/m^2	447 (17.3)	325 (15.7)	122 (23.8)	<0.001

Healthy Diet Score				
[b] 4 - 5	50 (1.9)	38 (1.8)	12 (2.3)	0.240
[c] 2 – 3	1244 (48.2)	972 (46.9)	272 (53.1)	0.015
[d] 0 – 1	1290 (49.9)	1061 (51.2)	229 (44.6)	0.038
Blood Pressure (mmHg)				
[b] SBP<120 and DBP <80	311 (12.0)	270 (13.0)	41(8)	<0.001
[c] SBP, 120 – 139 or DBP, 80 – 89	985 (38.2)	806 (38.9)	179 (34.9)	0.010
[d] SBP ≥ 140 or DBP ≥ 90	1288 (49.8)	995 (48)	293 (57.1)	<0.001
Fasting Blood Glucose (mmol/l) [e]				
[b] <5.55	1011 (39.1)	844 (40.8)	167 (32.6)	<0.001
[c] 5.55 – 6.99	1193 (46.2)	953 (46.0)	167 (46.7)	0.004
[d] ≥7.00	380 (14.7)	274 (13.2)	106 (20.7)	<0.001
Total Cholesterol (mmol/l) [f]				
[b] < 5.18	662 (25.6)	563 (27.2)	99 (19.3)	<0.001
[c] 5.18 -6.21	1027 (39.7)	830 (40.1)	197 (38.4)	0.022
[d] ≥ 6.22	895 (34.6)	678 (32.7)	217 (42.3)	<0.001
Smoking Status				
[b] Never smoked	834 (32.3)	760 (34.1)	128 (25.0)	<0.001
[c] Previous smokers	932 (36.1)	748 (36.1)	292 (35.8)	0.009
[d] Current smokers	818 (31.7)	617 (29.8)	201 (39.2)	<0.001
Number of CVH metrics[g]				
0	154 (6.0)	118 (5.7)	36 (7.0)	<0.001
1	733 (28.4)	553 (26.7)	180 (35.1)	0.783
2	721 (27.9)	556 (26.8)	165 (32.2)	0.969
3	525 (20.3)	447 (21.6)	78 (15.2)	0.021
4	334 (12.9)	289 (14.0)	45 (8.7)	0.012
5	94 (3.6)	86 (4.2)	8 (1.6)	0.009
6	22 (0.9)	21 (1.0)	1 (0.2)	0.082
7	1 (0)	1 (0)	-	1.000

AHA, American Heart Association; AMI, acute myocardial infarction CVH, cardiovascular health; DBP, diastolic blood pressure; mmHg, millimetres of Mercury; mmol/l, millimole per litre; SBP, systolic blood pressure.
Trends across the surveys tested using logistic regression model adjusted for age and socioeconomic status.
[a]Values presented as number (%); [b]AHA ideal category (1 point); [c] AHA intermediate category (0 point); [d] AHA poor category (0 point); [e]mmol/l x 18 = mg/dl. [f]mmol/l x 38.6= mg/dl; [g] = b + c + d.

A restricted cubic spline curve showed that the risk of AMI decreased continuously with increasing CVH metrics across the range 2–7 (*p*-value for nonlinearity=0.07) (Figure 4). Table 7 shows the associations between CVH metrics and risk of AMI. Men who had ideal CVH metrics had a 72% reduced risk of AMI when compared with those who had poor CVH metrics (HR: 0.28; 95%CI: 0.15–0.55, $p < 0.001$) after adjustment for age, alcohol consumption and SES. On further adjustment for history of CHD and history of type 2 diabetes mellitus, (model 2), the association was minimally attenuated (HR: 0.29; 95%CI: 0.15–0.57, $p < 0.001$). The HR for the association of number of CVH metrics and risk of AMI, using participants with zero (0) score as reference, shows 87% reduced risk among those with 6 or more number of CVH metrics, after adjustment for age, alcohol intake and SES (HR: 0.13; 95%CI: 0.02–0.93, $p=0.042$) (Table 7). The association remained consistent on further adjustment for history of CHD and history of type 2 diabetes mellitus (model 2).

Summary of the associations in study I – IV is shown in Table 7.

Table 7. Summary of results of the associations between cardiovascular health metrics and the risk of cardiovascular events and all-cause mortality

Study (Outcome)		**Number of events/Total**	**Model 1**		**Model 2**	
			HR (95% CI)	P value	HR (95% CI)	P value
Study I (Acute myocardial infarction)	**CVH metrics**	513/2584				
	Poor [a]	381/1608	1	-	1	-
	Intermediate [a]	123/859	0.56 (0.46 – 0.69)	<0.001	0.58 (0.47 - 0.71)	<0.001
	Ideal [a]	9/117	0.28 (0.15 – 0.55)	<0.001	0.29 (0.15 - 0.57)	<0.001

	Number of CVH metrics [b]					
	0	36/154	1 (Reference)	-	1 (Reference)	-
	1	180/733	0.91 (0.64 – 1.30)	0.609	0.94 (0.66 – 1.35)	0.730
	2	165/721	0.85 (0.59 – 1.22)	0.378	0.92 (0.64 – 1.32)	0.637
	3	78/525	0.52 (0.34 – 0.77)	0.001	0.56 (0.37 – 0.83)	0.004
	4	45/334	0.47 (0.30 -0.73)	0.001	0.51 (0.33 – 0.79)	0.003
	5	8/94	0.29 (0.13 – 0.62)	0.001	0.32 (0.15 – 0.70)	0.004
	≥6	1/23	0.13 (0.02 – 0.93)	0.042	0.12 (0.02 – 0.89)	0.038
Study II (CVD death)	**CVH metrics score**	609/2607*				
	Inadequate	130/2607	1	-	1	-
	Average	435/2607	0.57 (0.47–0.70)	<0.001	0.64 (0.52–0.78)*	<0.001
	Optimum	44/2607	0.30 (0.21–0.42)	<0.001	0.35 (0.24–0.49)*	<0.001
Study III (Sudden cardiac death)	**CVH score**					
	0-2	162/1140	1	-	1	-
	3-4	115/1299	0.61 (0.48–0.78)	<0.001	0.70 (0.55–0.90)	0.005
	≥5	3/138	0.15 (0.05–0.48)	0.001	0.17 (0.05–0.53)	0.002
	Behavioural health scores					

	0	46/271	1	-	1	-
	1	135/1145	0.61 (0.43–0.85)	0.004	0.65 (0.47–0.91)	0.013
	2	90/933	0.52 (0.36–0.74)	<0.001	0.61 (0.4–0.87)	0.007
	≥3	9/228	0.20 (0.10–0.41)	<0.001	0.24 (0.12–0.50)	<0.001
	Biological health scores					
	0	39/156	1	-	1	-
	1	183/1598	0.35 (0.25–0.50)	<0.001	0.47 (0.30–0.72)	0.001
	2	53/729	0.23 (0.15–0.35)	<0.001	0.30 (0.18–0.50)	<0.001
	3	5/94	0.18 (0.07–0.45)	<0.001	0.22 (0.08–0.58)	0.002
(All-cause death)	**CVH score**					
	0-2	676/1140	1	-	1	-
	3-4	585/1299	0.74 (0.66-0.83)	<0.001	0.79(0.70-0.88)	<0.001
	≥5	28/138	0.33 (0.23-0.49)	<0.001	0.35 (0.24-0.52)	<0.001
	Behavioural health scores					
	0	177/271	1	-	1	-
	1	629/1145	0.72 (0.61–0.85)	<0.001	0.74 (0.62–0.87)	<0.001
	2	430/933	0.63 (0.53–0.75)	<0.001	0.67 (0.56–0.79)	<0.001
	≥3	53/228	0.30 (0.22–0.40)	<0.001	0.32 (0.23–0.44)	<0.001

	Biological health scores					
	0	118/156	1	-	1	-
	1	816/1598	0.49 (0.40–0.59)	<0.001	0.62 (0.49–0.79)	<0.001
	2	321/729	0.43 (0.35–0.53)	<0.001	0.55 (0.43–0.71)	<0.001
	3	34/94	0.37 (0.25–0.55)	<0.001	0.47 (0.31–0.70)	<0.001
Study IV	**LS7 score**					
(Total stroke)	0-2 (inadequate)	224/1109	1	-	1	-
	3-4 (average)	187/1273	0.65 (0.53– 0.79)	<0.001	0.69 (0.56-0.84)	<0.001
	5-7 (optimal)	17/138	0.49(0.30-0.81)	0.005	0.52(0.32-0.86)	0.01
(Ischaemic stroke)	0-2 (inadequate)	192/1109	1	-	1	-
	3-4 (average)	156/1273	0.63(0.51-0.78)	<0.001	0.67(0.54-0.84)	<0.001
	5-7 (optimal)	14/138	0.47(0.27-0.82)	0.007	0.50(0.29-0.87)	0.014

CVD, cardiovascular disease; CVH, cardiovascular health
Model 1: adjusted for age, alcohol consumption and socioeconomic status
Model 2: Model 1 plus history of coronary heart disease and history of type 2 diabetes mellitus
*Model 2: Model 1 plus high-density lipoprotein cholesterol; use of cholesterol lowering medications, use of antihypertensives, history of coronary heart disease, and history of type 2 diabetes mellitus.

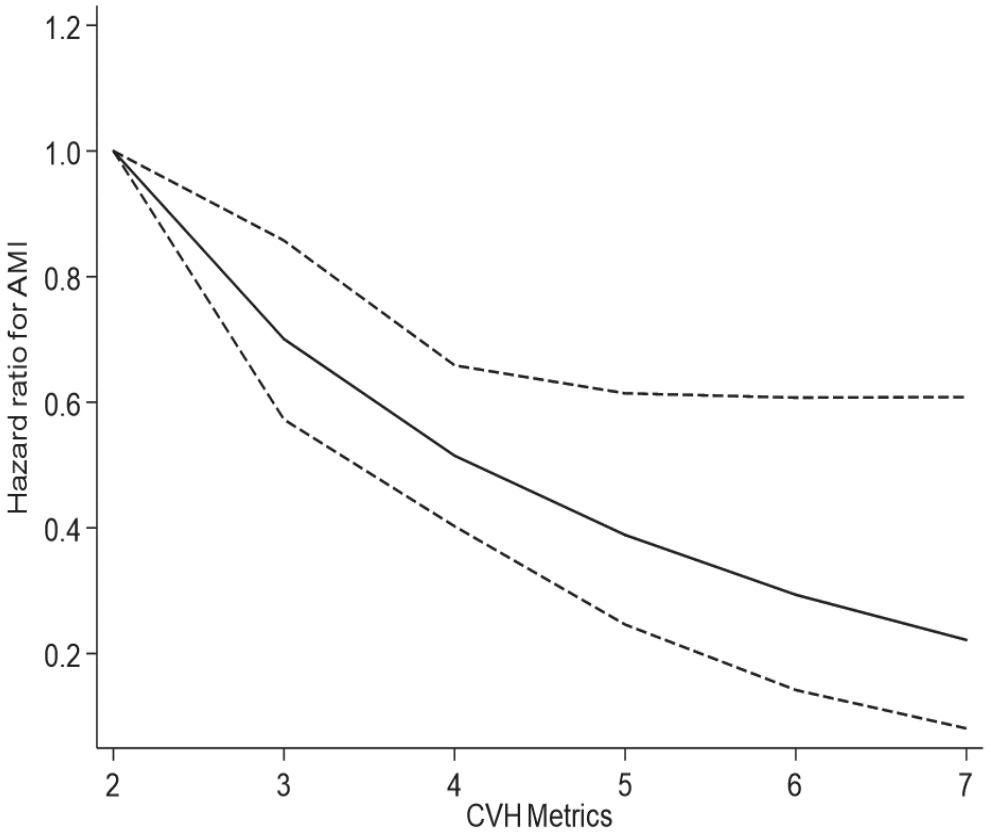

Figure 4. Cubic spline curve of hazard ratio for acute myocardial infarction (AMI) against cardiovascular health (CVH) metrics.
Restricted cubic spline functions were analysed with knots located at 5th, 35th, 65th and 95th percentiles of cardiovascular health metrics distribution in a multivariable adjusted model, with the reference category set at 2. The dashed lines represent the 95% confidence intervals.
The seven scores were grouped into three: poor (0–2), intermediate (3-4) and ideal (5–7). Higher scores represent better ideal CVH metrics.

5.2 STUDY II: CVH METRICS AND RISK OF CVD MORTALITY

At baseline, the mean age (SD) of all study participants was 53.1 (5.1) and 54.7 (4.2) for those who had CVD mortality (Table 5). During the median follow-up years of 25.8 [IQR 18.4–27.9] years, 609 cases of CVD mortality occurred. Among those that had the outcome of event, 246 (40.4%) had a history of CHD at baseline. Among CVD deaths recorded, 44 (7.2%), 435

(71%), and 130 (21.3%) had optimum, average, and inadequate CVH scores, respectively (Table 7).

The distribution of the CVH metrics among the KIHD study participants showed variations in the individual components and in the number of the ideal CVH metrics (Table 8). For the CVH behaviours, 77.9% of the participants attained the ideal physical activity level, 31.3% had ideal BMI, 32.2% never smoked, and <2% met the criteria for an ideal HDS. The cardiovascular health factors showed 12% of the participants had ideal blood pressure, 39% had ideal fasting blood glucose and 25.7% had ideal total cholesterol. However, only one participant achieved all the seven ideal CVH metrics.

A restricted cubic spline curve showed that the risk of CVD mortality increased gradually with increasing CVH score across the range 3–14 *(p*-value for nonlinearity =0.774) (Figure 5). Table 7 shows the association between CVH score and risk of CVD mortality. In analysis that adjusted for age, alcohol consumption and SES, men who had an optimum CVH score had a 70% reduced risk of CVD mortality when compared with those who had an inadequate CVH score (HR: 0.30; 95%CI: 0.21–0.42, p<0.0001). After further adjustment HDL-c, use of cholesterol lowering medication, use of antihypertensive medications, history of CHD and history of type 2 diabetes mellitus, (model 2), the association was minimally attenuated (HR: 0.35; 95%CI: 0.24–0.49, p<.0001). In subsidiary analysis that excluded men with any history of CVD at baseline, the respective association remained consistent (HR: 0.35; 95%CI: 0.21–0.59, p<.0001).

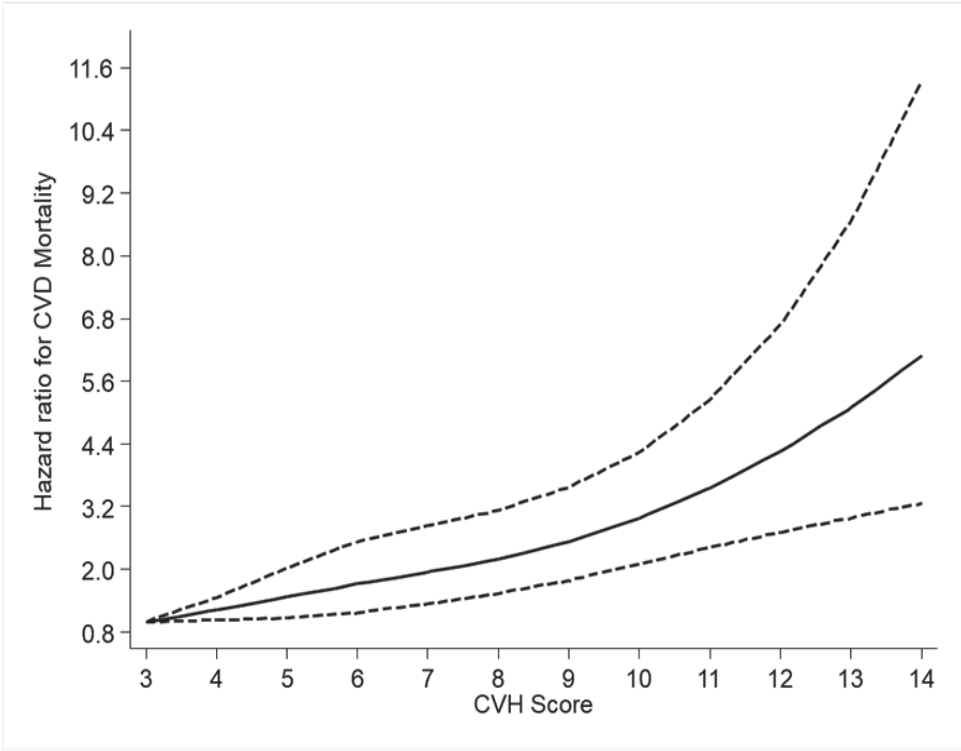

Figure 5. Dose-response curve of hazard ratio for cardiovascular disease mortality against cardiovascular health score.

Restricted cubic spline functions were analysed with knots located at 5th, 35th, 65th and 95th percentiles of cardiovascular health score distribution, with the reference category set at 3; adjusted for age; alcohol consumption; socioeconomic status; high-density lipoprotein cholesterol; use of cholesterol lowering medications, use of antihypertensives, history of coronary heart disease and history of type 2 diabetes mellitus. The dashed lines represent the 95% confidence intervals.

CVD, cardiovascular disease; CVH, cardiovascular health

Participants were assigned a score of 0 if they met the ideal level, with 1 and 2 for intermediate and poor levels respectively, based on the seven CVH metrics. In total, the CVH scores for each subject ranged from 0 to 14, with lower scores representing a better CVH score

Table 8. Distribution of cardiovascular health metrics among participants and based on cardiovascular death

Cardiovascular Health Metrics	Participants[a] (n=2607)	Cardiovascular Disease Death[a] (n=609)	Without CVD death during the follow-up [a] (n=1998)
Physical Activity			
Ideal (150mins/week of moderate-intensity or 75mins/week of vigorous intensity or both)	2032 (77.9)	457 (75)	1575 (78.8)
Intermediate (1-149 mins/week of moderate intensity physical activity or 1-74 mins/week of vigorous intensity or both)	21 (0.8)	5 (0.8)	16 (0.8)
Poor (no physical activity)	554 (21.3)	147 (24.1)	407 (20.4)
Body Mass Index			
Ideal (<25 kg/m^2)	817 (31.3)	149 (24.5)	668 (33.4)
Intermediate (25 – 29 kg/m^2)	1338 (51.3)	309 (50.7)	1029 (51.5)
Poor (≥ 30 kg/m^2)	452 (17.3)	151 (24.8)	301 (15.1)

Healthy Diet Score[b]			
Ideal (4 - 5)	50 (1.9)	10 (1.7)	40 (2.0)
Intermediate (2 – 3)	1242 (48.1)	300 (50.0)	942 (47.5)
Poor (0 – 1)	1290 (50.0)	290 (48.3)	1000 (50.5)
Blood Pressure (mmHg)			
Ideal (SBP <120 and DBP <80)	314 (12.0)	44 (7.2)	270 (13.5)
Intermediate (SBP, 120 – 139 or DBP, 80 – 89)	990 (38.0)	194 (31.9)	796 (39.8)
Poor (SBP ≥ 140 or DBP ≥ 90)	1303 (50.0)	371 (60.9)	932 (46.6)
Fasting Blood Glucose (mmol/l)[c]			
Ideal (<5.55)	1018 (39.0)	207 (34.0)	811 (40.6)
Intermediate (5.55 – 6.99)	1205 (46.2)	273 (44.8)	932 (46.6)
Poor (≥7.00)	384 (14.7)	129 (21.2)	255 (12.8)
Total Cholesterol (mmol/l)[d]			
Ideal (< 5.18)	669 (25.7)	123 (20.2)	546 (27.3)
Intermediate (5.18 -6.21)	1034 (39.7)	226 (37.1)	808 (40.4)
Poor (≥ 6.22)	904 (34.7)	260 (42.7)	644 (32.2)

Smoking Status			
Ideal (never smoked)	839 (32.2)	145 (23.8)	694 (34.7)
Intermediate (previous smokers)	937 (35.9)	218 (35.8)	719 (36.0)
Poor (current smokers)	831 (31.9)	246 (40.4)	585 (29.3)
Number of Ideal Cardiovascular Health Metrics			
0	157 (6.0)	55 (9.0)	102 (5.1)
1	740 (28.4)	208 (34.2)	532 (26.6)
2	725 (27.8)	183 (30.0)	542 (27.1)
3	532 (20.4)	98 (16.1)	434 (21.7)
4	336 (12.9)	59 (9.7)	277 (13.9)
5	94 (3.6)	5 (0.8)	89 (4.5)
6	22 (0.8)	1 (0.2)	21 (1.1)
7	1 (0.0)	0	1 (0.1)

DBP, diastolic blood pressure; mmHg, millimeters of Mercury; mmol/l, millimole per litre; SBP, systolic blood pressure.

5.3 STUDY III: IDEAL CVH METRICS AND RISK OF SCD AND ALL-CAUSE MORTALITY

Table 5 shows the characteristics of the study participants. During a median follow-up time of 25.8 years, 280 cases of SCD and 1289 all-cause deaths were recorded. The mean age at baseline for the 2577 men was 53 years. Only one person achieved all seven ideal metrics at baseline. Most of the participants (91.9%) were in the ideal FBG category. No participant with a behavioural health score of 4 had an SCD event.

A restricted cubic spline curve showed that the risk of SCD decreased continuously with increasing CVH metrics across the range 2–7 (*p* value for non-linearity = 0.54) (Figure 6). Table 7 shows the association between CVH score and the risk of SCD. Men who attained a CVH score ≥5 had an 85% reduced risk of SCD compared with those with a CVH score of 0–2 (HR 0.13; 95%CI 0.03–0.53; p=0.004) after adjustment for age, alcohol consumption and SES. The association was minimally attenuated on further adjustment for a history of CHD and a history of type 2 diabetes mellitus (model 2). Achieving a behavioural health score ≥3 showed a significant relationship with the risk of SCD compared with those with a score of 0 (HR 0.20; 95%CI 0.10–0.41; p <0.001). A similar significant association was observed with biological health scores.

For the association between CVH score and risk of all-cause mortality, the risk of all-cause mortality decreased continuously with increasing CVH scores across the range 2–7 (p value for non-linearity=0.16) (Figure 7)). Men who had a minimum CVH score of 5 were at 67% lower risk compared with those with a CVH score of 0–2 after adjustments for age, alcohol consumption and SES (Table 7). An ideal behavioural factor also showed a significant association, with men who achieved a behavioural health score of at least 3 having a 70% lower risk of all-cause mortality compared with those with a score of 0 (HR 0.30; 95%CI 0.22–0.40; p <0.001). These associations between CVH scores and the risk of SCD and all-cause mortality remained statistically significant after a sensitivity analysis excluding participants with a previous history of CHD at baseline.

In our analysis of the association of the individual components of CVH metrics and risk of SCD and all-cause mortality, an ideal BMI is associated with a 50% reduced risk of SCD. Specifically, ideal levels of BMI, smoking status, blood pressure, FBG and total cholesterol contributed significantly to a reduced risk of SCD. Men who achieved three or all four of the ideal behavioural factors had 80 and 70% lower risk of SCD and all-cause mortality, respectively, compared with those with no ideal behavioural factor.

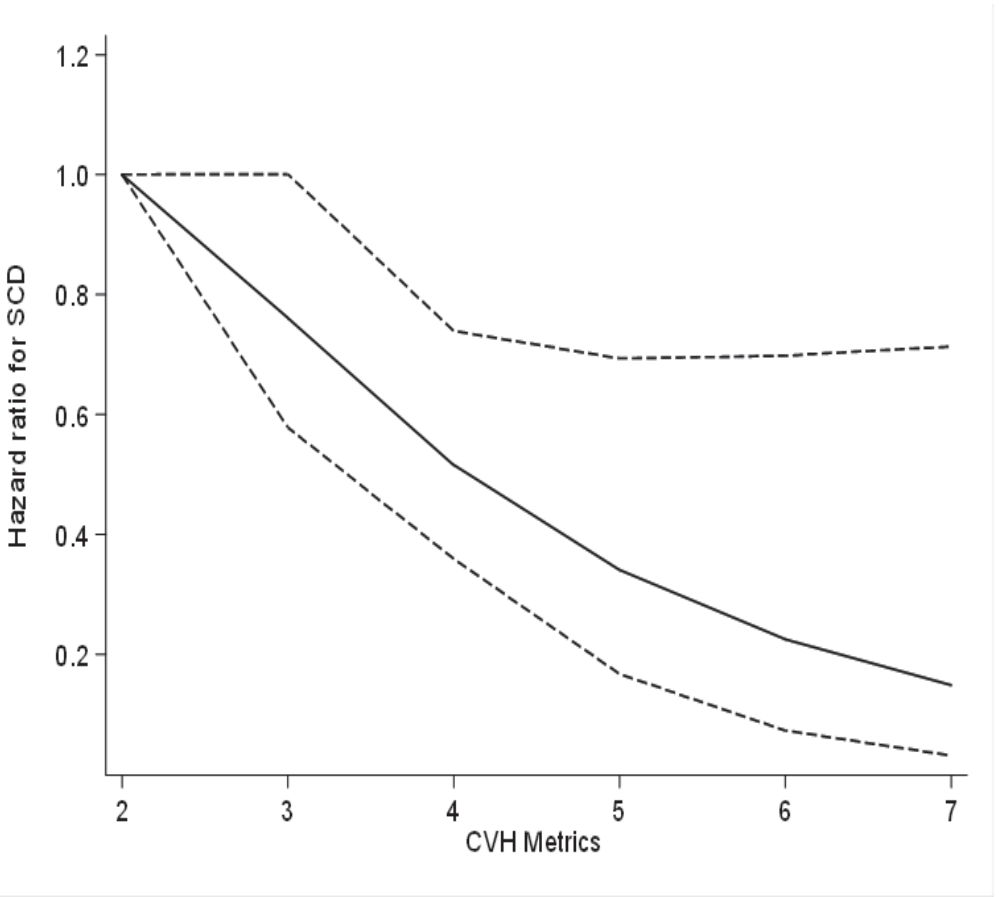

Figure 6. Restricted cubic curve of hazard ratio for sudden cardiac death (SCD) against cardiovascular health (CVH) metrics.

The seven scores were grouped into three: poor (0–2), intermediate (3-4) and ideal (5–7). Higher scores represent better ideal CVH metrics.

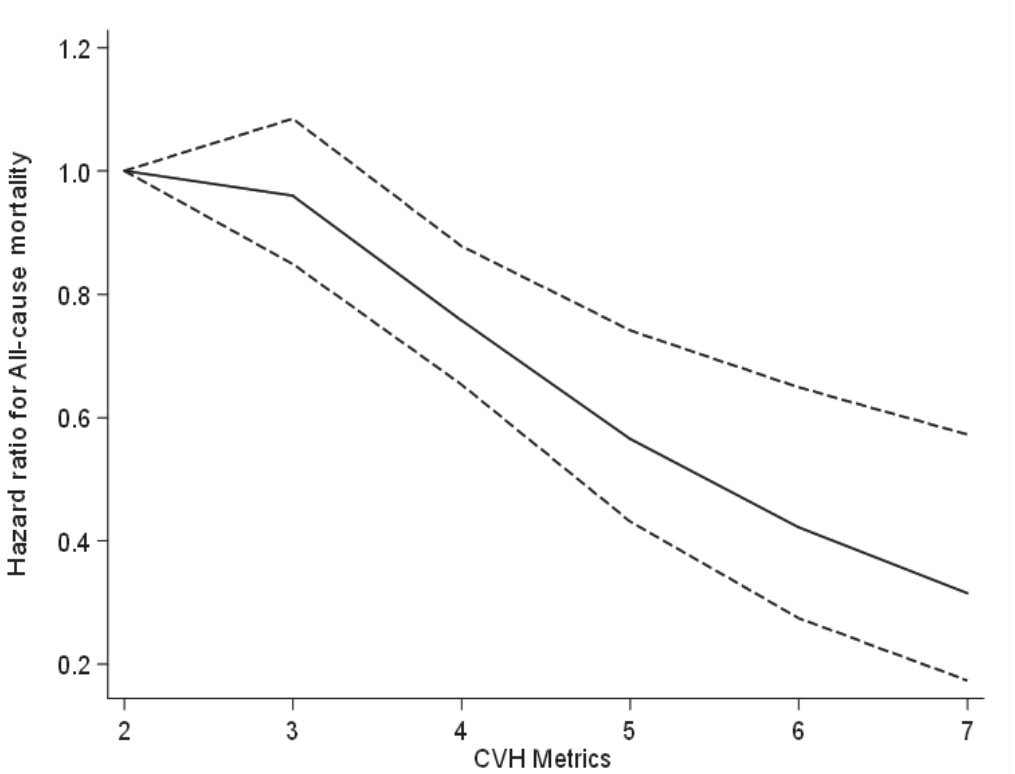

Figure 7. Restricted cubic curve of hazard ratio for all-cause mortality against cardiovascular health (CVH) metrics.
The seven scores were grouped into three: poor (0–2), intermediate (3-4) and ideal (5–7). Higher scores represent better ideal CVH metrics.

5.4 STUDY IV: LIFE'S SIMPLE7 AND THE RISK OF STROKE

During a median follow-up period of 26 (IQR, 16-30) years, 428 total stroke and 362 ischaemic stroke events were recorded among 2520 men. The baseline characteristics of the participants according to the stroke events and LS7 score are shown in Table 5. The mean age of participants who developed total and ischaemic stroke was 54.2 years. Restricted cubic spline curves showed that the risk of total stroke and ischaemic stroke decreased continuously with increasing LS7 metrics across the range 2-6 (*p*-values for nonlinearity for stroke and ischaemic stroke were 0.65 and 0.73 respectively) (Figure 8).

Table 7 shows the associations between LS7 and the risk of total and ischaemic stroke. Men who achieved at least five LS7 score (optimal) had a 48% lower risk of total stroke and 50% reduced risk of ischaemic stroke, when compared with those with 0 to 2 LS7 score (inadequate), after adjustment for potential confounders (HR, 95%CI: 0.52, 0.32 – 0.86 for total stroke and 0.50, 0.29 – 0.87 for ischaemic stroke).

Sensitivity analyses excluding men with history of CHD showed similar associations between LS7 and stroke risk following adjustment for age, alcohol consumption and SES (model 1). There was a 45% and 47% reduced risk of total and ischaemic stroke among men with optimal LS7 compared to those with inadequate LS7, respectively. Further analysis in the subgroup population without a history of type 2 diabetes mellitus showed that participants with optimal LS7 had 42% and 44% lower respective risk of total and ischaemic stroke than those with inadequate LS7 (p= 0.06 and 0.07 respectively)**.**

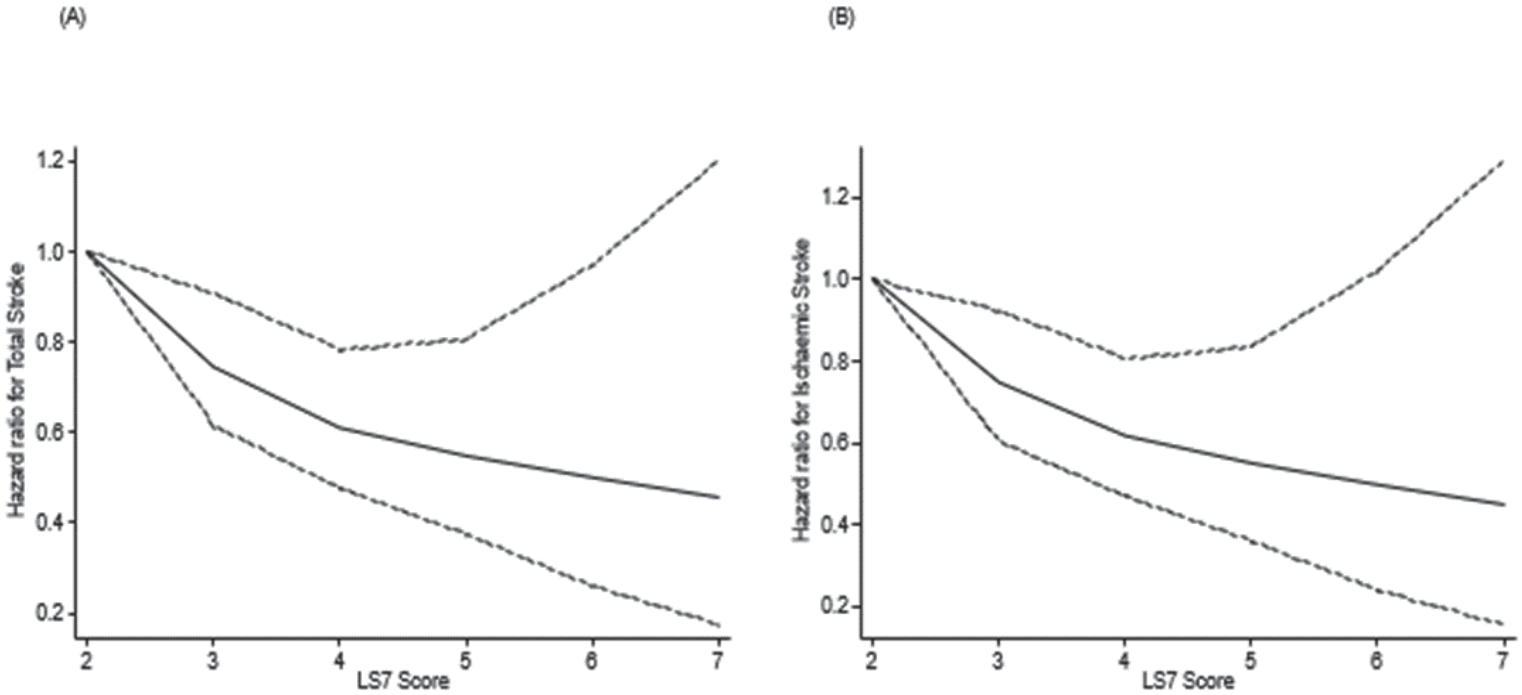

Figure 8. Restricted cubic curve of hazard ratio for total stroke (A) and ischaemic stroke (B) against Life's Simple 7 (LS7) score.

The LS7 score was then categorized into three groups: 0 – 2 (inadequate); 3 – 4 (average); and 5-7 (optimal). Higher scores represent better ideal CVH metrics.

5.5 SUMMARY OF RESULTS

The summary of the main results is presented in Table 9.

Table 9. Summary of results

Sub-study	Design	Study	N	No. of events (AMI, CVD death, SCD, all-cause death and stroke)	The main results
Study I	Prospective	KIHD	2584	513	Ideal CVH metrics was associated with 72% lower risk of AMI
Study II	Prospective	KIHD	2607	609	Optimum CVH score was associated with reduced risk of CVD mortality
Study III	Prospective	KIHD	2577	280 and 1289	Ideal CVH metrics at baseline was linearly associated with reduced risk of SCD and all-cause mortality
Study IV	Prospective	KIHD	2520	326 and 428	Optimal Life's Simple 7 score at baseline was associated with lower risk of total and ischaemic strokes

AMI, acute myocardial infarction; CVD, cardiovascular disease; KIHD, Kuopio ischaemic heart disease; N, number of participants; SCD, sudden cardiac death

6 DISCUSSION

The association of CVH metrics and the risk of cardiovascular events is summarised in Figure 9.

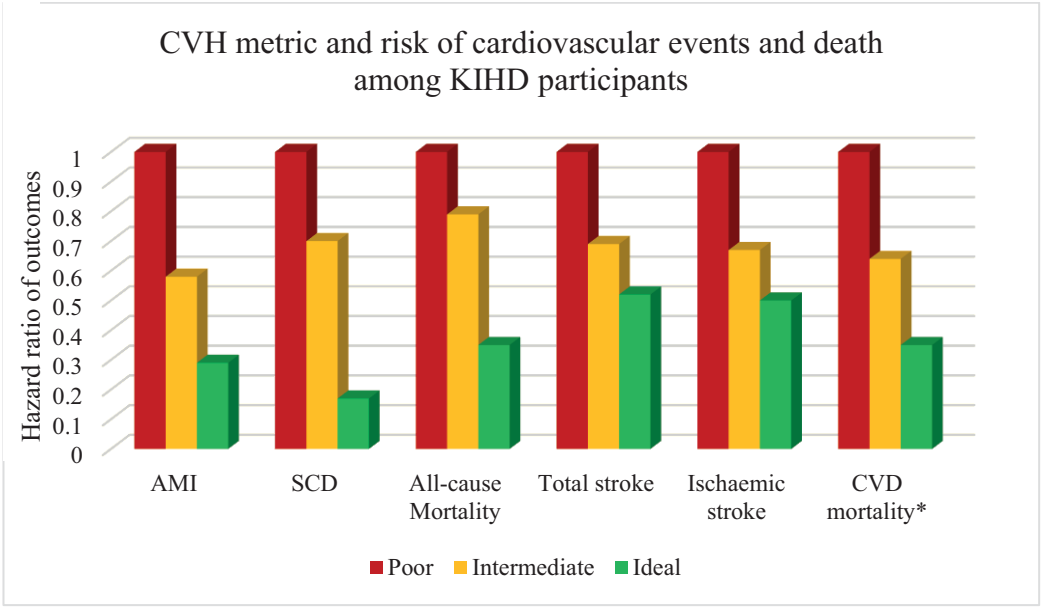

Figure 9: Summary of CVH metrics and the risk of cardiovascular events among KIHD study participants

*CVH score used was inadequate, average, and optimum corresponding to poor, intermediate and ideal in the figure; AMI, acute myocardial infarction; CVD, cardiovascular disease; CVH, cardiovascular health; SCD, sudden cardiac death

6.1 METHODOLOGICAL ASPECTS

The associations between risk factors and outcome events are revealed in prospective epidemiological studies. However, asymptomatic diseases may alter lifestyle behaviours as well as risk factors, thereby concealing true associations or perhaps reversing the causation. This could lead to lack of independence and confounding (Brotman et al., 2005). Additionally, individual variabilities, proper estimations and accurate measurements of exposures may affect the true associations.

The prospective nature of this research makes it appropriate to investigate the association between CVH metrics and the risk of cardiovascular events and mortality. Thus, with consistent evidence in the association of CVH metrics and the risk of cardiovascular events from different observational studies, causation may be inferred (Hill, 1965). This present research included middle-aged men at baseline with high participation rate; and according to the WHO, more than 30% of mortality in Finnish men is attributed to CVD (World Health Organization, 2018). This makes the study population for this research appropriate and the long follow-up proper to assess the effects of behavioural and biological health factors on future cardiovascular events and mortality. Additionally, the area of this study, eastern Finland, is known for its high prevalence of atherosclerotic CVDs, providing a suitable opportunity to investigate the association of CVH metrics and risk of cardiovascular events in men. Although the results may be generalized in male populations, it is also important to confirm the association in female populations.

The present population-based cohort study, involving men from eastern Finland, provides evidence that CVH metrics, as defined by AHA, is associated with AMI, CVD mortality, SCD, stroke and all-cause mortality. In this study, the better the ideal CVH score, the lower the risk of the cardiovascular events (Figure 9). However, very few participants attained the ideal levels of all the factors involved in the CVH metrics. The inverse relationship between ideal CVH metrics and risk of cardiovascular events were consistent irrespective of the CVH score range.

The categorization of CVH metrics in Studies I, III and IV was based on a conventional approach similar to other cohort studies worldwide (Dong et al., 2012, Kesireddy et al., 2019, Lin et al., 2015, Zhou et al., 2018) with score ranging from 0 to 7, while Study II used a score range of 0 to 14, also used in some other longitudinal studies (Ahmad et al., 2019, Garg et al., 2018, Gaye, Tafflet et al., 2017). Both CVH scoring types were consistent in their associations with cardiovascular events in the present study, thus making the findings of this research comparative with other global studies in different population groups. Therefore, it emphasizes the need to embrace AHA's CVH metrics for CVD prevention in high-risk populations and at individual levels to reduce the burden of CVD in Finland and globally. However, measures to improve on each of the seven components of the CVH metrics can vary amongst populations and countries, depending on existing lifestyles and health promotion programmes. For example, a smoking cessation programme may not be as effective in regions with already existing similar programmes, compared to an exercise programme in areas that initially do not take physical activity as a health priority. Specific example could be seen in a Brazilian versus a Finnish (present study) population with the frequency of ideal physical activity of 25% in Brazil (Machado et al., 2018) and 78% in Finland. This invariably implies that a health intervention on physical activity should be targeted more in Brazil for improvement on CVH metrics than in Finland. Therefore, interventions and health promotions based on this data need to consider the importance of each of the specific risk factors to a defined population.

The main outcomes in the present study are AMI, CVD mortality, stroke, SCD and all-cause mortality. The collection of the outcome events in this study were reliable based on data from the Finnish National Death Registry, national hospital discharge and death registers, due to the linkage of personal identity codes of the participants to these registers. The sources of the information were interviews, hospital documents, death certificates medico-legal and autopsy reports. The diagnostic classification of events was based on symptoms, electrocardiographic (ECG) findings, cardiac enzyme elevations, autopsy findings and history of CHD, together with the clinical and ECG findings of the paramedic staff.

6.2 CARDIOVASCULAR METRICS AND ACUTE MYOCARDIAL INFARCTION

In this study, middle-aged Finnish men with ideal CVH metrics had a reduced risk of AMI compared with those with poor CVH metrics. There was an inverse relationship between the number of CVH metrics and risk of AMI and a graded decline in the number (percentage) of participants that attained higher numbers of health metrics from 1 to 7 in this cohort. The risk of AMI decreased continuously in a linear dose-response manner with increasing number of CVH metrics. These strong associations were independent of several established risk factors.

No previous study has evaluated the association between ideal CVH and risk of AMI among middle-aged Finnish men. Our current results were consistent with previous findings from the Tromsø study which has evaluated a relationship between CVH and AMI among a Norwegian population (Wilsgaard et al., 2015); and the Prospective Epidemiological Study of Myocardial Infarction (PRIME) study (Gaye et al., 2017). In our study, men with ideal CVH (≥5 CVH metrics) at baseline had 71% lower risk of AMI compared with those that had poor CVH (0–2 CVH metrics). The Tromsø study reported about 13.7% reduction in incident myocardial infarction in men with ideal health metrics scores (≥4) compared to those with low health metrics scores (≤3) (Wilsgaard et al., 2015), while the PRIME study reported 84% reduced risk of myocardial infarction in men with ideal CVH status (5–7) compared to those with poor CVH status (0–2) (Gaye et al., 2017). Other studies have also substantiated similar inverse associations between CVH metrics and risk of CHD (Polonsky et al., 2017, Lachman et al., 2016, Xanthakis et al., 2014, Han et al., 2018).

There was only one participant who achieved all the seven CVH metrics, similar to the cohort in the PRIME study (Gaye et al., 2017); also yielding a lower percentage (< 0.1%) as compared to 0.1% in the ARIC population (Folsom et al., 2011) that achieved all the seven components of CVH. Similar to the northern Manhattan study (NOMAS) cohort (Dong et al., 2012), a small sample (4.5%) of our participants had 5 or more ideal health

factors, which is not optimal. The highest percentage of our participants (35.1%) that suffered definite AMI was found among men who had only one ideal metric. A CVH metrics score from one to two non-significantly reduced the risk of AMI by 6% when compared with men with none. However, among men who achieved additional two components (i.e., having 3 number of CVH metrics), there was a 48% significant decrease for the risk of AMI compared with those that had none (Table 7). This also shows that an additional achievement of CVH metrics from two to three can reduce the risk of definite AMI by 33%. This result supports the necessity for measures to be initiated to improve the management of risk factors for AMI among Finnish men. Non-smoking, increasing physical activity, healthy diet, and weight loss campaigns should be reinforced and appropriate policies to support them should be encouraged. While adequate control of blood glucose, total cholesterol and BP should remain paramount among individuals and health professionals. Our data hypothetically demonstrates the benefits in reducing the risk of AMI from intermediate (42%) to ideal (71%) CVH metrics when compared with poor CVH metrics. This supports the concept that interventions aimed at improving intermediate (3–4) to ideal (≥5) CVH metrics will cause over 25% reduction in the risk of AMI and its associated burden. Thus, promoting evidence-based interventions addressing the achievement of 5 or more of the seven ideal health metrics will reduce the burden of AMI among the Finnish population. The findings of this study suggest the importance of CVH metrics as a measure for AMI prevention to necessitate prompt and appropriate preventive and treatment measures. This will help reduce the risk of developing adverse cardiovascular outcomes in general.

6.3 CARDIOVASCULAR HEALTH METRICS AND CARDIOVASCULAR DISEASE MORTALITY

Using the AHA CVH metrics, we have assessed the association between CVH score and risk of CVD mortality among an apparently healthy Scandinavian population. The study showed that men with an optimum or average CVH score had substantially lower risk of CVD mortality when

compared with men with inadequate CVH score. The associations were independent of several established risk factors. Additionally, this finding remained persistent after the exclusion of men with any history of CVD at baseline. A dose–response analysis showed that the risk of CVD mortality increased gradually with increasing CVH score across the range 3–14.

Our recent findings are consistent with earlier studies conducted in other populations. In the Northern Manhattan Study, the relationship between the number of ideal CVH metrics and the risk of CVD was studied. The study revealed that there was a 59% lower risk of CVD events and 41% lower risk of all-cause mortality among participants with 5–7 ideal CVH metrics, when compared with those having 0–1 ideal CVH metrics (Dong et al., 2012). Similar results were seen using data from the NHANES, where participants who had at least five ideal CVH metrics had reduced mortality from diseases of the circulatory system when compared to those who had no ideal health metric. Also, the risk for mortality from CVD was decreased by 88%, when comparing participants with minimum of 5 to those with no ideal CVH metrics (Ford, Greenlund & Hong, 2012). The Framingham Offspring Study reported a similar result, showing a unit increase in CVH score was associated with a 13% reduced risk of CVD. Each participant had the CVH score constructed by recoding the seven metrics, with a score of 1 indicating the ideal category for AHA metrics (versus 0 for non-ideal metrics); thus, the CVH score varied from a minimum of 0 (indicating poor CVH) to a maximum of 7 (reflecting ideal cardiovascular health) (Xanthakis et al., 2014). This was reverse of the coding of the CVH score in this current study (where 0 was ideal, 1 for intermediate and 2 for poor levels), nevertheless the results were similar.

Among the Chinese population, Zhou and colleagues found an inverse association between ideal CVH metrics and risk of many cardiovascular endpoints including total CVD events and deaths from all cause and CVD (Zhou et al., 2018). Similar findings were observed in the Kailuan Study, where a strong inverse relationship between ideal CVH metrics and risk of CVD was reported, with participants having 6–7 ideal CVH metrics had 82% lower risk for CVD events when compared to those with 0 ideal CVH metrics (Wu et al., 2012, Liu et al., 2014). This study

provides further insight on the prevalence of AHA CVH metrics among middle-aged men living in Eastern Finland. The distribution of the individual components of the metrics shows that most men attained the ideal physical activity according to AHA CVH metrics. However, ideal HDS was the least achieved among this KIHD study population.

Similar findings have been reported in the United States. For instance, in the Aerobics Center Longitudinal Study (ACLS) cohort (Artero et al., 2012), and the Mediators of Atherosclerosis in South Asians Living in America (MASALA) study participants, where more than half of the participants had ideal physical activity while very few achieved the ideal HDS or quality diet (Yang et al., 2012). Several studies have reported independent associations of individual risk factors such as physical inactivity, unhealthy diet, smoking, high blood pressure, overweight or obesity and the risk of CVD outcomes (Yang et al., 2012, Jahangir, De Schutter & Lavie, 2014, Stevens et al., 2016, Buttar, Li & Ravi, 2005, Lichtenstein et al., 2006, Cepeda-Valery et al., 2011, Taghizadeh, Vonk & Boezen, 2016, Artham et al., 2008, Carter et al., 2015, Warburton, Nicol & Bredin, 2006, Park et al., 2012). However, focusing on these factors individually can mask their cumulative effects on CVD mortality. For instance, in the current study, 77.9% of the participants maintained ideal physical activity level, whereas in the same population group, only 1.9% attained the ideal HDS. If physical activity is isolated as an approach to reduce CVD mortality among this population group, it may not achieve the set goal in the prevention of CVD mortality, if healthy diet is not considered and improved. Optimum CVH score compared to inadequate CVH score is strongly associated with reduced risk of CVD mortality among the Scandinavian population. Therefore, AHA CVH metrics is a welcome approach for public health awareness and to monitor the cardiovascular health among Scandinavian population. However, a future study is needed to investigate how CVH score can also be applied in Scandinavian women for the risk of CVD mortality.

6.4 CARDIOVASCULAR HEALTH METRICS AND RISK OF SUDDEN CARDIAC DEATH AND ALL-CAUSE MORTALITY

This was the first study to assess the association of AHA's CVH metrics and the risk of SCD among the general population, men with a CVH score of 5–7 at baseline had 83% reduced risk of SCD after a median follow-up period of 25.8 years. Similarly, there was 65% lower risk of all-cause mortality among men with a CVH score of at least 5 compared with those with a CVH score of 0–2. The associations were consistent with linear dose–response relationships.

The distribution of ideal CVH metrics among the participants in our study is comparable with earlier studies. The most frequent metrics in our study was an ideal FBG, similar to the People's Republic of China-USA (PRC-USA) Collaborative Study cohort (Zhou et al., 2018). Also, both the PRC-USA Collaborative Study and our study have diet as the least frequent ideal metrics. There is no similar study on the association of the AHA's CVH metrics and the risk of SCD, but researchers have shown existing associations between ideal CVH and some cardiovascular outcomes and mortality (Dong et al., 2019, Dong et al., 2012, Fang, Jiang & Fan, 2016, Lachman et al., 2016). Thus, in the PRC-USA Collaborative Study, a 54% lower risk of all-cause mortality was observed among participants with four to seven ideal metrics compared with those with zero to two ideal metrics (Zhou et al., 2018). Similar findings were shown in the northern Manhattan study and the Three City study (Dong et al., 2012, Gaye et al., 2017) and were summarized in a recent meta-analysis of prospective studies (Fang, Jiang & Fan, 2016). Our findings are consistent with existing evidence on the association of ideal CVH and the risk of all-cause mortality.

Obesity, smoking, hypertension, and diabetes have been identified as risk factors for SCD and vigorous physical activity can increase the risk of SCD (Laukkanen, Jari A. et al., 2013, Kuriachan, Sumner & Mitchell, 2015). Our study shows a similar pattern of association. It may not be surprising that ideal physical activity did not show an independent significant association with the risk of SCD compared with those participants with poor physical activity because it incorporated vigorous physical activity,

which might be a cause of sudden death (Kuriachan, Sumner & Mitchell, 2015, Albert et al., 2000, Kohl et al., 1992). The findings remained consistent after excluding men with a previous history of CHD at baseline.

The assessment for the applicability of the AHA's CVH metrics among middle-aged Finnish men, who are at higher risk of death from diseases of the circulatory system (Official Statistics of Finland, (OSF), 2018), shows that the metrics may be applicable to European populations and could be used for health promotion purposes to reduce the burden of CVD and future SCD risk, limiting the possible use of drugs or electrical devices for prevention purposes (Japundžić-Žigon et al., 2018). Thus, campaigns and policies that are aimed at improving CVH metrics should be encouraged. Health professionals can use these metrics to assess and identify people at risk of SCD and encourage early modification of the CVH metrics to improve quality of life. To improve levels of behavioural factors, participants can start from those factors that they can realistically control.

6.5 LIFE'S SIMPLE 7 AND STROKE

In this prospective study of middle-aged Finnish population, higher LS7 score, a measure of AHA's CVH metrics, was associated with considerably reduced risk of total and ischaemic stroke. Men who adhered to at least five of the LS7 factors (optimal), compared with those who achieved inadequate LS7 level (0 to 2), had a 48% and 50% lower risk of total and ischaemic stroke, respectively.

Consistent with our findings, a US study reported that white participants in the optimal CVH category, compared with those in the inadequate CVH category, had 51% lower risk of incident stroke (Kulshreshtha et al., 2013). This association, however, was not significant among the black participants in the study, showing possible variations for AHA's CVH metrics application in different population groups. However, a pooled study-level analysis of 127,536 participants from nine prospective observational studies in the general population, showed that those participants with the highest ideal CVH metrics had 69% lower risk of stroke (with 3390 recorded stroke events) (Fang, Jiang & Fan, 2016).

Another meta-analysis supports this finding with approximately 70% lower risk of stroke among participants in the most category of ideal CVH metrics (Guo, Zhang, 2017); although the main outcome event is not specific for ischaemic stroke due to the limited studies on the association between AHA's CVH metrics or LS7 and the risk of ischaemic stroke. Nevertheless, a study from China, with specific outcomes of total and ischaemic stroke, found that individuals who achieved the highest ideal CVH metrics had 76% and 78% lower risk of total and ischaemic strokes respectively (Qian et al., 2013).

In this current study, participants with optimal LS7 at baseline had lower risk of stroke than those in the inadequate LS7 group, implying that maintaining optimal LS7 can reduce future risk of total and ischaemic stroke in the Finnish population. This contrasts with earlier studies that have shown no evidence of associations between CVH metrics and stroke in European populations (Lachman et al., 2016, Gaye et al., 2017). Our study thus provides evidence that optimal LS7 can be targeted by Europeans, particularly the Finnish populace, and if maintained can reduce the future risk of total stroke, and ischaemic stroke specifically. It further confirms the cardiovascular benefits of achieving more of AHA's ideal CVH metrics among European populations. Therefore, there is need to target the ideal components of CVH metrics in the general population. Thus, not smoking, healthy diet, regular physical activity, maintaining normal BMI, controlling BP, normal blood glucose and total cholesterol levels should be a concern for middle-aged individuals for stroke risk reduction.

Awareness of the LS7 can ensure the acceptability of a scoring system that enables people place themselves in the corresponding inadequate, average or optimal LS7 groups, with the goal to achieving or maintaining optimal LS7. Furthermore, since the risk factors involved in the LS7 are well-known modifiable risk factors (which have shown significant relationship with reduced risk of stroke (Imano et al., 2018, De Caterina et al., 2010, Howard, McDonnell, 2015, O'Donnell et al., 2010)), it makes it easier to be tracked, upgraded and monitored. It also means that if achieving higher LS7 scores become a target for health improvement and promotion, the associated future risk of strokes can be reduced in the

general population. Thus, healthcare workers can use this LS7 approach for stroke risk classification in people; and for monitoring and measuring the progress for a healthier lifestyle.

6.6 STRENGTHS AND LIMITATIONS

The strengths of the study lie in the relatively large number of participants, being a representative sample of middle-aged male population in eastern Finland. This cohort was not clinically selected, and the participation rate was high (82.9%). They were well characterized and followed-up for a long period. The prospective nature of the study and long follow-up period is another strength to study the effect of CVH metrics on outcome data. Data on AMI, SCD, stroke, CVD mortality and all-cause mortality were collected through hospital documents, death certificates, autopsy reports and medico-legal reports, which may have better validity than self-reported diagnoses. Furthermore, there were no losses to follow-up in this well-documented outcome data due to participants' linkage to the unique Finnish national code available to all residents.

The analyses in this study controlled for many covariates based on their role as established CVD risk factors and potential confounders. However, some limitations of this research warrant mentioning. First, the results are based on Finnish men and therefore cannot be generalized to other population groups, since it did not include women and other ethnicities. Also, causality cannot be confirmed because of the observational design. Second, there could be misclassification bias given the use of self-administered questionnaires to obtain information on some of the components of the CVH metrics. Also, the substitution of salt intake with the intake of processed meat might have some effect in the computation of the HDS in this research. However, in the Finnish diet and lifestyle recommendations on the use of salt in the 1980s, the intake of processed meats fell under convenience foods to be avoided because they were among the sources of excess salt in the Finnish diet (Kuusipalo, Määttänen-Bourke, 2013). Third, given the long period of follow-up and the use of baseline assessments, it is likely that the levels of CVH metrics may change over time. This could be due to some potential factors such as

ageing, disease, modification of lifestyle and medication use, such as use of lipid-lowering and antihypertensive drugs, thereby leading to the underestimation of true associations due to regression dilution bias. Therefore, it would be interesting to investigate further how the longitudinal evolution of the CVH metrics or interventions to improve ideal CVH influences the rates of cardiovascular events and all-cause mortality.

7. CONCLUSIONS

Based on the findings from the studies I to IV, the following four conclusions were made:

1. Ideal CVH metrics was strongly and continuously associated with the risk of AMI, among middle-aged Finnish men. Fewer men achieved ideal CVH levels; thus, applicability of AHA's CVH metrics among Finnish population should be encouraged and promoted with a target to move the general population towards achieving ≥5 components of the CVH metrics.
2. The CVH score was strongly and continuously associated with the risk of CVD mortality among a middle-aged Finnish population, and this was independent of other conventional risk factors. This shows the value of coexistent effects of risk factor combinations on the risk of fatal CVD events in a male population.
3. Baseline ideal CVH values are strongly and linearly associated with the future risk of SCD and all-cause mortality among Finnish men.
4. There is a strong inverse linear association between baseline LS7 scores and the risk of total and ischaemic strokes among a middle-aged male Finnish population. The study emphasizes the importance of risk factor control and beneficial lifestyle in stroke risk reduction.

8. RECOMMENDATIONS

8.1 RECOMMENDATIONS FOR CARDIOVASCULAR DISEASE PREVENTION

In this thesis, the results indicate that higher levels of ideal CVH metrics, as defined by the AHA, were associated with reduced future risk of AMI, stroke, CVD mortality, SCD and all-cause mortality. Many factors are associated with CVD risk, however, focusing on improving one lifestyle risk factor may not proffer the expected protective effect. Thus, having a composite of risk factors as included in the CVH metrics, and aiming to improve them collectively could be a better approach towards reducing future risks of cardiovascular events. Based on this work and previously published studies, maintaining ideal CVH metrics may be potentially beneficial in preventing cardiovascular events.

In order to lower the risk of AMI, stroke, CVD mortality, SCD and all-cause mortality, the general population should be encouraged to target and sustain the ideal levels of physical activity, BMI, blood pressure, blood glucose and total cholesterol levels. They should also be advised to quit smoking or to remain non-smokers, while maintaining a healthy diet. These, collectively, proffer a better way towards improving cardiovascular health than focusing on improving only one of the components of CVH metrics. Therefore, interventions that will help the population to achieve more ideal CVH metrics should be emphasized and embraced as a wide scale health promotion tool to reduce risk of cardiovascular events and improve CVH in the general population.

Furthermore, healthcare providers can use the optimal CVH scores or the ideal CVH metrics as a target in treating and promoting better cardiovascular health, while policy makers can develop health policies that will improve the cardiovascular health in the general population. Consequently, the outcome of this research can have significant positive impact on national health and socio-economy of Finland, Europe, and the world.

8.2 RECOMMENDATIONS FOR THE FUTURE

Further research is needed in this field to ascertain if the protective association of higher ideal CVH metrics on cardiovascular events and all-cause mortality can be replicated among Finnish women and other ethnicities. The AHA's CVH metrics has been studied extensively in North America and Europe than in other regions of the world. The way forward will be further study on this metric's applicability in other regions, for example in Africa, for the possible development of CVD preventive measures in such areas. Also, the trends in changes of the CVH metrics and interventions on the included factors over the period of follow-up among study participants should be studied to confirm the results of our studies. Additionally, CVH metrics can be examined in association with the risk of other chronic disease outcomes, such as cancer and diabetes.

In the future, introducing CVH metrics in form of a digital application for portable devices and making it accessible, can be a useful tool for people to calculate their CVH metrics at ease. If this is promulgated, it can trigger people's interest to monitor and improve their CVH scores, which when maintained, can reduce CVD burden and improve CVH in general. Furthermore, future research and results in Finland can be used as evidence to upgrade the FINRISK-calculator developed by the Finnish institute of health and welfare (THL), which currently, is limited to myocardial infarction or CHD and stroke, with selected risk factors.

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ORIGINAL PUBLICATIONS (I - IV)

I

Ideal cardiovascular health and risk of acute myocardial infarction among Finnish men

Isiozor N M, Kunutsor S K, Voutilainen A, Kurl S, Kauhanen J and Laukkanen J A

Atherosclerosis 289; 126–131**,** 2019

II

American heart association's cardiovascular health metrics and risk of cardiovascular disease mortality among a middle-aged male Scandinavian population

Isiozor N M, Kunutsor S K, Voutilainen A, Kurl S, Kauhanen J and Laukkanen J A

Annals of Medicine 51(5-6): 306-313, 2019.

III

Association between ideal cardiovascular health and risk of sudden cardiac death and all-cause mortality among middle-aged men in Finland.

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Nzechukwu M Isiozor[1], Setor K Kunutsor[2,3], Ari Voutilainen[1], Sudhir Kurl[1], Jussi Kauhanen[1] and Jari A Laukkanen[1,4,5]

Abstract

Background: Strong associations have been demonstrated between the American Heart Association's cardiovascular health (CVH) metrics and various cardiovascular outcomes, but the association with sudden cardiac death (SCD) is uncertain. We examined the associations between these CVH metrics and the risks of SCD and all-cause mortality among men in Finland.

Methods and results: We used the prospective population-based Kuopio Ischaemic Heart Disease cohort study, which consists of men between 42 and 60 years of age at baseline. CVH metrics were computed for 2577 men with CVH scores at baseline ranging from 0 to 7, categorized into CVH scores of 0–2 (poor), 3–4 (intermediate) and 5–7 (ideal). Multivariate Cox regression models were used to estimate the hazards ratios (HRs) and 95% confidence intervals (CIs) of ideal CVH metrics for SCD and all-cause mortality. During a median follow-up period of 25.8 years, 280 SCDs and 1289 all-cause mortality events were recorded. The risks of SCD and all-cause mortality decreased continuously with increasing number of CVH metrics across the range 2–7 (p value for non-linearity for all <0.05). In multivariable analyses, men with an ideal CVH score had an 85% reduced risk of SCD compared with men with a poor CVH score (HR 0.15; 95% CI 0.05–0.48; $p = 0.001$). For all-cause mortality, there was a 67% lower risk among men with an ideal CVH score compared with those with a poor CVH score (HR 0.33; 95% CI 0.23–0.49; $p < 0.001$).

Conclusions: Ideal CVH metrics were strongly and linearly associated with decreased risks of SCD and all-cause mortality among middle-aged men in Finland.

Keywords

Cardiovascular health metrics, sudden cardiac death, all-cause mortality, risk factors, men

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Introduction

Sudden cardiac death (SCD) accounts for about half of all deaths from cardiovascular disease (CVD).[1] Estimates from death certificate data suggest that 15% of all deaths in western countries are caused by SCD.[2] Common risk factors for CVD may contribute to the development of SCD and risk stratification techniques can help to identify patients at risk of SCD, although effective prevention is challenging.[2]

A decade ago, the American Heart Association (AHA) developed metrics for ideal cardiovascular health (CVH) to assess the cardiovascular status of

[1]Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Finland
[2]National Institute for Health Research, Bristol Biomedical Research Centre, University Hospitals Bristol NHS Foundation Trust and University of Bristol, UK
[3]Translational Health Sciences, Bristol Medical School, Musculoskeletal Research Unit, University of Bristol, UK
[4]Faculty of Sport and Health Sciences, University of Jyvaskyla, Finland
[5]Central Finland Health Care District, Department of Internal Medicine, Jyvaskyla, Finland

Corresponding author:
Nzechukwu Isiozor, Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Yliopistonranta 1, 70210 Kuopio, Finland.
Email: nzechuis@uef.fi

the population. The metrics focused on seven modifiable health behaviours and biological factors affecting cardiovascular risk: smoking, body mass index (BMI), physical activity, diet, fasting blood glucose (FBG), total cholesterol and blood pressure.[3] Although several studies have established strong associations between these CVH metrics and various cardiovascular outcomes,[4–6] there is still a lack of research available on the association between the AHA's CVH metrics and the risk of SCD. To the best of our knowledge, no study has yet evaluated the association between the CVH metrics and the risk of SCD. We therefore aimed to evaluate the prospective relationship between the ideal CVH metrics and the risk of SCD and all-cause mortality among a middle-aged Finnish population.

Methods

Study population

This study used the ongoing population-based Kuopio Ischemic Heart Disease (KIHD) study. The KIHD study was initially designed to investigate the different risk factors for developing CVD and other chronic diseases among middle-aged men in Kuopio and the surrounding communities.[7] Briefly, the study commenced in 1984 with men randomly selected from the national population register who were aged 42–60 years at baseline. Of the 3235 eligible men, 2682 volunteered to participate in this study. Women were included 11 years after the baseline examinations. The present analysis is based on the initial cohort of 2577 men with non-missing data on ideal CVH metrics, relevant covariates and SCD. The research protocol (KIHD) was approved by the Research Ethics Committee of the University of Eastern Finland, Kuopio (reference number 143/97). The study protocol conformed to the ethical guidelines of the Declaration of Helsinki. All participants included in the study gave informed consent.

Data collection

A self-administered questionnaire was mailed to each participant prior to their visit to the study centre. The participants were then invited to the study centre for interviews and clinical examination. A trained research nurse was responsible for interviewing all the study participants, who also underwent a health examination. Details of the assessment for blood pressure, BMI, nutritional status, smoking status, alcohol consumption, physical activity, prevalent medical conditions and socioeconomic status (SES) have been discussed previously.[6] The SES scale ranges from 0 to 25, with 0 indicating the highest and 25 the lowest SES score.

Laboratory methods

Participants provided blood specimens between the hours of 8 and 10 in the morning following abstinence from alcohol ingestion for three days, smoking for 12 hours and eating for 12 hours. After the participant had rested for 30 minutes in a supine position, the blood sample was drawn from the antecubital vein with a Terumo Venoject VT-100PZ vacuum (Terumo Corp., Tokyo), without the use of a tourniquet. The cholesterol contents of the serum lipoprotein fractions and triglycerides were measured enzymatically (Boehringer Mannheim). Serum high-density lipoprotein cholesterol (HDL-C) and its sub-fractions were separated from fresh serum samples using ultracentrifugation and precipitation. Blood glucose was measured by the glucose dehydrogenase method (Merck, Darmstadt, Germany) after precipitation of proteins by trichloroacetic acid.[8]

CVH metrics

The CVH metrics adopted in this study conformed with the CVH metrics developed by the AHA and consisted of seven health behavioural and biological factors, including a healthy diet score (HDS), physical activity, BMI, smoking status, blood pressure, FBG and plasma total cholesterol.[3,6] (Supplementary Table 1, available online). Thus the ideal CVH metric consists of the following seven components.

1. An HDS of 4–5 – that is, four to five components of the following: at least 4.5 cups/day of fruits and vegetables; at least two 3.5-ounce servings/week of fish; $<$1500 mg/day of sodium; $\leq$36 ounces/week of sweets/sugars; and at least three 1-ounce servings/day of wholegrains. The salt intake in this study was substituted by the intake of processed meat, which has been shown to contain high levels of salt (sodium).[9]
2. Physical activity consisting of $\geq$150 minutes/week moderate intensity physical activity (MET 3–6) or $\geq$75 minutes/week of vigorous intensity aerobic physical activity (MET $>$6), or an equivalent combination.
3. A smoking status of never smoked.
4. BMI $<$25 kg/m^2.
5. Blood pressure $<$120/$<$80 mmHg.
6. FBG $<$5.55 mmol/l.
7. Total cholesterol $<$ 5.18 mmol/l.

Ascertainment of SCD and all-cause mortality outcomes

SCD was defined as death that occurred within 1 h of the onset of an abrupt change in symptoms or within 24 h after the onset of symptoms when the clinical findings did not reveal a non-cardiac cause of sudden death. Deaths that occurred unwitnessed during the night, such as being found dead in bed, were classified as those whose death occurred within 24 h of the start of symptoms. Patients who were successfully resuscitated from ventricular tachycardia and/or ventricular fibrillation were also defined. The deaths due to aortic aneurysm rupture, cardiac rupture or tamponade, and pulmonary embolism, cancer, or other non-cardiac co-morbidities were not included as SCDs. The diagnostic classification of events was based on symptoms, electrocardiographic (ECG) findings, cardiac enzyme elevations, autopsy findings (80%) and history of coronary heart disease, together with the clinical and ECG findings of the paramedic staff. Out-of-hospital SCDs and non-SCDs were documented. All hospital documents (including medical records, laboratory and ECG findings from the hospital and paramedical staff, and the use of medications and defibrillators) were available to use.[10,11] All deaths that occurred by the end of 2014 were checked against the hospital documents, health centre wards and death certificates. There was no loss to follow-up. All the documents related to the death were cross-checked in detail by to doctors. The Independent Events Committee, masked to the clinical data, classified the deaths. Censoring was carried out on the date from the baseline visit to first development of SCD, death, loss to follow-up, or the end of the observation period (31 December 2014).

Statistical analysis

The baseline characteristics of the participants were summarized using descriptive statistics, presented as mean (standard deviation) or median (interquartile range) values for continuous variables, and as number (percentage) for categorical variables. We explored the shape of the relationship between the CVH metrics (as a continuous variable) and the risk of outcomes using restricted cubic splines with knots at the 5th, 35th, 65th and 95th percentiles of the CVH metrics distribution in a multivariate adjusted model. Multivariate Cox regression models were used to estimate the hazards ratios (HRs) and 95% confidence intervals (CIs) of SCD and all-cause mortality for the baseline ideal CVH metrics, behavioural factors and biological health factors after the confirmation of no major departure from the proportionality assumptions using Schoenfeld residuals.[12] The CVH metrics were dichotomized, with a score of 1 given for every ideal component and 0 for poor and intermediate components, generating a CVH score ranging from 0 to 7. The seven scores were categorized into three groups: 0–2 (poor); 3–4 (intermediate); and $\geq$5 (ideal) CVH; a CVH score of 0–2 was used as the referent. Based on the ideal components of the two factors that constitute CVH metrics – that is, the behavioural (physical activity, smoking, BMI and HDS) and biological health factors (blood pressure, FBG and total cholesterol) – health scores of 0, 1, 2, $\geq$3 and 0, 1, 2, 3 were generated, respectively, with a 0 score as the referent.

Hazard ratios were calculated with adjustment in two models. Model 1 used age, alcohol consumption and SES, whereas model 2 used model 1 plus a history of coronary heart disease (CHD) and a history of type 2 diabetes mellitus. These covariates were selected based on their previously established roles as risk factors and potential confounders, taking into consideration factors in the CVH metrics. All statistical analyses were performed using Microsoft Windows software and IBM SPSS Statistics 25. A two-sided p value <0.05 was considered statistically significant.

Results

Baseline characteristics

Table 1 shows the characteristics of the study participants. During a median follow-up time of 25.8 years, 280 cases of SCD and 1289 all-cause deaths were recorded. The mean age at baseline for the 2577 men was 53 years. Only one person achieved all seven ideal metrics at baseline (Supplementary Table 2, available online). Most of the participants (91.9%) were in the ideal FBG category. No participant with a behavioural health score of 4 had an SCD event.

CVH metrics and risk of SCD and all-cause mortality

A restricted cubic spline curve showed that the risk of SCD decreased continuously with increasing CVH metrics across the range 2–7 (p value for non-linearity = 0.54) (Figure 1). Table 2 shows the association between CVH score and the risk of SCD. Men who attained a CVH score $\geq$5 had an 85% reduced risk of SCD compared with those with a CVH score of 0–2 (HR 0.13; 95%CI 0.03–0.53; $p = 0.004$) after adjustment for age, alcohol consumption and SES. The association was minimally attenuated on further adjustment for a history of CHD and a history of type 2 diabetes mellitus (model 2). Achieving a behavioural health score $\geq$3 showed a significant relationship with the risk of SCD compared with those with a score

Table 1. Baseline characteristics and cardiovascular health scores in the KIHD cohort.

Cohort characteristics	All participants ($N = 2577$)	Men without sudden cardiac death event ($N = 2297$)	Sudden cardiac death ($N = 280$)	All-cause mortality ($N = 1289$)	Cardiovascular health score			
					0–2 ($N = 1140$)	3–4 ($N = 1299$)	≥5 ($N = 138$)	*P* value[a]
Age (years)	53.1 ± 5.1	52.9 ± 5.2	54.4 ± 4.2	54.6 ± 4.3	53.4 ± 4.9	52.9 ± 5.3	51.9 ± 5.7	0.001
Socioeconomic status	12.3 ± 5.1	12.1 ± 5.2	13.4 ± 4.8	13.4 ± 5	13 ± 5.0	11.9 ± 5.1	10.0 ± 5.2	<0.001
Alcohol/week (g)	31.8 (6.3–91.6)	30.7 (6.2–89.2)	39.7 (7.3–112.9)	38 (6.4–115.5)	44 (9.3–118.4)	26.1 (4.6–80.0)	11.4 (1–36)	<0.001
History of coronary heart disease	646 (25.1)	518 (22.6)	128 (45.7)	420 (32.6)	343 (30.1)	280 (21.6)	23 (16.7)	<0.001
History of diabetes mellitus	151 (5.9)	117 (5.1)	34 (12.1)	116 (9.0)	124 (10.9)	25 (1.9)	2 (1.4)	<0.001
Ideal CVH score	2.7 ± 1.1	2.8 ± 1.1	2.3 ± 1.0	2.5 ± 1.0	1.7 ± 0.5	3.4 ± 0.5	5.2 ± 0.4	<0.001
Systolic blood pressure (mmHg)	134.1 ± 17.1	133.5 ± 16.9	139.7 ± 17.6	136.6 ± 18.0	138.4 ± 16.6	132.1 ± 16.5	118.6 ± 12.4	<0.001
Smoker	818 (31.7)	697 (30.3)	121 (43.2)	539 (41.8)	453 (39.7)	350 (26.9)	15 (10.9)	<0.001
Body mass index (kg/m^2)	26.9 ± 3.6	26.8 ± 3.5	28.1 ± 4.1	27.3 ± 3.9	28.4 ± 3.4	25.9 ± 3.2	23.5 ± 2.0	<0.001
Total cholesterol (mmol/l)	5.9 ± 1.1	5.9 ± 1.1	6.1 ± 1.1	6.0 ± 1.1	6.2 ± 1.0	5.7 ± 1.1	4.9 ± 0.7	<0.001

Data presented as mean ± SD, median (interquartile range) or no. (%) values.
Socioeconomic status was defined as a combined measure of income, education, occupation, occupational prestige, material standard of living and housing conditions. The scale ranges from 0 to 25, with 0 indicating the highest and 25 the lowest.
[a]Statistical significance for categorical variables was tested using the χ^2 method and the analysis of variance procedure for continuous variables.

Figure 1. Restricted cubic curve of hazards ratio for sudden cardiac death (SCD) against cardiovascular health (CVH) metrics. Restricted cubic spline functions were analysed with knots located at the 5th, 35th, 65th and 95th percentiles of the CVH distribution, with the reference category set at 2; adjusted for age, alcohol consumption, socioeconomic status, history of coronary heart disease and history of type 2 diabetes mellitus. The dashed lines represent the 95% confidence intervals.

of 0 (HR 0.20; 95%CI 0.10–0.41; $p < 0.001$). A similar significant association was observed with biological health scores.

For the association between CVH score and risk of all-cause mortality, the risk of all-cause mortality decreased continuously with increasing CVH scores across the range 2–7 (p value for non-linearity = 0.16) (Figure 2). Men who had a minimum CVH score of 5 were at 67% lower risk compared with those with a CVH score of 0–2 after adjustments for age, alcohol consumption and SES (Table 2). An ideal behavioural factor also showed a significant association, with men who achieved a behavioural health score of at least 3 having a 70% lower risk of all-cause mortality compared with those with a score of 0 (HR 0.30; 95%CI 0.22–0.40; $p < 0.001$). These associations between CVH scores and the risks of SCD and all-cause mortality remained statistically significant after a sensitivity analysis excluding participants with a previous history of CHD at baseline (Supplementary Table 3, available online).

Our analysis of the association of the individual components of CVH metrics and risks of SCD and all-cause mortality is shown in Supplementary Table 4 (available online). An ideal BMI is associated with a 50% reduced risk of SCD. Specifically, ideal levels of BMI, smoking status, blood pressure, FBG and total cholesterol contributed significantly to a reduced risk of SCD. Men who achieved three or all four of the ideal behavioural factors had 80 and 70% lower risks of SCD and all-cause mortality, respectively, compared with those with no ideal behavioural factor.

Table 2. Association of cardiovascular health score, behavioural and biological health scores and risk of sudden cardiac death and all-cause mortality.

	Sudden cardiac death					All-cause mortality				
		Model 1		Model 2			Model 1		Model 2	
	n/*N* (280/2577)	Hazards ratio (95% CI)	*P*	Hazards ratio (95% CI)	*P*	*n*/*N* (1289/2577)	Hazards ratio (95% CI)	*P*	Hazards ratio (95% CI)	*P*
CVH score										
0–2	162/1140	1		1		676/1140	1		1	
3–4	115/1299	0.61 (0.48–0.78)	<0.001	0.70 (0.55–0.90)	0.005	585/1299	0.74 (0.66–0.83)	<0.001	0.79 (0.70–0.88)	<0.001
≥5	3/138	0.15 (0.05–0.48)	0.001	0.17 (0.05–0.53)	0.002	28/138	0.33 (0.23–0.49)	<0.001	0.35 (0.24–0.52)	<0.001
Behavioural health scores										
0	46/271	1	–	1	–	177/271	1	–	1	–
1	135/1145	0.61 (0.43–0.85)	0.004	0.65 (0.47–0.91)	0.013	629/1145	0.72 (0.61–0.85)	<0.001	0.74 (0.62–0.87)	<0.001
2	90/933	0.52 (0.36–0.74)	<0.001	0.61 (0.4–0.87)	0.007	430/933	0.63 (0.53–0.75)	<0.001	0.67 (0.56–0.79)	<0.001
≥3	9/228	0.20 (0.10–0.41)	<0.001	0.24 (0.12–0.50)	<0.001	53/228	0.30 (0.22–0.40)	<0.001	0.32 (0.23–0.44)	<0.001
Biological health scores										
0	39/156	1	–	1	–	118/156	1	–	1	–
1	183/1598	0.35 (0.25–0.50)	<0.001	0.47 (0.30–0.72)	0.001	816/1598	0.49 (0.40–0.59)	<0.001	0.62 (0.49–0.79)	<0.001
2	53/729	0.23 (0.15–0.35)	<0.001	0.30 (0.18–0.50)	<0.001	321/729	0.43 (0.35–0.53)	<0.001	0.55 (0.43–0.71)	<0.001
3	5/94	0.18 (0.07–0.45)	<0.001	0.22 (0.08–0.58)	0.002	34/94	0.37 (0.25–0.55)	<0.001	0.47 (0.31–0.70)	<0.001

n/*N*: number of events/total; CVH: cardiovascular health.

Reference group to which the hazard ratios are compared are 0–2 for ideal CVH and 0 for ideal behavioural and biological health factors.

Model 1: Adjusted for age, alcohol consumption and socioeconomic status.

Model 2: Model 1 plus history of coronary heart disease and type 2 diabetes mellitus.

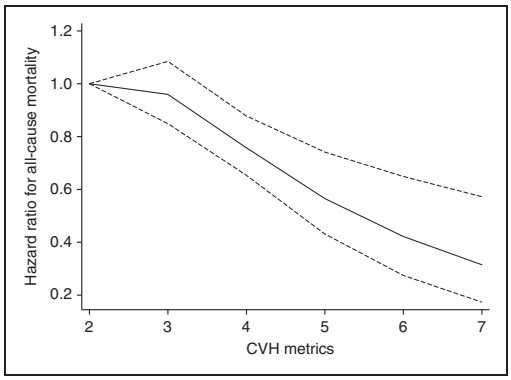

Figure 2. Restricted cubic curve of hazards ratio for all-cause mortality against cardiovascular health (CVH) metrics. Restricted cubic spline functions were analysed with knots located at the 5th, 35th, 65th and 95th percentiles of CVH distribution, with the reference category set at 2; adjusted for age, alcohol consumption, socioeconomic status, history of coronary heart disease and history of type 2 diabetes mellitus. The dashed lines represent the 95% confidence intervals.

Discussion

In this prospective study of Finnish men, the first study to assess the association of AHA's CVH metrics and the risk of SCD among the general population, men with a CVH score of 5–7 at baseline had 83% reduced risk of SCD after a median follow-up period of 25.8 years. Similarly, there was 65% lower risk of all-cause mortality among men with a CVH score of at least 5 compared with those with a CVH score of 0–2. The associations were consistent with linear dose–response relationships.

The distribution of ideal CVH metrics among the participants in our study is comparable with earlier studies. The most frequent metric in our study was an ideal FBG, similar to the People's Republic of China-USA (PRC-USA) Collaborative Study cohort.[13] Also, both the PRC-USA Collaborative Study and our study have diet as the least frequent ideal metric. There is no similar study on the association of the AHA's CVH metrics and the risk of SCD, but researchers have shown existing associations between ideal CVH and some cardiovascular outcomes and mortality.[4,14–17] Thus, in the PRC-USA Collaborative Study, a 54% lower risk of all-cause mortality was observed among participants with four to seven ideal metrics compared with those with zero to two ideal metrics.[13] Similar findings were shown in the northern Manhattan study and the Three City study[4,18] and were summarized in a recent meta-analysis of prospective studies.[16] Our findings are consistent with existing evidence on the association of ideal CVH and the risk of all-cause mortality.

Obesity, smoking, hypertension and diabetes have been identified as risk factors for SCD and vigorous physical activity can increase the risk of SCD.[10,19] Our study shows a similar pattern of association (Supplementary Table 4, available online). It may not be surprising that ideal physical activity did not show an independent significant association with the risk of SCD compared with those participants with poor physical activity because it incorporated vigorous physical activity (Supplementary Table 1, available online), which might be a cause of sudden death.[19–21] The findings remained consistent after excluding men with a previous history of CHD at baseline.

The assessment for the applicability of the AHA's CVH metrics among middle-aged Finnish men, who are at higher risks of death from diseases of the circulatory system,[22] shows that the metrics may be applicable to European populations and could be used for health promotion purposes to reduce the burden of CVD and future SCD risk, limiting the possible use of drugs or electrical devices for prevention purposes.[23] Thus, campaigns and policies that are aimed at improving CVH metrics should be encouraged. Health professionals can use these metrics to assess and identify people at risk of SCD and encourage early modification of the CVH metrics to improve quality of life. To improve levels of behavioural factors, participants can start from those factors that they can realistically control.

The strengths of this study lie in the relatively large number of participants in a representative sample of the population of middle-aged men in Eastern Finland. They were well characterized and followed up during the study period with well-documented outcome data. However, some limitations of this study warrant mentioning. First, the results are based on Finnish men and therefore cannot be generalized to other population groups. Also, causality cannot be confirmed. Second, there could be misclassification bias given the use of self-administered questionnaires to obtain information on some of the components of the CVH metrics. Also, the substitution of salt intake with the intake of processed meat might have some effect in the computation of the HDS in this study. However, in the Finnish diet and lifestyle recommendations on the use of salt in the 1980s, the intake of processed meats fell under convenience foods to be avoided because they were among the sources of excess salt in the Finnish diet.[24] Third, given the long period of follow-up and the use of baseline assessments, it is likely that the levels of CVH metrics may change over time. This could be due to some potential factors such as ageing, disease, modification of lifestyle

and use of lipid-lowering and antihypertensive drugs, thereby leading to the underestimation of true associations as a result of regression dilution bias. Therefore, it would be interesting to investigate further how the longitudinal evolution of the CVH metrics or interventions to improve ideal CVH influences the rates of SCD and all-cause mortality.

Baseline ideal CVH values are strongly and linearly associated with the future risks of SCD and all-cause mortality among Finnish men. Interventions that will help the population to achieve more ideal CVH metrics should be emphasized and embraced as a wide scale health promotion tool to reduce SCD and to improve CVH in the general population.

Author contribution

NI, SKK and JL contributed to the conception and design as well as the acquisition, analysis and interpretation of the work. AV contributed to the acquisition and analysis for the work. SK and JK contributed to the acquisition of the work. NI drafted the manuscript. All authors critically revised the paper and gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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IV

Life's simple 7 and the risk of stroke in Finnish men: A Prospective Cohort Study

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Life's Simple 7 and the risk of stroke in Finnish men: A prospective cohort study

Nzechukwu M. Isiozor [a,*], Setor K. Kunutsor [b,c], Ari Voutilainen [d], Jussi Kauhanen [d], Jari A. Laukkanen [a,d,e]

[a] Institute of Clinical Medicine, University of Eastern Finland, Kuopio, Finland
[b] National Institute for Health Research Bristol Biomedical Research Centre, University Hospitals Bristol and Weston NHS Foundation Trust and the University of Bristol, United Kingdom
[c] Translational Health Sciences, Bristol Medical School, Musculoskeletal Research Unit, University of Bristol, Bristol, United Kingdom
[d] Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland
[e] Central Finland Health Care District, Department of Internal Medicine, Jyvaskyla, Finland

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ABSTRACT

Background: Population-wide preventive measures constitute important approaches towards reducing stroke risk and its associated burden. We sought to examine the association between American Heart Association's (AHA) Life's Simple7 (LS7) score and the risk of stroke in men.

Methods: The study is based on the prospective population-based Kuopio Ischaemic Heart Disease cohort comprising men (42–60 years) without pre-existing history of stroke at baseline (1984–1989). LS7 was computed from AHA's cardiovascular health metrics for 2520 men and includes data on diet, physical activity, body mass index, smoking status, blood pressures, total cholesterol and blood glucose. Participants were classified into three LS7 groups based on the number of ideal metrics: low (0–2), medium (3–4) and high (5–7). Multivariable Cox regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of LS7 scores for total and ischaemic stroke.

Results: During a median follow-up of 26 years, 428 total and 362 ischaemic incident stroke events were recorded. The risk of both stroke outcomes decreased continuously with increasing LS7 scores across the range 2–6. Men with high LS7 had 48% (HR: 0.52; 95%CI: 0.32–0.86) lower risk of total stroke when compared with those with low LS7. The association was similar for the risk of ischaemic stroke, with 50% (HR: 0.50; 95%CI: 0.29–0.87) lower risk among men with high LS7 compared with those with low LS7.

Conclusion: LS7 was strongly, inversely and linearly associated with risk of total and ischaemic strokes among a middle-aged male Finnish population.

1. Introduction

Among noncommunicable disease, stroke remains a leading cause of death and total disability-adjusted life years (Hay et al., 2017; World Health Organization, 2020). Most cases of strokes are due to cerebral ischaemia(Béjot et al., 2016). In many developed countries, the decline in stroke incidence and mortality can be attributed to evolving preventive strategies, awareness and modification of risk factors(Albers et al., 2000; GBD and Stroke Collaborators, 2019). However, with the dramatic global demographic shift towards an aging population, there is a predicted increase in the total number of incident strokes(Béjot et al., 2016). This therefore makes the prevention of stroke, through beneficial modulation of risk factors, a crucial target particularly for first time events in the general population.

The American Heart Association (AHA) developed cardiovascular health (CVH) metrics to reduce cardiovascular disease (CVD) and stroke burden and mortality(Lloyd-Jones et al., 2010). The AHA's ideal CVH metrics, termed Life's Simple 7 (LS7), consists of diet, physical activity, body mass index (BMI), smoking, blood pressures (BP), total cholesterol and fasting blood glucose (FBG) levels (Table 1). Studies have demonstrated evidence of associations between these individual components and the risk of stroke(Imano et al., 2018; Howard and McDonnell, 2015;

* Corresponding author at: Institute of Clinical Medicine, University of Eastern Finland, Yliopistonranta 1, 70211 Kuopio, Finland.
E-mail address: nzechukwu.isiozor@uef.fi (N.M. Isiozor).

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Table 1
Definition of cardiovascular health metrics.

Cardiovascular health metric	Poor	Intermediate	Ideal
Healthy diet score	0–1	2–3	4–5 components[a]
Physical activity	No physical activity	1–149 min/week of moderate intensity physical activity or 1–74 min/week of vigorous intensity or both	≥150 min/week moderate intensity (MET 3–6) or ≥ 75 min/week of vigorous intensity (MET >6) or combination
Body mass index, kg/m^2	≥ 30	25–29.9	<25
Smoking status	Current smokers	Previous smokers ≤12 months	Never smoked >12 months
Blood pressure, mmHg	SBP ≥140 or DBP ≥90	SBP, 120–139 or DBP, 80–89	SBP <120 and DBP <80
Fasting blood glucose[b], mmol/l	≥7.00	5.55–6.99	<5.55
Plasma total cholesterol[c], mmol/l	≥ 6.22	5.18–6.21	< 5.18

DBP, diastolic blood pressure; MET, metabolic equivalent; mmHg, millimetre mercury; SBP, systolic blood pressure.

[a] The components are: ≥4.5 cups/day of fruits and vegetables, ≥two 3.5-oz servings/week of fish, <1500 mg/day of sodium (substituted with ≤2 servings/week of processed meats), ≤ 36 oz/week of sweets/sugars and ≥ three 1-oz servings/day of whole grains.

[b] mmol/l x 18 = mg/dl.

[c] mmol/l x 38.6 = mg/dl.

O'Donnell et al., 2010; Kurth et al., 2002). Therefore, the optimal combination with regular assessment of these key characteristics might be a relevant and feasible tool to motivate people for risk factor reduction in general populations.

There is consistent evidence that ideal CVH metrics is associated with lower risk of CVD events(Han et al., 2018; Isiozor et al., 2019a, 2019b; Wu et al., 2019; Qian et al., 2013). However, fewer studies, such as REGARDS study in the US, Kailuan study and China-PAR project in China (Kulshreshtha et al., 2013; Qian et al., 2013; Han et al., 2018) and recently UK Biobank study(Cao et al., 2021), have evaluated stroke event as separate outcomes rather than been included as a part of the composite CVD outcome. Furthermore, there is limited published data on the prospective associations between LS7 and the risk of stroke and its subtypes, particularly among European populations with different risk factor profiles. Published meta-analyses on the CVH metrics and CVD events have mainly included studies from Asia and the US (Guo and Zhang, 2017; Fang et al., 2016). In the few European studies, the association has been consistent, with varying statistical significance differences (Ahmed et al., 2020; Lachman et al., 2016; Gaye et al., 2017; Cao et al., 2021). The rarity of European-based studies on this topic, particularly from northern Europe, raises the question if AHA's LS7 risk factor assessment can be applied in other regions for the prevention of stroke.

In view of this, we used data from the Finnish Kuopio Ischaemic Heart Disease (KIHD) study to investigate the prospective relationship between LS7 and the risk of total and ischemic stroke among an apparently healthy northern European population.

2. Methods

2.1. Study design and population

The KIHD is an ongoing prospective cohort study designed to explore risk factors for CVD, stroke and other chronic diseases among middle-aged population from Eastern Finland (Salonen et al., 1992). The baseline examination was conducted between 1984 and 1989 in randomly selected white men aged 42–60 years; 2682 of them (82.9% of those eligible) volunteered to participate in the study. After excluding men with prevalent stroke (57), missing data on CVH factors and covariates (105), 2520 men were included in this current analysis (Supplement Fig. 1). All provided written informed consent. This study was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Research Ethics Committee of the University of Eastern Finland (Ref. no. 143/97).

2.2. Measurements of exposures and covariates

Detailed description of baseline data collection using both self-reported questionnaires and face-to-face interviews have been described previously (Isiozor et al., 2019b). A self-administered questionnaire was used to collect information on smoking status and the duration of smoking of each participant prior to visiting the study centre. To quantitatively assess the dietary intake of foods and beverages at the baseline of the KIHD study, a 4-day food record diary was used. These 4 days were to be consecutive – three workdays and one weekend day. Participants filled these records by household measures and delivered them at study visits. In the subsequent study visits, food records were interview-checked(Salonen et al., 1992). A structured quantity-frequency method using the Nordic Alcohol Consumption Inventory on drinking behaviour over the previous 12 months, in addition to a dietary record over 4 days, were used to assess alcohol consumption (Salonen et al., 1991). Participants physical activity were assessed using the KIHD 12-Month Leisure-Time Physical Activity Questionnaire (modified from the Minnesota leisure time activity questionnaire), a 7-day leisure time activity recall, the 24-h total activity recording and the occupational activity interview (Lakka et al., 1994). For every type of physical activity, the subjects were required to record the frequency (number of sessions/month), average duration (hours and minutes per session) and intensity. All metabolic indices were calculated using the product of duration of each activity and the caloric coefficient of the specific activity and intensity class. The intensity was expressed in metabolic units (MET), which is the ratio of metabolic rate during activity to the metabolic rate at rest. A trained nurse checked and completed the questionnaire in an interview.

Information about education, occupation and previous medical records were obtained using detailed questionnaires. The adulthood socioeconomic status (SES), scale ranging from 0 through 25 (0 highest; 25 lowest SES), was generated from the combined measure of current income, current and previous occupations, highest level of education, perception of financial security, housing tenure, and an index of material living conditions (from a 12-item list) (Laukkanen et al., 2015). A self-administered questionnaire was used to obtain information on the medical history, use of medications, and family history of diseases from participants. All information was checked during medical examination.

Physical measurements including height, weight and BP were conducted during baseline examinations by a research nurse. BMI was calculated as weight (in kg) divided by height (in meters-squared) (kg/m^2). Resting BP was measured with a random-zero sphygmomanometer (Hawskley, UK) between 8 am and 10 am after 5 and 10 min of rest in a seated position (Laukkanen et al., 2012). The mean BP values were used for the systolic and diastolic BP.

Participants provided fasting blood samples between 8 am and 10 am after abstaining from alcohol intake for 3 days, smoking, and eating for 12 h. Details on the blood sample collections and measurements of blood-based markers have previously been described (Salonen et al., 1992; Isiozor et al., 2019b). The cholesterol contents of serum lipoprotein fractions and triglycerides were measured enzymatically. Blood glucose was measured by glucose dehydrogenase method (Merck, Darmstadt, Germany) after precipitation of proteins by trichloroacetic acid.

2.3. Life's Simple 7

The AHA's CVH metrics was used to develop the LS7 in this study; similar to the Jackson Heart Study (JHS) and the National Health and Nutrition Examination Surveys (NHANES) study (Kesireddy et al., 2019; Lin et al., 2015). It consisted of ideal levels of seven CVH factors at baseline (Table 1), including a healthy diet score (HDS), physical activity, BMI, smoking status, BP FBG and plasma total cholesterol(Lloyd-Jones et al., 2010; Isiozor et al., 2019b). The LS7 components are:

1) An HDS of 4–5, i.e., four to five components of: ≥4.5 cups/day of fruits and vegetables; ≥2 3.5-oz servings/week of fish; ≤36 oz/week of sweets/sugars; ≥3 1-oz servings/day of wholegrains; and < 1500 mg/day of sodium (substituted in this study with the recommended secondary dietary goal of ≤2 servings/week of processed meat). Processed meats have been shown to contain high levels of salt (sodium)(Susic and Frohlich, 2012). Furthermore, in the 1980s, the Finnish diet and lifestyle recommendations on the use of salt included the intake of processed meats under convenience foods to be avoided because they were among the sources of excess salt in the Finnish diet (Kuusipalo and Määttänen-Bourke, 2013). The AHA in its recommendations has indicated that the HDS is not meant to be comprehensive but can be used as a practical tool to guide healthy dietary intake (Lloyd-Jones et al., 2010).
2) Physical activity of ≥150 min/week moderate intensity physical activity (MET 3–6) or ≥ 75 min/week of vigorous intensity aerobic physical activity (MET >6), or an equivalent combination.
3) A smoking status of never smoked.
4) BMI <25 kg/m^2.
5) BP <120/<80 mmHg.
6) FBG <5.55 mmol/l.
7) Total cholesterol <5.18 mmol/l.

The summary score of LS7 was generated from the summation of AHA's ideal CVH metrics, ranging from 0 to 7 (a point for each AHA's ideal category and zero point for intermediate and poor categories). The LS7 score was then categorized into three groups: 0–2(low); 3–4(medium); and ≥ 5(high); the low(0–2) LS7 score served as the referent comparison. We also calculated for the global CVH score ranging from 0 (poorest) to 14 (most ideal) (points assigned are 2 for ideal, 1 for intermediate and 0 for poor metric). Based on the 25th, 50th and 75th percentiles of global CVH, poor CVH = 0–6; intermediate CVH = 7–8; and ideal CVH = 9–14.

2.4. Ascertainment of follow-up events

The Finnish part of Monitoring of Trends and Determinants in Cardiovascular Diseases (FINMONICA) stroke register was used to ascertain the incident strokes between 1984 and 1992 (Kurl et al., 2003; Karppi et al., 2012; Kunutsor et al., 2018). Information on total number of incident strokes between 1993 and December 31, 2017, was obtained using computerized linkage to the national hospital discharge registry and death certificate registers in Finland. Stroke was diagnosed based on sudden onset of clinical signs or focal or global disturbance of cerebral function lasting more than 24 h (except in the case of sudden death or interruption by surgical intervention) with no apparent cause other than a vascular origin. A neurologist classified the diagnostic information from hospitals using diagnostic criteria like the FINMONICA and complying with the International Classification of Diseases (ICD)– 9 (codes 430–439) and ICD-10 (codes I60–I68 and G45–G46). Each definite stroke was classified into an ischaemic stroke (ICD-9 codes 433–434; ICD-10 code I63) or a haemorrhagic stroke (ICD-9 codes 430–431; ICD-10 codes I60–I61). The ICD-9/10 codes of 436 and 164 were not included in this classification of definite stroke. Computed tomography(CT) was performed in 90% of the patients by 1993, and CT, MRI and autopsy reached 100% by 1997. The FINMONICA stroke register data were annually re-checked(Kurl et al., 2005; Kunutsor et al., 2020). The first stroke was considered as the end point if a participant had multiple non-fatal strokes during follow-up. Thus, censoring of stroke events were done on first date event; if no stroke but dead before 01/01/2018, censoring was on date of death; if no stroke and alive to the end of 2017, censoring was at the end of observation; or loss to follow-up. Every resident of Finland has a unique personal identifier that is used in registers to track for follow-up.

2.5. Statistical analysis

Descriptive statistics were used to summarize the baseline characteristics of the participants. Continuous variables were presented as mean (standard deviation) or median (interquartile range, IQR) values and categorical variables as number (percentage). Analysis of variance and chi-squared tests were used to assess the differences in baseline characteristics of continuous and categorical variables respectively. The shapes of the relationships between LS7 (as continuous variable) and the risk of stroke outcomes were explored using restricted cubic splines with knots at the 5th, 35th, 65th and 95th percentiles of the LS7 distribution in multivariable Cox models adjusted for age, alcohol consumption, SES, a history of coronary heart disease (CHD) and type 2 diabetes mellitus. Hazard ratios (HR) and 95%confidence intervals (CIs) were estimated by using Cox proportional hazards regression models, after no major departure from the proportional hazards assumption was confirmed using Schoenfeld residuals(Therneau and Grambsch, 2000). Three progressive models were used to calculate the HRs. Model 1 adjusted for age; model 2 adjusted for model 1 plus alcohol consumption (in grams/week) and socioeconomic status; and model 3adjusted for model 2 plus use of antihypertensive and cholesterol lowering medications and a history of type 2 diabetes mellitus (to provide some measure of control of diabetes). In the sensitivity analyses, men with a history of CHD were excluded. Covariates were selected based on their known roles as risk factors and potential confounders, whiles taking into consideration the components of LS7. All statistical analyses were performed using SPSS 25 for Windows (IBM Corp.) and Stata version 12 (Stata Corp, College Station, TX). Two-sided P values <0.05 were considered statistically significant.

3. Results

During a median follow-up period of 26 (IQR, 16–30) years, 428 total stroke and 362 ischaemic stroke events were recorded. The baseline characteristics of the participants are shown in Table 2 and Supplement Table 1. The mean age of participants who developed total stroke was higher than those who did not develop stroke at the end of follow-up (54.2 vs 52.8 years). On average, older people had the least LS7 scores with the mean age decreasing from the low LS7 (0–2) to the high LS7 (≥5) ($P = 0.01$). Men with low LS7 had lower SES compared to men with high LS7 ($P < 0.001$). Men with high LS7 level consumed the least alcohol per week (median [IQR]: 11.4 [1.0–36.0]) compared to other LS7 groups (median [IQR] for low and medium LS7 are 44.0 [9.3–118.5] and 26.6 [4.8–81.1] respectively, $P < 0.001$).

Restricted cubic spline curves showed that the risk of total stroke and ischaemic stroke decreased continuously with increasing LS7 metrics across the range 2–6 (P-values for nonlinearity for stroke and ischaemic stroke were 0.65 and 0.73 respectively) (Fig. 1A and B).

Table 3 shows the associations between LS7 and risk of total and ischaemic stroke. Men who achieved high LS7 score (5–7) had a 48% lower risk of total stroke and 50% lower risk of ischaemic stroke, when compared with those with low LS7 score (0–2), after adjustment for potential confounders (HR, 95%CI: 0.52, 0.32–0.86 for total stroke and 0.50, 0.29–0.87 for ischaemic stroke). The hazard function curves across the categories of LS7 for total and ischaemic stroke are shown in Fig. 2. Analyses using global CVH score showed similar results. Compared with men in poor CVH category, those who achieved ideal CVH had ≥50%

Table 2
Baseline characteristics of the KIHD study cohort.

Characteristics	All participants (N = 2520)	Men without stroke (N = 2092)	Total stroke (N = 428)	Ischaemic stroke (N = 362)	LS7 score			*P*-value*
					0–2 (low) (N = 1109)	3–4 (medium) (N = 1273)	≥5 (high) (N = 138)	
Age (years)	53.0 ± 5.2	52.8 ± 5.3	54.2 ± 4.4	54.2 ± 4.3	53.4 ± 4.9	52.8 ± 5.3	51.9 ± 5.6	0.01
Socioeconomic status	12.3 ± 5.1	12.1 ± 5.1	13.0 ± 5.2	13.2 ± 5.1	13 ± 5	11.9 ± 5.1	10 ± 5.2	<0.001
Alcohol/week (g)	31.9 (6.4–92.5)	32.0 (6.3–92.0)	29.8 (6.4–95.1)	27.3 (5.3–93.0)	44.0 (9.3–118.5)	26.6 (4.8–81.1)	11.4 (1.0–36.0)	<0.001
History of coronary heart disease	622 (24.7)	493 (23.6)	129 (30.1)	121(33.4)	328 (29.6)	271 (21.3)	23 (16.7)	<0.001
History of type 2 diabetes mellitus	144 (5.7)	108 (5.2)	36 (8.4)	31 (8.6)	117 (10.6)	25 (2.0)	2 (1.4)	<0.001
Hypertension medication	539 (21.4)	437 (20.9)	102 (23.8)	85 (23.5)	264 (23.8)	247(19.4)	28(20.3)	0.031
Cholesterol lowering medication	16 (0.6)	13 (0.6)	3 (0.6)	3 (0.8)	7(0.6)	9 (0.7)	–	0.611
Systolic blood pressure (mmHg)	134.0 ± 17.0	133.1 ± 16.6	138.7 ± 18.3	138.9 ± 18.4	138.2 ± 16.6	132.0 ± 16.5	118.6 ± 12.4	<0.001
Smoker	802 (31.8)	671 (32.1)	131 (30.6)	110 (30.4)	442 (39.9)	345 (27.1)	15 (10.9)	<0.001
Body mass index (kg/m^2)	26.9 ± 3.6	26.8 ± 3.5	27.4 ± 3.7	27.4 ± 3.7	28.4 ± 3.4	25.9 ± 3.2	23.5 ± 2.0	<0.001
Total cholesterol (mmol/l)	5.9 ± 1.1	5.9 ± 1.1	6.0 ± 1.2	6.0 ± 1.2	6.2 ± 1.0	5.7 ± 1.1	4.9 ± 0.7	<0.001
LS7								
0	26(1.0)	19(0.9)	7(1.6)	7 (1.9)				
1	252 (10.0)	202 (9.7)	50(11.7)	46(12.7)				
2	831 (33.0)	664(31.7)	167(39.0)	139(38.4)				
3	812 (32.2)	684(32.7)	128(29.9)	108(29.8)				
4	461 (18.3)	402(19.2)	59(13.8)	48(13.3)				
5	115 (4.6)	103(4.9)	12(2.8)	9(2.5)				
6	22 (0.9)	17(0.8)	5(1.2)	5(1.4)				
7	1 (<0.1)	1(<0.1)	0	–				

KIHD, Kuopio Ischaemic Heart Disease; LS7, Life's Simple 7.
Data presented as mean ± standard deviation (SD), median (interquartile range) or no. (%) values.
Socioeconomic status (SES) was defined as a combined measure of income, education, occupation, occupational prestige, material standard of living and housing conditions. The scale ranges from 0 to 25, with 0 indicating the highest and 25 the lowest.
* *P*-value for analysis of variance and chi-squared tests for continuous and categorical variables respectively.

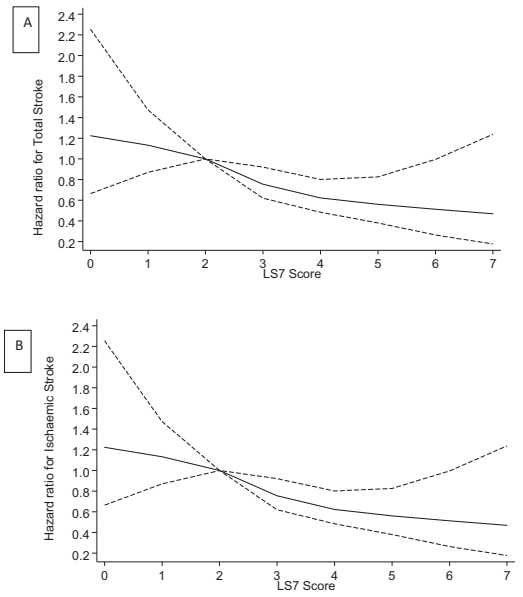

Fig. 1. Restricted cubic curve of hazard ratio for total stroke (A) and ischaemic stroke (B) against Life's Simple 7 (LS7) score.

lower risk of total and ischaemic stroke after age- and full-adjustments (Table 4). Furthermore, a unit increase in CVH score was associated with 14% and 15% lower risk of total and ischaemic stroke respectively.

Sensitivity analyses excluding men with history of CHD showed similar associations between LS7 and stroke risk following adjustment for age, alcohol consumption and SES (model 1). The HRs (95%CIs) for high versus low LS7 are 0.55(0.32–0.96) and 0.53(0.28–0.98), respectively (Supplement Table 2).

4. Discussion

In this prospective study of middle-aged Finnish population, higher LS7 score, a summary measure of AHA's CVH metrics, was associated with considerably lower risk of total and ischaemic stroke. Only one participant achieved all the seven ideal metric. However, men without stroke at baseline, who were found to report adhering to at least five of all the LS7 factors (high LS7score), compared with those who were found to achieve low LS7score (0–2), had a 48% and 50% lower risk of total and ischaemic strokes, respectively. The findings were also consistent with the association of the global CVH score and the risk of total and ischaemic stroke. Thus, a unit increase in global CVH score was associated with 14% and 15% lower risk of total and ischaemic stroke, respectively.

Studies in the US, China and recently, the UK, have reported evidence of relationships between CVH metric and risk of stroke(Kulshreshtha et al., 2013; Ahmed et al., 2020; Qian et al., 2013; Han et al., 2018; Cao et al., 2021). Findings from northern Europe are rare. However, consistent with our findings, a US study reported that white participants in the optimal CVH category, compared with those in the inadequate CVH category, had 51% lower risk of incident stroke(Kulshreshtha et al., 2013). This association, however, was not significant

Table 3
Association between Life's Simple 7 and the risk of stroke among 2520 men in the KIHD study.

	Total stroke			Ischaemic stroke		
LS7 score	0–2[a] (low)	3–4 (medium)	5–7 (high)	0–2[a] (low)	3–4 (medium)	5–7 (high)
n/N	224/1109	187/1273	17/138	192/1109	156/1273	14/138
P-values for linear trends		<0.001			<0.001	
Model 1						
HR (95%CI)	1	0.62 (0.51–0.76)	0.45 (0.27–0.74)	1	0.61 (0.49–0.75)	0.43 (0.25–0.74)
P value*		<0.001	0.001		<0.001	0.002
Model 2						
HR (95%CI)	1	0.65 (0.53–0.79)	0.49 (0.30–0.81)	1	0.63 (0.51–0.78)	0.47 (0.27–0.82)
P value*		<0.001	0.01		<0.001	0.008
Model 3						
HR (95%CI)	1	0.68 (0.56–0.83)	0.52 (0.32–0.86)	1	0.66 (0.53–0.82)	0.50 (0.29–0.87)
P value*		<0.001	0.01		<0.001	0.013

Model 1: adjusted for age.
Model 2: Model 1 plus alcohol consumption and socioeconomic status.
Model 3: Model 2 plus use of antihypertensive and cholesterol lowering medications, and history of type 2 diabetes mellitus.
n/N, number of events/Total; HR, hazard ratio; CI, Confidence interval.
* *P*-values are for the HRs computed from cox regression analysis; HRs <0.05 are considered statistically significant.
[a] Reference category.

among the black participants in the study, showing possible variations for AHA's CVH metrics application in different population groups. Similarly, studies from the UK reported that adults who had ideal CVH were consistently at lower risk of stroke (and its subtypes) compared with those with poor CVH (Cao et al., 2021); and men with optimal CVH (excluding diet) had 60% lower risk of stroke compared with those in the inadequate category after 20 years of follow-up(Ahmed et al., 2020). However, a pooled study-level analysis of 127,536 participants from nine prospective observational studies in the general population, showed that those participants with the highest ideal CVH metrics had 69% lower risk of stroke (with 3390 recorded stroke events)(Fang et al., 2016). Another meta-analysis supports this finding with approximately 70% lower risk of stroke among participants in the most category of ideal CVH metrics(Guo and Zhang, 2017); although the main outcome event is not specific for ischaemic stroke due to the limited studies on the association between AHA's CVH metrics or LS7 and the risk of ischaemic stroke. Nevertheless, a study from China, with specific outcomes of total and ischaemic stroke, found that individuals who achieved the highest ideal CVH metrics had lower risks of total and ischaemic strokes(Qian et al., 2013), similar to a later finding in the Chinese population where those who met all ideal metrics had 79% lower risk of stroke(Han et al., 2018).

Some of the earlier studies among European populations from the EPIC-Norfolk cohort(Lachman et al., 2016) comprising of middle-aged and older European participants, and the Three-City French cohort (Gaye et al., 2017) of elderly population showed no significant difference in the association between participants in the healthiest CVH categories and the risk of stroke compared with those in the unhealthy or poor category. This could be due to the difference in the study populations, study design, shorter mean follow-up periods (<10 years), adjusted covariates and difference in CVH components (e.g., diet scores). Nevertheless, the results are consistent with our significant findings.

Our study thus supports evidence that higher LS7 can be targeted by Europeans, particularly the Finnish populace, to reduce the future risk of total stroke, and ischaemic stroke specifically. It further confirms the cardiovascular benefits of achieving higher ideal CVH among European populations. In using the American CVH metric to examine European population, it is important to consider the variability in each country's stroke prevalence, lifestyle differences (e.g., diet, physical activities as influenced by different work culture), insurance and medical practice (e.g., more primary health care in Europe) across countries as they may influence the strength of the associations between LS7 and incident stroke and stroke subtypes. Nevertheless, there is need to target the ideal components of CVH metrics in the general population. Thus, not smoking, healthy diet, regular physical activity, maintaining normal BMI, controlling BP, normal blood glucose and total cholesterol levels should be a concern for middle-aged men for stroke risk reduction.

Awareness of the LS7 can ensure the acceptability of a scoring system that enables people place themselves in the corresponding low, medium or high LS7 groups, with the goal to achieving or maintaining high LS7 score. Furthermore, since the risk factors involved in the LS7 are well-known modifiable risk factors (which have shown significant relationship with lower risk of stroke (Howard and McDonnell, 2015, O'Donnell et al., 2010, De Caterina et al., 2010, Imano et al., 2018)), most of them can be tracked, upgraded and monitored aided by modern technology, though possible challenges shall persist in tracking and measuring diet. Thus, should achieving higher LS7 scores become a target for health improvement and promotion, the associated future risk of strokes can potentially be reduced in male population. However, this warrants further investigation to ascertain if treatments, upgrading and maintaining higher LS7 scores shall proffer the same protective effect on stroke.

The major strength of the study is the relatively large number of the participants who are representative of middle-aged men in Eastern Finland. Study participants were well characterized with detailed baseline risk factor assessments and no loss to long follow-up due to the unique personal linkage to the Finnish registries.

Some limitations to this study also warrant mention. First, the results of this study focused on white males and cannot be generalized to other population groups and females. Second, we only had data on baseline measurements of our exposures; due to errors in measurements, changes in lifestyle, chronic disease and aging, assessments using baseline measurements of an exposure could underestimate the true strength of an association between an exposure and disease outcome due to the phenomenon of regression dilution bias. This is especially so in cohorts with long follow-up duration. Since the effects of regression dilution bias would be underestimation of the association, the true associations are expected to be stronger. Third, the use of processed meat to substitute for sodium content in the metric could lead to biases. Nevertheless, the AHA committee considered processed meats as part of the goals for a healthy diet. Since over 16% salt intake is attributed to processed meat in Europe (Ni Mhurchu et al., 2011; Meneton et al., 2009) with NaCl content of processed meats in Finland estimated at 1200 mg/100 mg (Pietinen, 1981), it was considered a proper substitute for sodium intake among the secondary dietary options by AHA(Lloyd-Jones et al., 2010). Finally, we were unable to assess the association between LS7 and haemorrhagic stroke, because of limited number of these events; this is consistent with the observation that approximately 80% of all stroke cases are ischaemic strokes(Béjot et al., 2016).

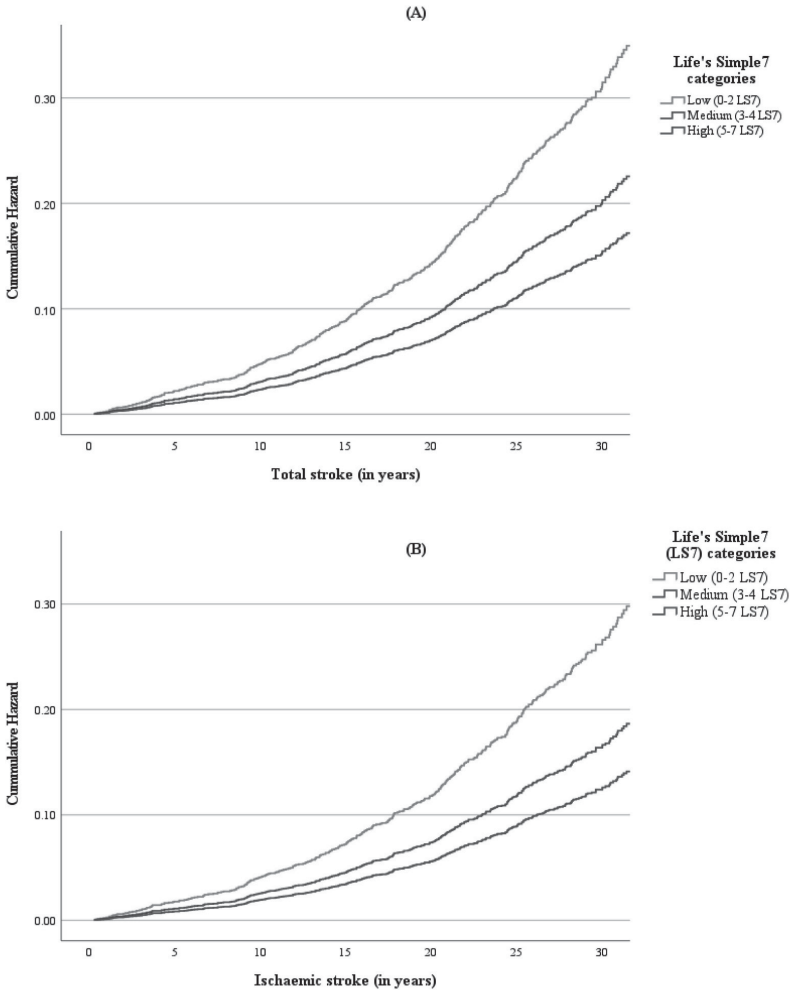

Fig. 2. Hazard function curve of Life's Simple 7 for total stroke(A) and ischaemic stroke(B). Adjusted for age, alcohol consumption and socioeconomic status.

In conclusion, there is an inverse linear association between baseline LS7 scores and the risk of total and ischaemic strokes among a middle-aged male Finnish population. The results of this study may contribute towards applying LS7 for the implementation of prevention strategies of stroke in the general male population from northern Europe. However, further large-scale studies are needed to confirm or refute the associations.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ypmed.2021.106858.

Data availability

The data that support the findings of this study are available from any qualified investigator upon reasonable request.

Credit author statement

Nzechukwu M. Isiozor: Conception and design as well as the acquisition, analysis and interpretation of the work; Writing- Original draft preparation and revision of the manuscript for intellectual content.

Setor K. Kunutsor: Conception and design as well as the acquisition, analysis and interpretation of the work; Writing- reviewing, editing and revision of the manuscript for intellectual content.

Ari Voutilainen: Acquisition and analysis for the work. Jussi Kauhanen: Methodology, investigation and acquisition of data.

Jari A. Laukkanen: Conception and design as well as the acquisition, analysis and interpretation of the work; Writing- reviewing, editing and revision the manuscript for intellectual content.

Declaration of conflicting interests

None to declare.

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Table 4
Association between global CVH and the risk of stroke among 2520 men in the KIHD study.

Global CVH score	N	Total stroke			Ischaemic stroke		
		Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
		HR (95%CI): *P* value*	HR (95%CI): *P* value*	HR (95%CI): *P* value*	HR (95%CI): *P* value*	HR (95%CI): *P* value*	HR (95%CI): *P* value*
Poor	706	1	1	1	1	1	1
Intermediate	950	0.62 (0.50–0.77): <0.001	0.63 (0.50–0.79): <0.001	0.66 (0.53–0.83): <0.001	0.58 (0.45–0.73): <0.001	0.58 (0.46–0.74): <0.001	0.61 (0.48–0.79): <0.001
Ideal	864	0.44(0.35–0.56): <0.001	0.47 (0.37–0.60): <0.001	0.50 (0.39–0.64): <0.001	0.41 (0.31–0.53): <0.001	0.44 (0.33–0.57): <0.001	0.46 (0.35–0.61): <0.001
CVH score (per-unit increment)	2520	0.83 (0.79–0.87): <0.001	0.84 (0.80–0.89): <0.001	0.86 (0.81–0.90): <0.001	0.82 (0.79–0.87): <0.001	0.83 (0.78–0.87): <0.001	0.85 (0.80–0.90): <0.001
Number of ideal CVH							
0	26	1	1	1	1	1	1
1	252	0.46 (0.21–1.02): 0.056	0.48 (0.22–1.06): 0.069	0.58 (0.26–1.31): 0.190	0.42 (0.19–0.94): 0.034	0.44 (0.20–0.97): 0.042	0.52 (0.23–1.17): 0.114
2	831	0.39 (0.18–0.82): 0.014	0.41 (0.19–0.88): 0.021	0.54 (0.25–1.20): 0.13	0.32 (0.15–0.68): 0.003	0.34 (0.16–0.73): 0.005	0.43 (0.20–0.96): 0.039
3	812	0.28 (0.13–0.60): 0.001	0.30 (0.14–0.65): 0.002	0.41 (0.18–0.91): 0.028	0.23 (0.11–0.50): <0.001	0.25 (0.12–0.54): <0.001	0.33 (0.15–0.73): 0.007
4	461	0.21 (0.10–0.47): <0.001	0.24 (0.11–0.52): <0.001	0.32 (0.14–0.73): 0.007	0.17 (0.08–0.38): <0.001	0.19 (0.09–0.42): <0.001	0.25 (0.11–0.57): 0.001
5	115	0.16 (0.06–0.40): <0.001	0.18 (0.07–0.46): <0.001	0.25 (0.09–0.66): 0.005	0.12 (0.04–0.31): <0.001	0.14 (0.05–0.37): <0.001	0.18 (0.06–0.50): 0.001
6–7	23	0.31 (0.10–0.97): 0.044	0.34 (0.11–1.08): 0.044	0.45 (0.14–1.44): 0.177	0.30 (0.10–0.96): 0.042	0.34 (0.11–1.06): 0.06	0.42 (0.13–1.37): 0.15

Model 1: adjusted for age.
Model 2: Model 1 plus alcohol consumption and socioeconomic status.
Model 3: Model 2 plus use of antihypertensive and cholesterol lowering medications, and history of type 2 diabetes mellitus.
CVH, cardiovascular health metric; N, number of participants.
Global CVH score: poor, 0–6; intermediate, 7–8; ideal, 9–14.
* *P*-values are for the HRs computed from cox regression analysis; HRs <0.05 are considered statistically significant.

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NZECHUKWU MICHAEL ISIOZOR

Cardiovascular disease (CVD) causes more than half of all deaths across the European Region. Evidence in some population groups reveal the cardiovascular benefits of the American-developed cardiovascular health (CVH) metrics. However, the application of this metrics among the northern European population is limited, and awareness of its potential benefits to reduce the burden of CVD and improve CVH in Finland is low. This thesis provides information on the association of CVH metrics and the risk of cardiovascular events and all-cause mortality among a Finnish population.

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