Diet and Physical Activity for the Prevention of Cardiovascular Disease

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Diet and Physical Activity for the Prevention of Cardiovascular Disease

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DOCTORAL DISSERTATION

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Abstract:

Introduction: Cardiovascular disease (CVD) is the most common cause of mortality and morbidity in the world. The role of lifestyle, such as diet and physical activity, is an important factor in the prevention of CVD.

Aim: The aim of this work was to investigate the role of diet and leisure-time physical activity in the primary prevention of CVD.

Methods: Data from the prospective Malmö Diet and Cancer Study (MDCS) cohort were utilised in four of the studies. The MDCS includes over 30 000 individuals and baseline data collection took place in the 1990s, leading to a follow-up time of approximately 20 years. Baseline data collection consisted of a dietary assessment, a lifestyle questionnaire, and anthropometric measurements. The dietary assessment comprised of a 7-day menu book, a food frequency questionnaire, and an interview. The relevant outcomes were obtained from health registries and the final date of follow-up was 31 December 2016. The fifth study was a Cochrane systematic review and meta-analysis and was conducted on randomised controlled trials (RCTs) comparing the effects of high and low added sugar intake on CVD.

Results: Adhering to the dietary recommendations regarding the intake of fruit and vegetables, and fibre was associated with a reduced risk of abdominal aortic aneurysm (AAA) and peripheral arterial disease (PAD) in the MDCS. A high intake of plant foods and fibre-rich products was associated with a reduced risk of AAA (hazard ratio (HR) for vegetables 0.91; 95% confidence interval (CI) 0.84-0.98 and HR for fruit 0.89 95% CI 0.82-0.96). Total leisure-time physical activity (HR 0.96; 95% CI 0.92-0.99), as well as several moderate- (e.g., cycling and golf) and high-intensity activities (e.g., running and swimming), reduced the risk of cardiovascular mortality. The systematic review revealed no RCTs on added sugar for the primary prevention of CVD. Twenty-one trials were identified investigating the effects of added sugar intake on risk factors for CVD, showing that a low added sugar intake was associated with lower systolic blood pressure (mean difference (MD) 1.44, 95% CI 0.08-2.80; I^2 = 27%, 14 studies; 873 participants), and lower diastolic blood pressure (MD 1.52, 95% CI 0.67-2.37; I^2 = 0%; 13 studies; 873 participants), and lower levels of total cholesterol (MD 0.11, 95% CI 0.01-0.21; I^2 = 0%; 16 studies; 763 participants) and triglycerides in the blood (MD 0.10, 95% CI 0.03-0.17; I^2 = 3%; 14 studies; 725 participants). The overall quality of evidence was low in the systematic review.

Conclusions: A lifestyle characterised by a diet rich in fruit, vegetables, and other fibre-rich products, and moderate- or high-intensity physical activity on a weekly basis, was associated with a reduced risk of CVD in the MDCS. More high-quality RCTs with long-term follow-up are needed to evaluate the role of added sugar in the primary prevention of CVD.

Key words: cardiovascular disease, abdominal aortic aneurysm, peripheral arterial disease, cardiovascular mortality, primary prevention, diet quality, dietary fibre, added sugar, leisure-time physical activity, Malmö Diet and Cancer Study, Cochrane review

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Papers included in this thesis

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Paper I

Nordkvist S, Sonestedt E, Acosta S. Adherence to diet recommendations and risk of abdominal aortic aneurysm in the Malmö Diet and Cancer Study. Sci Rep. 2018;8(1):2017.

Paper II

Bergwall S, Acosta S, Sonestedt E. Intake of fibre and plant foods and the risk of abdominal aortic aneurysm in a large prospective cohort study in Sweden. European Journal of Nutrition. 2020;59(5):2047-56.

Paper III

Kulezic A, Bergwall S, Fatemi S, Sonestedt E, Zarrouk M, Gottsäter A, et al. Healthy diet and fiber intake are associated with decreased risk of incident symptomatic peripheral artery disease – A prospective cohort study. Vascular Medicine (United Kingdom). 2019;24(6):511-8.

Paper IV

Bergwall S, Johansson A, Sonestedt E, Acosta S. High versus low-added sugar consumption for the primary prevention of cardiovascular disease (review). Cochrane Database of Systematic Reviews. 2022;2022(1).

Paper V

Bergwall S, Acosta S, Ramne S, Mutie P, Sonestedt E. Leisure-time physical activities and the risk of cardiovascular mortality in the Malmö Diet and Cancer study. BMC Public Health. 2021;21(1):1948.

Papers not included in this thesis

Lilja E, Bergwall S, Sonestedt E, Gottsäter A, Acosta S. The association between dietary intake, lifestyle and incident symptomatic peripheral arterial disease among individuals with diabetes mellitus: insights from the Malmö Diet and Cancer study. Therapeutic Advances in Endocrinology and Metabolism. 2019;10.

Bergwall S, Ramne S, Sonestedt E, Acosta S. High versus low added sugar consumption for the primary prevention of cardiovascular disease (protocol). Cochrane Database of Systematic Reviews. 2019;2019(4).

Populärvetenskaplig sammanfattning

Hjärt- och kärlsjukdomar är väldigt vanliga och drabbar många. Denna grupp av sjukdomar är den vanligaste dödsorsaken i världen och därför är det väldigt viktigt att finna hur man kan förhindra att hjärt- och kärlsjukdomar utvecklas. Att förhindra att en sjukdom utvecklas kallas för prevention och är denna avhandlings huvudsakliga fokus. Det finns många sätt att förhindra sjukdom, till exempel genom att äta nyttigt och motionera ordentligt.

I denna avhandling har vi undersökt hur kost och fysisk aktivitet påverkar risken att utveckla olika hjärt- och kärlsjukdomar senare i livet. Detta har gjorts genom att ungefär 28 000 medelålders och äldre personer folkbokförda i Malmö registrerade sina levnadsvanor på 90-talet och sen har dessa personer följts genom åren. Då har det varit möjligt att se om de har drabbats av sjukdomar, gått bort, eller fortsatt leva ett friskt liv.

Denna avhandling har undersökt flera olika delar av kosten och träning för att försöka förstå om det finns en koppling mellan dessa och framtida hjärt- och kärlsjukdomar.

I tre arbeten undersökte vi om vår kost påverkar risken för två kärlsjukdomar, bråck på stora kroppspulsådern och pulsåderförkalkning i benen. Bråck på kroppspulsådern är en sjukdom som orsakas av en vidgning av den stora kroppspulsådern i magen som i värsta fall kan leda till att den brister. Risken för att personen dör är i sådana fall väldigt hög. Pulsåderförkalkning i benen orsakas av att de stora kärlen i kroppen blivit igensatta av fett och kalk, ungefär som att ha stopp i avloppet hemma. Detta gör att det blir svårare för blodet att färdas genom kroppen, ner till benen. Pulsåderförkalkning i benen behöver inte leda till att individen uppvisar symptom. Det första symptomet vid pulsåderförkalkning i benen är smärta i musklerna vid promenad medan smärtan upphör i vila, så kallad fönstertittarsjuka. Om pulsåderförkalkningen förvärras uppstår smärta i vila, fotsår eller vävnadsdöd (delar av foten blir svart), och kan leda till att foten behöver amputeras. Vi fann att ett högt intag av frukt och grönsaker och fiber minskar risken att drabbas av bråck på kroppspulsådern och pulsåderförkalkning i benen i framtiden. Ytterligare analyser gjordes på olika typer av frukt och grönsaker och bråck på stora kroppspulsådern och där fann vi att speciellt bladgrönsaker (till exempel spenat) är bra att äta för att minska risken för denna sjukdom.

I det fjärde arbetet sammanställde vi alla randomiserade interventionsstudier som har gjorts om tillsatt socker och hjärt-och kärlsjukdom. Detta samanställdes för att kunna säga något om hur forskningsläget ser ut just nu. Tillsatt socker är allt socker som inte finns naturligt i mat, till exempel socker som tillsätts i läsk. Vi fann ingen forskning på effekten av tillsatt socker och insjuknande i hjärt- och kärlsjukdomar, utan den mesta

forskningen undersöker hur tillsatt socker exempelvis påverkar kolesterolnivåer i blodet och blodtrycket, vilka är kända riskfaktorer för hjärt- och kärlsjukdomar. Vi kunde i detta arbete dra slutsatsen att ett högt intag av tillsatt socker möjligtvis leder till förhöjt kolesterol och högre blodtryck, men vi kunde inte dra några slutsatser om tillsatt socker ökar risken för hjärt- och kärlsjukdomar.

Utöver att fokusera på kostens roll i att minska risken att drabbas av sjukdomar, undersökte vi också hur träning påverkar risken att dö i en hjärt- och kärlsjukdom. Vi var intresserade av i vilken omfattning personer var fysiskt aktiva på fritiden, det vill säga hur mycket tid de lägger ner på träning utöver transport till och från jobb och under arbetstid. De fick också fylla i vilken typ av träning de ägnade sig åt, till exempel löpning eller simning. Resultaten visade att aktiviteter som är högintensiva (det vill säga att man får en rejäl pulshöjning och blir svettig) är bäst för att minska risken att dö i en hjärt- och kärlsjukdom. Löpning var den aktivitet som minskade risken mest och som alltså är mest fördelaktig att utöva när det gäller att minska risken för att dö i en hjärt- och kärlsjukdom. Men det räcker att träna högintensivt ungefär 30 minuter i veckan för att få den bästa effekten.

Sammanfattningsvis så har denna avhandling undersökt kost och träning och hur dessa faktorer kan påverka risken att drabbas av en hjärt- och kärlsjukdom. Vi har kommit fram till att det är viktigt att äta mycket frukt och grönsaker och att försöka minska på mängden tillsatt socker. Träning är också väldigt bra, och speciellt högintensiv sådan, men det är inte nödvändigt att träna väldigt mycket för att uppnå de bästa hälsoeffekterna. Kost och träning är två viktiga pelare i folkhälsan och denna avhandling har förhoppningsvis ökat kunskapen om hur dessa kan minska förekomsten av hjärt- och kärlsjukdomar.

Popular scientific summary

Cardiovascular diseases are very common and are the most common cause of death worldwide. It is therefore very important to investigate how these diseases can be avoided. The prevention of cardiovascular diseases is the main focus of this thesis. There are many ways to prevent diseases, for example by eating healthily and exercising.

The studies described in this thesis were carried out to investigate several aspects of diet and exercise in an attempt to understand the potential connection between these and the future development of cardiovascular diseases. This was done using data from about 30 000 residents of Malmö who registered their lifestyle habits in the 1990s. These individuals were then followed throughout the years to establish whether they had become ill, died, or continued to live a healthy life.

In three of the studies the effects of diet on the risk of developing two vascular diseases, abdominal aortic aneurysm, and peripheral arterial disease, were investigated. Abdominal aortic aneurysm is a localised widening of the abdominal aorta that may grow and, in the worst case, rupture. If the aorta ruptures, there is a very high risk that the individual will die. Peripheral arterial disease is caused by the deposition of fat and calcium on the inner walls of the arteries, leading to blocked arteries, usually affecting the legs. This makes it more difficult for blood to travel down to the legs. Some patients do not experience any symptoms of peripheral arterial disease. Others may experience pain in the muscles when walking, while it disappears when resting. As the peripheral arterial disease progresses, pain at rest, foot ulcers and black discoloration of parts of the foot may develop, which might require amputation of the foot. A high intake of fruit and vegetables was found to reduce the risk of developing abdominal aortic aneurysm and peripheral arterial disease. Further analyses were conducted on different types of fruit and vegetables and abdominal aortic aneurysm, and it was found that leaf vegetables (such as spinach) were especially beneficial in reducing the risk of this disease.

In the fourth study trials on the effects of added sugar on cardiovascular disease were surveyed to evaluate the current state of research. “Added sugar” means all sugar that does not exist naturally in food, for example the sugar that is added to soft drinks. No research could be found on the effect of added sugar on the risk of developing cardiovascular diseases. Most research has been carried out to investigate how added sugar affects cholesterol levels and blood pressure, which are known risk factors for cardiovascular diseases. From the results of this study, it was concluded that a high intake of added sugar could lead to increased cholesterol and blood pressure, but it could not be determined whether added sugar directly increased the risk of cardiovascular diseases.

The effects of how exercise on the risk of dying of a cardiovascular disease were also explored. The individuals were asked to fill in a questionnaire on the kinds of exercise they did in their spare time, for instance swimming or running. The results showed that physical activities that raise the pulse considerably and cause sweat reduce the risk of dying of a cardiovascular disease. Running was the activity that reduced this risk the most and it was best in reducing the risk of dying of a cardiovascular disease. However, it was found to be sufficient to exercise at a high level of intensity for about 30 minutes per week in order to achieve the best effect.

After studying the effects of diet and exercise, and how these lifestyle factors can affect the risk of cardiovascular diseases, it was concluded that it is important to eat plenty of fruit and vegetables and to try to reduce one's intake of added sugar. Exercise is also very beneficial, especially intense exercise, but it is not necessary to exercise for extreme amounts of time to obtain the best health effects. Diet and exercise are two important pillars in public health and the work presented in this thesis has hopefully increased our knowledge on how these can reduce the occurrence of cardiovascular diseases.

Abbreviations

AAA	Abdominal aortic aneurysm
ABI	Ankle-brachial index
BMI	Body mass index
CI	Confidence interval
CVD	Cardiovascular disease
CVM	Cardiovascular mortality
EFSA	European Food Safety Association
EPIC	European Prospective Investigation into Cancer and Nutrition
HDL	High-density lipoprotein
HR	Hazard ratio
ICD	International Classification of Disease
IQR	Interquartile range
LDL	Low-density lipoprotein
MD	Mean difference
MDCS	Malmö Diet and Cancer Study
MET	Metabolic equivalent tasks
PAD	Peripheral arterial disease
RCT	Randomised Controlled Trial
SD	Standard deviation
SE	Standard error
SSB	Sugar sweetened beverage
WHO	World Health Organization

Overview of included papers

	Paper I	Paper II	Paper III	Paper IV	Paper V
Title	Adherence to diet recommendations and risk of abdominal aortic aneurysm in the Malmö Diet and Cancer Study	Intake of fibre and plant foods and the risk of abdominal aortic aneurysm in a large prospective cohort study in Sweden	Healthy diet and fibre intake are associated with decreased risk of incident symptomatic peripheral artery disease – A prospective cohort study	High versus low-added sugar consumption for the primary prevention of cardiovascular disease	Leisure-time physical activities and the risk of cardiovascular mortality in the Malmö Diet and Cancer Study
Study sample	Malmö Diet and Cancer Study cohort, with dietary assessment (n=26 133)	Malmö Diet and Cancer Study cohort, with dietary assessment (n=26 133)	Malmö Diet and Cancer Study cohort, with dietary assessment (n=26 010)	All RCTs on added sugar and CVD	Malmö Diet and Cancer Study cohort, with lifestyle assessment (n=25 876)
Aim	To explore the association between a diet quality index, specific dietary components, and the development of AAA.	To investigate the association between fibre and plant foods intake and the risk of AAA.	To explore the association between a diet quality index, specific dietary components, and the development of PAD.	To compare the effects of high versus low added sugar consumption on CVD.	To investigate the associations between leisure-time physical activity and specific activities and CVM.
Method	Analyses of the relation between diet quality index and risk of AAA.	Analyses of the relation between fibre and plant food intake and risk of AAA.	Analysis of the relation between diet quality index and risk of PAD.	Systematic review and meta-analysis of RCTs according to the Cochrane methodology.	Analysis of the relation between physical activity and risk of CVM.
Main results	Adherence to recommendations for fruit and vegetable intake was associated with a reduced risk of AAA.	A high intake of fruit, berries, vegetables, in particular leaf vegetables, was associated with reduced risk of AAA.	Adherence to recommendations for fruit and vegetable, and fibre intake was associated with reduced risk of PAD.	No RCTs on added sugar and CVD. Review on blood lipids and blood pressure. Modest effect, favouring a low added sugar intake for prevention of CVD.	Moderate- and high-intensity physical activities, in particular running, were associated with a reduced risk of CVM.

Background

The concept of epidemiology first appeared in the early 19th century in Spain and was defined as "the science of epidemics of infectious diseases"(1). The term is derived from the Greek word epi, meaning upon, and demos, meaning people. In the mid-20th century, the definition was broadened to include not only infectious diseases leading to the formal definition used today:

> "Epidemiology is the science of the distribution of diseases and other health-related features in human populations and of the factors that influence this distribution." (1)

Epidemiologic knowledge helps guide public health initiatives and policies and is often key in disease prevention. The following definition provides a fundamental understanding of the concept of public health:

> "Public Health is the entirety of theoretical and practical activities that are related to health and deal with populations as a whole but not specifically with their individual members." (1)

One of the first known applications of epidemiology in the field of public health was made by John Snow during a cholera epidemic in London in 1853. He showed, by applying epidemiological methods, that the cause of the cholera epidemic was poor-quality drinking water. The cholera epidemic was stopped by simply removing the handle of the pump causing pollution of the water after which, no future outbreaks of cholera were reported in that area. Although epidemiological research is still conducted on infectious diseases and the management of disease outbreaks, modern epidemiology is often concerned with risk factors associated with developing diseases, such as the relationship between smoking and lung cancer (1).

This doctoral thesis is based on public health and epidemiological research. The specific topics covered are the roles of diet, including specific dietary components, and physical activity in the prevention of cardiovascular disease (CVD), including abdominal aortic aneurysm (AAA) and peripheral arterial disease (PAD). Each topic is addressed to provide a detailed understanding of the background, definition and, epidemiology of each component covered in this work.

Diet

Dietary components

The nutrients found in food can be broadly divided into three categories: protein, fat, and carbohydrates. These are called macronutrients, and they provide the energy necessary for the survival of an organism. A combination of macronutrients is required to maintain health, but the optimal proportions between these components have been shown to vary between populations and contexts (2). Nonetheless, the World Health Organization (WHO) recommends the following energy distributions for macronutrients: protein 10-15%, fat 15-30%, and carbohydrates 55-75% (3). The Nordic Nutrition Recommendations, published in 2012, give different dietary recommendations for macronutrients, expressed as a percentage of energy intake (E%), namely: protein 10-20 E%, fat 25-40 E% and carbohydrates 45-60 E% (4). The Nordic Nutrition Recommendations are the result of a long-standing collaboration between the Nordic countries in setting guidelines and recommendations for dietary composition and nutrient intake, based on the current nutritional conditions (4).

Protein is sometimes referred to as the building block of the body, it is necessary for the development of cells and the production of enzymes and hormones. Protein is typically found in meat, dairy products, eggs, and legumes (5). Fat provides an important source of energy and, at the right amount, is vital for building and repairing cells, producing hormones and for providing concentrated energy for the body. Fat is divided into saturated and unsaturated (which contains monounsaturated and polyunsaturated fat) and it is generally recommended that the amount of saturated fat (found, for example, in dairy products) in the diet should be decreased and the amount of unsaturated fat (found, for example, in fish, oil, and nuts) be increased (6).

Carbohydrates are the most important source of energy, and are therefore a vital component of our diet. These have traditionally been divided into two broad categories: simple (e.g., glucose) and complex (e.g., starch). However, grouping carbohydrates according to their chemical classification is of little biological value and it has therefore been suggested that carbohydrates instead be categorised into: dietary fibre, which is digested in the large intestine, and glycaemic carbohydrates, which are digested in the small intestine (7).

Although macronutrients are important dietary components, it can be argued that these categories are broad, and that deciphering the specific diet-disease relationship from macronutrients alone can be difficult. Micronutrients in the diet are therefore also crucial. Vitamins (e.g., vitamin A and D) and minerals (e.g., iron and zinc) are the two categories most often referred to when discussing micronutrients. Insufficient intake of

micronutrients can have detrimental effects on health. For example, iron deficiency is the leading cause of anaemia worldwide, and vitamin A deficiency among children can lead to blindness and fatal infections (8). Food and beverages usually contain a mixture of macro- and micronutrients and it is therefore important to study the role of eating patterns and the products consumed, rather than only focusing on a single nutrient, especially when new dietary recommendations are formulated (9). For example, beans are a nutrient-dense food, containing polysaccharides, oligosaccharides, protein, polyphenols, and a number of vitamins and minerals (10).

History

The manner in which dietary patterns has evolved through history has to a large extent depended on food availability. During Antiquity (approximately 800 BC to AD 500) the main food source was grains. Other food products also existed, for example cheese and fish, but these were not as common. During this time, cooking practises evolved, allowing for instance the cooking of meat. Cultivation of fruit and vegetables also became widespread during this time (11).

From the beginning of the Middle Ages up to the middle of the 19th century, famines and food shortages were common in Europe and the nutritional status of humans was generally poor. Deficiency of vitamins and minerals, as well as protein, was widespread and many were chronically undernourished. Food intake was determined by what was locally available and due to the lack of choice, very monotonous. From approximately 1850, food security improved radically, as new, and more effective agricultural machines emerged, allowing for more effective production and cultivation of food. Improvements in food quality could also be seen as, for example, official meat inspections at butcheries became mandatory (11). As their health and longevity improved, individuals in Western societies started basing their diet not only on what was available but also on personal preferences. The International Vegetarian Society was, for instance, founded in 1908, and promoted plant-based nutrition for improved health status (12).

In the period following the Second World War, the concept of overnutrition was introduced, as the relationship between a diet rich in saturated fat and increased risk of heart disease was first suggested (13). Cardiometabolic conditions, including obesity, were becoming an increasingly common health problem in Western societies, while food shortage was, and still is, a major public health issue in other parts of the world (11).

Fibre

Definition

The European Food Safety Association (EFSA) defines fibre as "non-digestible carbohydrates plus lignin" (7). A more detailed definition, now used by most countries in the world, including Sweden, is provided by the Codex Alimentarius Commission, stating that fibre means carbohydrate polymers with three or more monomeric units that are not hydrolysed or absorbed by the small intestine. These carbohydrate polymers must be either: edible and naturally occurring in food, or obtained from raw material by physical, enzymatic or chemical methods, or be synthetic (14). Traditionally, fibre has been divided into soluble (e.g., pectin and beta glucans) and non-soluble fibre (e.g., cellulose), but this categorisation is used less today as the solubility of the fibre has little to do with its physiological effects. Instead, it is more relevant to base the fibre categorisation on the viscosity of the fibre. High-viscosity fibres, such as pectin, beta glucans, and psyllium, have more beneficial effects on cholesterol and glycaemic control than low-viscosity fibres, such as inulin and wheat dextrin (15).

Recommended intake

Based on the evidence available concerning the health benefits of a high intake of fibre, the EFSA recommends that adults consume >25 g/day (7). Similarly, the Nordic Nutrition Recommendations state that adults should consume at least 25-35 g/day (approximately 3 g/MJ) (4). However, a review conducted in 2017, with the aim of assessing fibre intake in Europe, found that in most countries, the mean intake was well below the recommended level (16). The Swedish Food Agency (Livsmedelsverket) has concluded that individuals in Sweden have a mean fibre intake of 20 g/day, which is still below the recommended level (17). The most common types of fibre intake in Sweden can be seen in Figure 1.

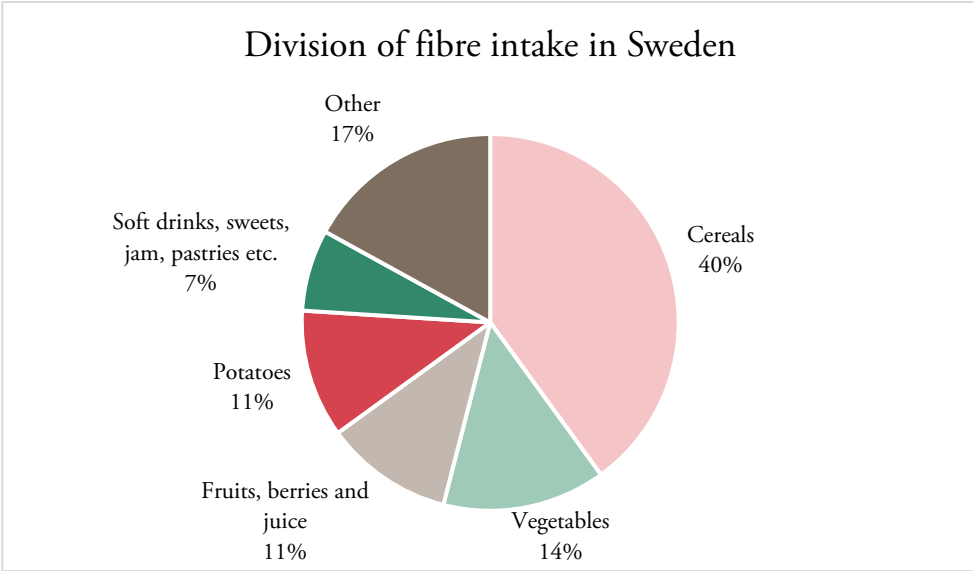


Figure 1: Distribution of fibre intake according to food groups in Sweden (Based on the results from Riksmaten 2010-2011 (18), based on a daily average intake of 20g per person.)

Health benefits

The health benefits of fibre depend for example, on the solubility, fermentability, and viscosity of the fibre (19), but can nonetheless be described in broad terms. In comparison to glycaemic carbohydrates, which are digested in the small intestine, most types of fibre are digested in the large intestine leading to a prolonged feeling of satiety (20). A high intake of fibre also leads to increased faecal bulk, decreased transit time and a reduction in postprandial blood glucose response (21).

Evidence suggests that an intake of fibre >25 g/day is associated with reduced risk of type 2 diabetes, and coronary heart disease, and is important for maintaining a healthy weight (7). A high intake of fibre has also been shown to be associated with a decreased risk of colorectal cancer (22-26), all cause- and cardiovascular mortality, and stroke (26). Moreover, an association has been established between a low dietary fibre intake and risk factors for CVD (e.g., elevated cholesterol and hypertension) (26, 27).

Fruit and vegetables

Recommended intake

The WHO recommends an intake of fruit and vegetables exceeding 400 g per day (i.e., five portions) which does not include potatoes, sweet potatoes, cassava, or other starchy roots (28). The recommended intake in the Swedish food-based dietary guidelines is >500 g/day (not including potatoes), and should consist of approximately 50% fruit and 50% vegetables (29).

Regional differences in fruit and vegetable intakes makes it difficult to estimate the intake levels in countries worldwide (30). However, it has been suggested that insufficient intake of fruits and vegetables is a major problem in many countries (31, 32). Moreover, insufficient supplies of fruit and vegetables remains a serious concern in many less affluent countries, constituting a significant obstacle to meeting the recommended intake level (33). According to the results of Riksmaten 2010-2011 (18), the low intake of fruit and vegetables is also of concern in Sweden. The mean daily intake of vegetables, pulses and roots was found to be 172 g: being 169 g/day for men and 182 g/day for women. The total mean intake of fruit and berries was found to be 128 g/day: 147 g/day for women and 105 g/day for men (18).

Health benefits

In addition to being a main source of fibre, fruits and vegetables are also rich in micronutrients such as manganese, potassium, and vitamin C (7). The health benefits associated with a high intake of fruit and vegetables are numerous and well-documented. Maintaining a high intake of fruit and vegetables is associated, for example, with reduced risks of CVD, cancer, all-cause mortality (34), depression (35), metabolic syndrome (36), and inflammatory bowel disease (37).

Added sugar

Definition

Sugars are carbohydrates, including all mono- and disaccharides, and can be divided into two categories: intrinsic and extrinsic. Intrinsic sugar is that naturally occurring in foods, such as fructose, glucose, and sucrose in fruit and vegetables, and lactose in milk, while extrinsic sugar is added to the food product. Numerous terms are used to describe extrinsic sugar, e.g., 'free sugar', 'non-milk extrinsic sugar' and 'added sugar', but they have in common the fact that they are added during the processing or preparation of food or beverages, and are thus not found naturally in the foods. One definition of

added sugar, given in the Nordic Nutrition Recommendations is that added sugars include "sucrose, fructose, glucose, starch hydrolysates (glucose syrup and high-fructose corn syrup), and other isolated sugar preparations used as such or added during food preparation and manufacturing" (4). The WHO uses the term 'free sugar' instead, which has the same definition as that of added sugar with the exception that fruit juices are also included in the definition of free sugars (38). There are numerous types of added sugar, the most common ones being sucrose (white sugar), honey and high fructose corn syrup (39). In Sweden, sucrose is the most commonly used type of added sugar and the main sources of added sugar are sweetened beverages, cakes, sweets, and chocolate (18).

Recommended intake

There are no health benefits associated with consuming added sugar (40). Although glucose is needed for the brain to function, this can be acquired by consuming naturally occurring carbohydrates, such as starch in potatoes and bread, as these will be broken down into glucose in the body (41).

The global recommendation for sugar intake, provided by the WHO, states that the intake of free sugars, for both children and adults, should be <10% of the total energy intake, and for further health benefits the intake should be <5%. The Nordic Nutrition Recommendations likewise state that the intake of added sugar should be kept below 10 E% (4). These recommendations were primarily developed based on compelling evidence of the strong association between added sugar intake and dental caries, as well as the relationship between added sugar intake and body weight (38). To put these recommendations into context, 5% of the total energy intake for adults is equivalent to about 30g of sugar per day. One 330ml can of Coca-Cola contains 35g of sugar (42).

There is increasing concern that the intake of added sugar is increasing worldwide, especially in the form of sugar-sweetened beverages (SSB) (38). However, different definitions of sugar used in different countries, makes comparing added sugar intake between countries difficult (43). In a number of high-income countries, the intake of added sugar appears to be plateauing or decreasing, according to national nutrition surveys. However, it is important to bear in mind that the added sugar intake is still among the highest in the world in some developed countries, such as the US (43). In Sweden, it is estimated that 40% of adults consume sugar above the recommended intake level (41). In many low- and middle-income countries, the consumption of added sugar is increasing rapidly, predominantly in the form of SSBs. In response to the high consumption of added sugar, some countries have implemented sugar taxes or restrictions on advertising as measures to curb sugar intake (44).

Physical activity

Definition

The WHO defines physical activity as "any bodily movement produced by skeletal muscles that requires energy expenditure" (45). Figure 2 illustrates the 2020 WHO guidelines on physical activity and sedentary behaviour. Physical activity can be undertaken in several contexts and settings, and is most often divided into four different domains: occupation, domestic, transportation, and leisure-time (45).

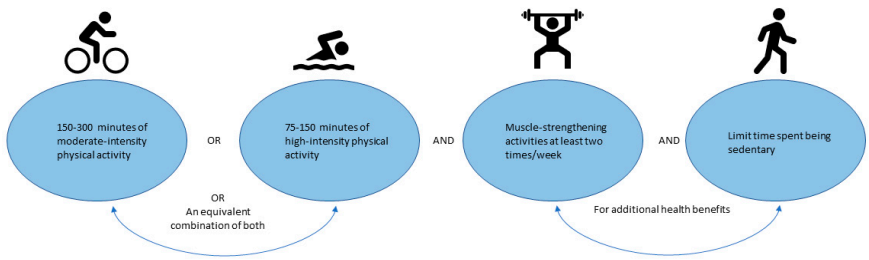


Figure 2: The 2020 WHO guidelines on weekly physical activity and sedentary behaviour for adults aged 18-64 years

History

Physical activity has been part of human life for as far back as records go. In ancient Greece, physical activity was incorporated into the education of youths and participation in organised games was greatly encouraged. Athletes maintained high status and numerous athletic festivals were held, the pinnacle being the Panhellenic Games at Olympia. During the era of the Roman Empire, physical activity was primarily highlighted for its role in militarism. The downfall of the Roman Empire led to a general decrease in physical activity as the church became a dominant power, and physical fitness was condoned, while monasticism was encouraged. As organised sports again became increasingly prevalent in Europe in the 17th century, scholars turned their attention to the potential risk and benefits to health of physical exercise. Although the results were fragmented at first, the health benefits of regular physical activity were eventually established in the early 20th century (46).

Physical activity derived from occupation has also shifted throughout history and the various kinds of physical labour over time have affected, and continue to affect the health of individuals. From hunting and gathering, to agriculture and finally to

industry, humankind's health has improved in terms of wellness and longevity. Epidemiological studies carried out in the mid-20th century compared the health of individuals with sedentary occupations to those engaged in heavy, physical labour. The results showed that individuals with sedentary occupations developed hypertension up to 15 years earlier than those with physically demanding professions, and that they were more likely to develop other cardiovascular conditions (47). Moreover, a recent study in Norway found a positive association between occupational physical activity and longevity amongst men, but not women, after adjusting for socioeconomic factors (48). This is in line with the WHO's guidelines for physical activity, in which individuals are recommended to limit the time spent being sedentary due to the poor health outcomes (e.g., mortality, CVD, and cancer) associated with substantial sedentary habits (45).

Global trends

Figure 3 shows the prevalence of insufficient physical activity in the world in 2011, for men and for women, respectively. The highest prevalence of physical inactivity can be observed primarily in South America, Europe, and the Middle East, for both men and women; insufficient physical activity being defined as less than five times 30 minutes of moderate activity per week or less than three times 20 minutes of vigorous activity per week, or equivalent. Generally, men are more physically inactive than women, as can be seen when comparing the two maps.

In Sweden, 67% of the population aged 16 to 84 years reported that they were adequately physically active (defined as >150 minutes of pulse raising physical activity per week), in 2021 (49).

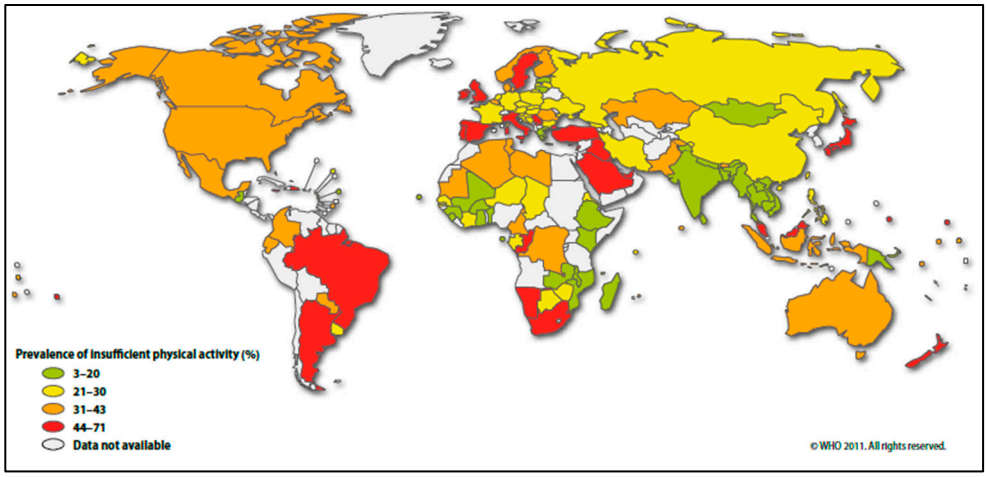


Figure 3a: World map of the prevalence of insufficient physical activity, in males (aged >15, age standardised), based on surveys conducted on a random sample of the general population in each country. Reprinted from the Global Atlas on Cardiovascular Disease, Prevention and Control (50)

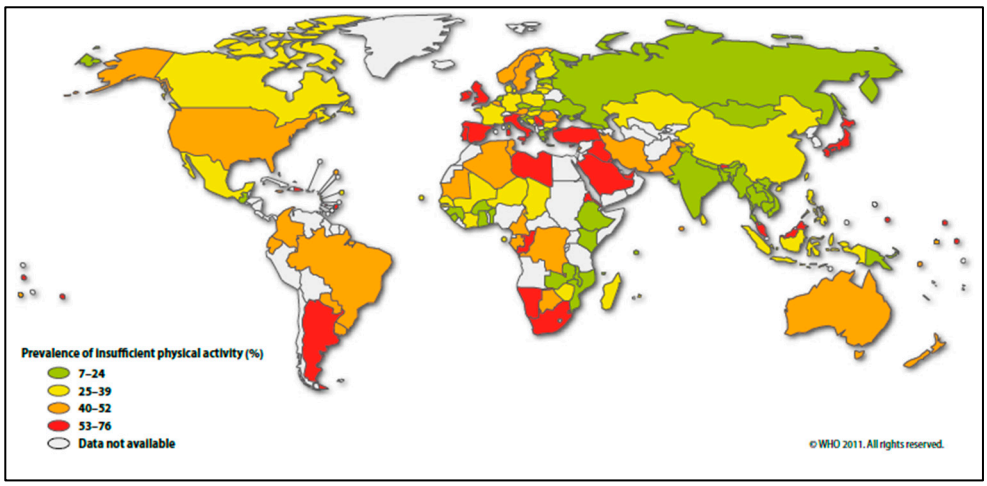


Figure 3b: World map of the prevalence of insufficient physical activity, in females (aged >15, age standardised), based on surveys conducted on a random sample of the general population in each country. Reprinted from the Global Atlas on Cardiovascular Disease, Prevention and Control (50)

Cardiovascular disease

Definition

Cardiovascular diseases (CVD) are the group of diseases affecting the heart and blood vessels. CVDs cover a plethora of different diseases and conditions but can be divided into those due to atherosclerosis, and other CVDs. Atherosclerosis is a condition affecting the walls of the arteries where fatty material and cholesterol (plaque) are deposited, causing narrowing of the vessels, resulting in the obstruction of blood flow. The CVDs resulting from atherosclerosis are ischaemic heart disease or coronary artery disease, cerebrovascular disease, and diseases of the aorta and peripheral arteries. CVDs not resulting from atherosclerosis include congenital heart disease and rheumatic heart disease (50). About 80% of strokes are ischaemic due to atherosclerosis, while 20% are haemorrhagic. Of haemorrhagic strokes, two-thirds are intracerebral spontaneous haemorrhage, which mainly occur due to small-vessel disease secondary to hypertensive angiopathy and cerebral amyloid angiopathy, and not primarily atherosclerosis (51).

History and epidemiology

CVD is not a modern occurrence and has existed in some form for thousands of years. The findings of atherosclerosis in mummies more than 2000 years old, disproves the perception that CVD is a modern affliction (52). Leonardo da Vinci, also studied the human body, and presented the first known description of coronary artery disease in the 16th century, during a post-mortem examination of a man who had passed away peacefully in Florence (53).

CVD has long been a serious problem, and its impact on present day humans is considerable. CVD is the most common cause of death worldwide; ischaemic heart disease being responsible for 16% of deaths, followed by stroke at 11%. CVD is also the leading cause of disability in the world (50). CVD is the most common cause of death in all income groups, based on gross national income, except for the low-income countries (where the main cause of death is neonatal conditions). In high-income countries, deaths resulting from ischaemic heart disease and stroke have decreased in recent decades, by 16% and 21%, respectively, but still remain the leading causes of death. Hypertensive heart disease has simultaneously become a more frequent cause of death, and has risen from the 18th to the 9th most common cause of death in high-income countries (54). Figure 4 shows the distribution of deaths from CVD in the world for the most common CVDs, for men and women.

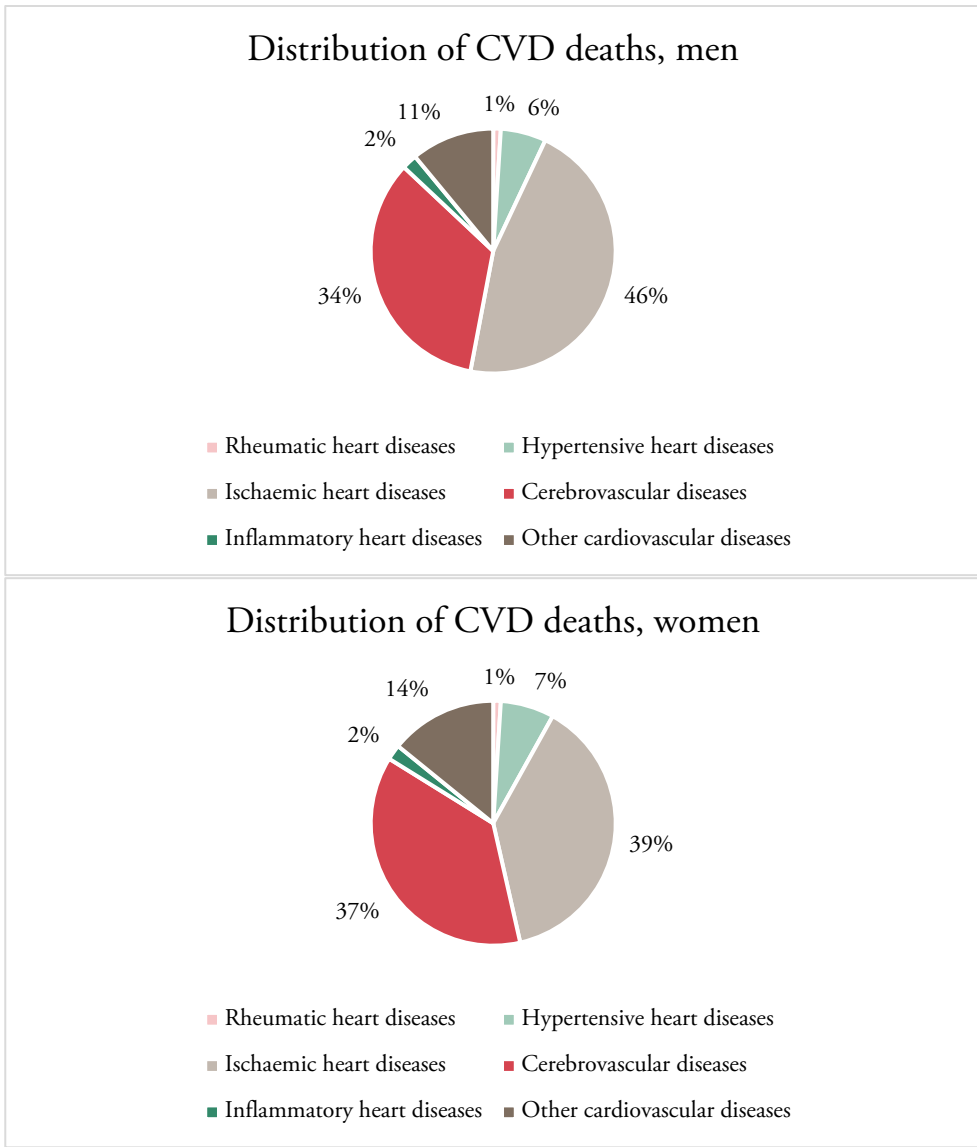


Figure 4: The distribution of CVD deaths for men and women. Data derived from the Global Atlas on Cardiovascular Disease Prevention and Control (50).

Risk factors

The known risk factors for CVD can be divided into modifiable and non-modifiable, and there is compelling scientific evidence that these risk factors play a key role in the aetiology of atherosclerosis. Modifiable risk factors are related to an individual's lifestyle, often coexist in the same person, and include tobacco and alcohol use, physical inactivity, and an unhealthy diet. Non-modifiable risk factors for CVD include advanced age, male sex, and genetic predisposition. Some risk factors are considered metabolic, and include hypertension, overweight and obesity, diabetes, and elevated blood lipids (50, 55-58).

Abdominal aortic aneurysm

Definition

Abdominal aortic aneurysm, commonly denoted AAA, is a disease affecting the aorta. It is most commonly defined as an aortic diameter ≥30 mm, located between the diaphragm and the aortic bifurcation (59). An AAA can develop over several years, and its growth rate may be exponential (60). The pathophysiology of AAAs can be regarded as four events: infiltration of the vessel wall by lymphocytes and macrophages; destruction of elastin and collagen in the media and adventitia by proteases; loss of smooth muscle cells with thinning of the media; and neovascularization (61).

Epidemiology

Estimating the incidence and prevalence of AAA is difficult, primarily because post-mortem examinations are less common today, meaning that patients with AAA may go undetected and are hence undiagnosed (59). The incidence and prevalence of AAA are thus most likely higher than that noted in registers. Nonetheless, it has been estimated that the prevalence of AAA in Sweden is 1.5% amongst men aged 65 years who participated in screening (62). However, in a study comprising 540 participants in which the prevalence of AAA in Norsjö municipality, in northern Sweden, was compared in 1999 and in 2010, it was found that the prevalence in men was 16.9% in 1999, but had fallen to 5.7% in 2010. The corresponding results for women were 3.5% in 1999 and 1.1% in 2010 (63). In a systematic review, including 56 studies the global prevalence of AAA in 2013 was estimated to be 6% for men and 1.6% for women. It is important to bear in mind that there are regional differences in the prevalence of AAA, which can be explained in part by age and sex distributions, as well as the use of different definitions of AAA in different countries (64).

As of 2018, screening for AAA has been implemented in the UK, the USA, and Sweden. A register-based cohort study conducted in Sweden, aimed at elucidating the harms and benefits of screening men for AAA, concluded that screening had no major effects on AAA-related mortality. The authors of the study suggested that the observed decline in mortality from AAA probably had little to do with screening and more to do with the continuing decline in the number of smokers in Sweden (65). However, other researchers have concluded that AAA screening is both a cost-effective and an effective preventive measure to reduce AAA mortality (62).

Risk factors

Mortality resulting from a ruptured AAA (Figure 5) exceeds 80% (66) and it is therefore vital to elucidate the risk factors associated with AAA. The most well-established risk factor for AAA is smoking, and there is strong evidence that current smokers have a five times higher risk of AAA, than non-smokers (67, 68). It has also been shown that women who smoke have a higher risk of AAA than men who smoke. Advanced age, male sex, hypertension, and atherosclerosis are other established risk factors for AAA (63, 68). AAA and CVD have similar aetiology and therefore share some risk factors (69). However, research has revealed some important differences in risk factors between AAA and coronary heart disease (CHD). Smoking and elevated diastolic blood pressure have been shown to be more strongly associated with the risk of AAA than with CHD (70). Moreover, a diabetes diagnosis acts protectively against AAA, an association not yet clearly understood (71), while diabetes is a major risk factor for CHD (70).

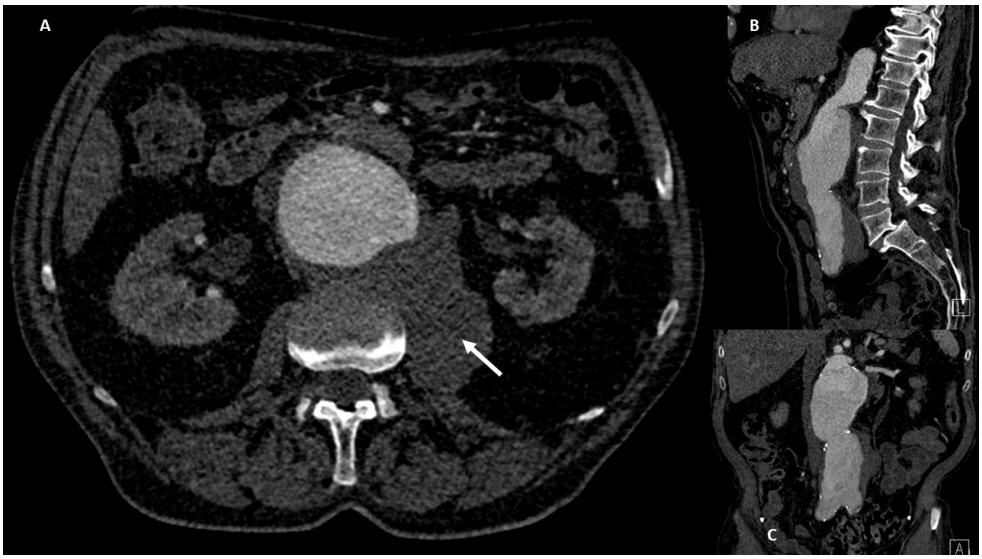


Figure 5: Results of a radiological examination of a 75-year-old man with acute onset of abdominal pain. Computed tomography of the abdomen with intravenous contrast enhancement and imaging in the arterial phase. The images in the transversal (A), sagittal (B) and coronary view (C) show a 7 cm (antero-posterior diameter) large abdominal aortic aneurysm with a rupture into the left psoas muscle (arrow; A). The patient died.

Repair of AAA

There are two main surgical methods for aneurysm repair: open aneurysm repair and endovascular aneurysm repair (EVAR). Open aneurysm repair is traditionally performed by laparotomy, where the aneurysmal part of the aorta is replaced with an artificial graft. EVAR is a newer method and considered less invasive than open repair. In EVAR a stent graft is introduced into the vascular blood stream via an artery in the groin. The stent graft is released and expands so that the aneurysmal part of the aorta is excluded from the blood stream (72).

Peripheral arterial disease

Definition

Peripheral arterial disease (PAD) is a cardiovascular disease primarily affecting the lower extremities of the body. The spectrum of PAD can vary greatly and can be asymptomatic, present as intermittent claudication, or in the most severe cases, lead to gangrene and amputation. The end stage of PAD is chronic limb-threatening ischaemia (73).

The most common method of evaluating the presence of PAD is by measuring the ankle-brachial index (ABI), which is the ratio of the systolic blood pressure at the ankle to that in the arm. An ABI of ≤0.90 is used in both clinical practice and research to diagnose PAD (74). The logic behind the ABI is that PAD alters the arterial flow in the legs at rest, and subsequently the blood pressure at the ankle falls. The ABI is estimated to have 80% sensitivity and 95% specificity, making it an appropriate measure for diagnosing PAD (73). Figure 6 shows the result of a radiological examination of an individual diagnosed with PAD.

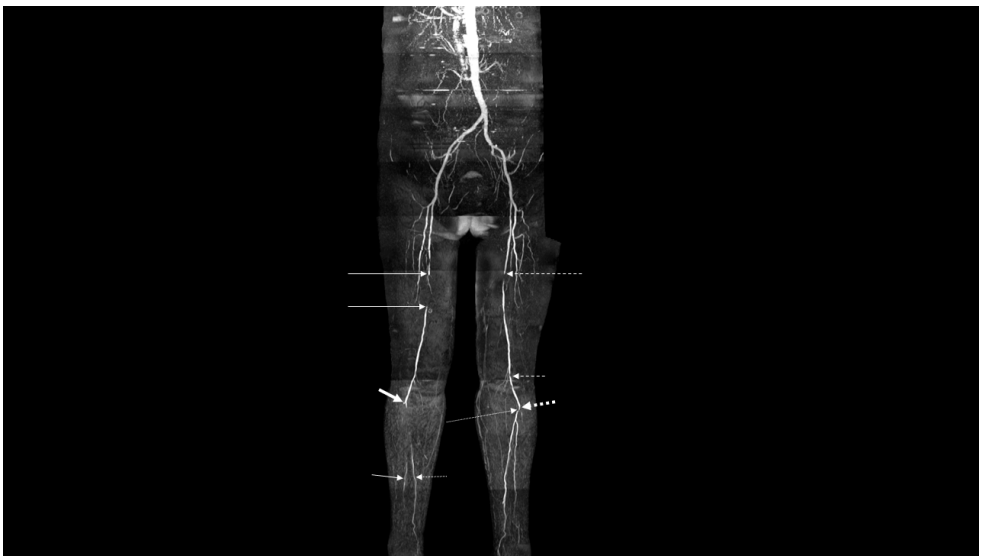


Figure 6: A 79-year-old female with hypertension and type 2 diabetes was admitted with less than 24-hours of pain, pallor, and perishing cold in the right lower extremity. Sensory and motor function in the right foot were preserved. ABI was 0.3 in the right foot and 0.6 in the left foot. Acute magnetic resonance angiography imaging showed normal appearance of the aorta, and common, external, and internal iliac, and common and deep femoral arteries bilaterally. On the right side, there was a 7 cm long occlusion of the middle part of the superficial femoral artery (between the long thin arrows). The popliteal artery was seen without stenosis. Occlusion was seen at the origin of the anterior tibial artery (short thick arrow) and the whole length of the tibiofibular trunk. Refill of contrast is seen in both fibular (short arrow) and posterior tibial (short, dotted arrow) arteries. On the left side, there was a short occlusion of the middle part of the superficial femoral artery (long dashed arrow), short stenosis of the proximal part of the popliteal artery (short dashed arrow), occlusion at the origin of the anterior tibial artery (short thick dotted arrow) and short severe stenosis of the tibiofibular trunk (long dotted arrow). The posterior tibial and fibular arteries were preserved. The patient was judged to have multi-segmental atherosclerotic lesions bilaterally.

Epidemiology

Assessing the global prevalence of PAD is difficult due to a lack of validated methods of detecting asymptomatic PAD in low- and middle-income countries (73). Estimates have nonetheless been made, and the global prevalence of PAD was deemed to increase by 23%, from 164 million cases to 202 million, between 2000 and 2010. Almost 70% of all PAD cases in 2010 were identified in low- and middle-income countries. PAD is also rated as the third most common cause of atherosclerotic morbidity (after coronary artery disease and stroke) (75). In Sweden, the prevalence of PAD has been estimated to 18% for individuals aged >60 years, and the prevalence of chronic limb-threatening ischaemia approximately 1% (76).

Risk factors

PAD is relatively uncommon in individuals aged <40 years, affects approximately 10% of individuals aged >70, and for individuals aged >80 the prevalence of PAD is one in six, thereby making advanced age a major risk factor for PAD (75). Diabetes is another risk factor and individuals with diabetes are also at a significantly higher risk of amputation (77). Smoking is another risk factor that is strongly associated with the risk of PAD, as well as dyslipidaemia and hypertension (74).

Aims

Overall aim

The overall aim of the work presented in this doctoral thesis was to investigate the role of diet and physical activity in the prevention of CVD from a population-based perspective.

Specific aims

- To investigate the role of diet quality on the risk of AAA and PAD
- To explore the role of fibre in the risk of developing AAA
- To synthesise the current research on added sugar and CVD
- To study various leisure-time physical activities and their association with the risk of cardiovascular mortality

Participants and methods

The studies presented in Papers I, II, III and V have similar methodology and the same study population and will be described first. The methods used in the systematic review (Paper IV) are addressed at the end of this chapter.

The Malmö Diet and Cancer Study

Papers I, II, III and V are based on findings from data collected in the Malmö Diet and Cancer Study (MDCS), a prospective cohort study based in Malmö, southern Sweden. Although the MDCS was originally designed to investigate the relationship between diet and cancer (78), its use has been extended to other exposures and disease endpoints. Figure 7 shows the timeline of MDCS from its initiation in the 1980s to the final endpoint that was used in this work.

Individuals living in Malmö, a city of 350 000 inhabitants, were primarily invited to participate by letter. If there was no response to the first letter, two more letters were sent to each individual. In addition to the personal letters, advertisements were posted in local newspapers, in public places, and at primary health care centres. Women born from 1923 to 1950 and men born from 1923 to 1945 were eligible to participate in the study. The wider age span set for women was motivated by the desire to study breast cancer among pre-menopausal women. Participants were also required to comprehend the Swedish language and be able to complete the extensive questionnaire. In total, 74 138 individuals were qualified to participate according to the population register; 65 599 individuals were invited by letter, and 5505 volunteered based on the advertisements posted (79). Figure 8 shows the reasons for exclusion, and the study population for the whole MDCS and the studies included in this thesis. The information generated from the participants with complete data in the MDCS (n= 28 098) were used in Studies I, II, III, and V. In 1993, the MDCS became part of the European Prospective Investigation into Cancer and Nutrition (EPIC) study, organised by the International Agency for Research and Cancer (IARC). The rationale behind EPIC was to create a cross-disciplinary European collaboration in cancer research (80).

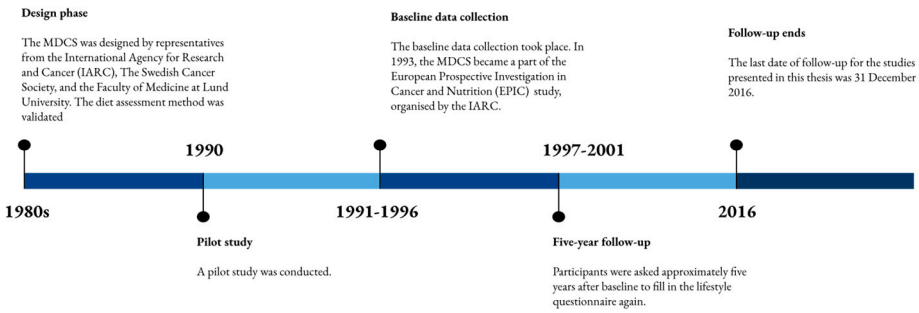


Figure 7: Timeline of the Malmö Diet and Cancer Study

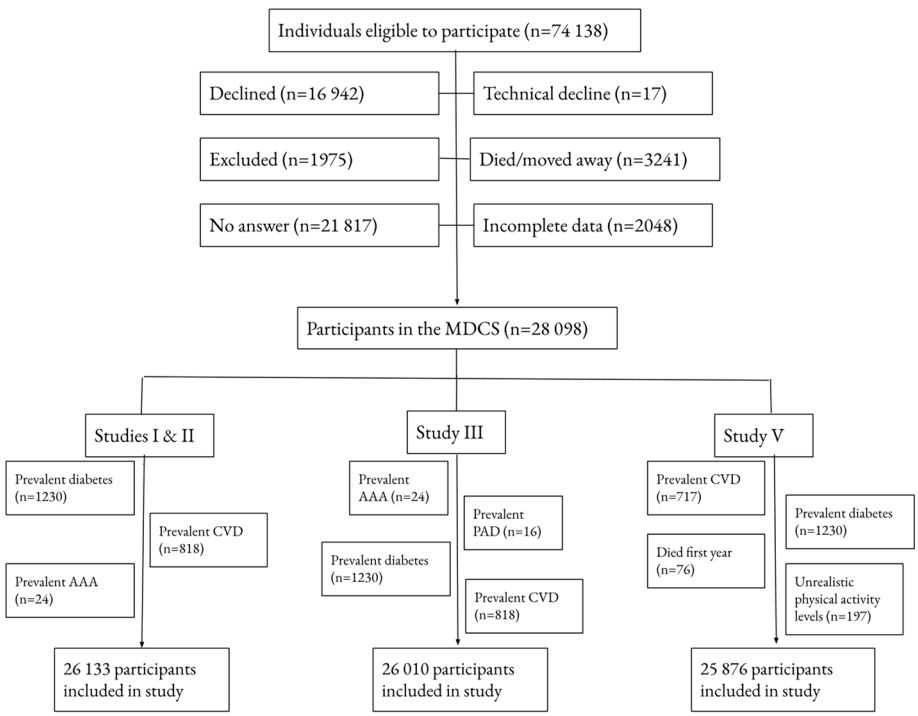


Figure 8: Flow chart of study populations and reasons for exclusion from the Malmö Diet and Cancer Study (Studies I, II, III and V)

Baseline data collection

The participants of the MDCS filled in a baseline dietary assessment, a self-administered lifestyle questionnaire and underwent anthropometric measurements at enrolment. All study participants also gave written informed consent, and the study was granted ethical approval from the Regional Ethical Review Board in Lund, Sweden. The dietary assessment consisted of a 7-day menu book, a food frequency questionnaire, and an interview. In the menu book participants were asked to record their cooked meals, cold beverages (including alcohol), medicines, natural remedies, and dietary supplements. The food frequency questionnaire was designed to map their general food pattern (to provide information not covered in the menu book), including the frequency and portion size, of foods with low day-to-day variation, such as hot beverages, sandwiches, snacks, and fruits. A booklet showing photographs of different portion sizes accompanied the questionnaire, and the participants chose which photograph best represented their own portion size. The interview was conducted by a dietician, partially to verify the information given in the menu book and the questionnaire. The participants were also asked to estimate their portion sizes and cooking patterns during the interview. The aim of the interview was also to ensure that there were no overlaps in food intake and that the overall food pattern was correct (81). The reported food intake of each participant was then converted into nutrient intake data using computer software and the Swedish Food Database, containing around 1600 basic foods, of the Swedish National Food Administration. If needed, additional recipes and foods were added to the database (81). The diet assessment method has shown good validity compared to a reference method, consisting of 18 days of weighed food records (82).

The lifestyle questionnaire was handed out to the participants at their first visit and was returned at the second, approximately two weeks later. The questionnaire was extensive and contained questions on, for instance: place of birth, education, occupation, social network and support, physical activity, tobacco consumption, alcohol consumption, previous weight and diet change, and medications and illnesses (83). The participants of the MDCS who were still alive and living in Sweden approximately five years after the baseline data had been collected were asked to fill in the entire lifestyle questionnaire again.

Assessments of exposures and outcomes

Diet quality index

The diet quality index utilised in studies I and III was developed by Drake and colleagues in 2011 (84). The index is based on Swedish nutrition recommendations 2005 and the Swedish dietary guidelines. The Swedish nutrition recommendations are based on the Nordic Nutrition Recommendations and include recommendations on the dietary macronutrient composition, the daily micronutrient intake as well as reference values for energy intake (4). These recommendations are based on current scientific evidence and are designed for healthy individuals. The Swedish dietary guidelines are published by the Swedish Food Agency (Livsmedelsverket). These guidelines are food-based, and the aim is to promote a diet that fulfils the Swedish nutrition recommendations (84).

The diet quality index was developed using a subsample of the MDCS cohort (n=12 991) in a cross-sectional design. The choice of diet components included in the diet index depended on three factors. First, the potential dietary component had to have been recorded at baseline in the MDCS. Second, the dietary components that were believed to have a relation to chronic diseases were primarily considered. Finally, the mutual dependence between the dietary components was assessed by testing their inter-correlation. Based on these factors the components included and their cut-off values were established, as given in Table 1:

Component	Cut-off
Saturated fat	≤14 E%
Polyunsaturated fat	5-10 E%
Fish and shellfish	≥300 g/week
Dietary fibre	2.4-3.6 g/MJ
Fruit and vegetables	≥400 g/day
Sucrose	≤10 E%

Table 1: Components of the diet quality index and their cut-offs

The cut-off for each component was based on the recommended level of intake in the Swedish nutrition recommendations (2005) and the Swedish dietary guidelines. However, the cut-off was not set at the recommended level for all of the components. Regarding saturated fat, only 2% of the study population adhered to the recommendation (≤10 E%), and therefore one standard deviation (SD) of the mean for the population was added in order to allow for higher adherence rates, giving a cut-off

of ≤14 E%. Similarly, the recommendation for dietary fibre has no definitive upper or lower limits, and the cut-off for the index was thus set at ±1 SD of the population mean, making the recommended intake 2.4-3.6 g/MJ. An upper limit of polyunsaturated fat intake was set due to potential adverse effects associated with an intake >10 E%. The fruit and vegetables component of the diet index excluded fruit juices; hence the cut-off was set at ≥400 g/day instead of the recommendation of ≥500 g/day, including a maximum of 100 g of fruit juices. Sucrose was included as a proxy for added sugar intake and sugar-rich foods, hence the recommended intake was for added sugar and not sucrose. The recommended intake for fish and shellfish is 2-3 times per week, which was estimated to be approximately 300 g/week. One point was awarded for each dietary component provided the recommendation was met. The total score for each individual therefore ranged from 0 (no recommendations met) to 6 (all recommendations met) (84).

Dietary fibre

In addition to being a component in the diet quality index explored in Studies I and III, fibre intake was investigated independently in Study II. It was not possible to divide fibre into different types in the food database. Therefore, the different fibre categories used in Study II were based on the most common sources of fibre in the study population. Cereals and bread were divided into the following groups, based on the fibre content: low-fibre soft bread (≤5.9% fibre), high-fibre soft bread (>6% fibre), high-fibre crisp bread and rusks (>10% fibre), high-fibre cereals (≥10% fibre) and low-fibre cereals (<10% fibre). Two composite variables were generated; whole grains (g/day) containing all high-fibre bread and cereals, and refined grains (g/day) containing all low-fibre bread and cereals.

Different types of fruit and vegetables were also analysed and categorised. Fruits were divided into citrus and non-citrus. Vegetables were grouped into root vegetables, leaf vegetables, carrots, cabbage, and total vegetable intake. All types of vegetable and citrus juices were included in the variable juice.

Overall fibre intake was expressed as a percentage of energy intake (E%). The composite variables whole grains and refined grains were expressed as servings/1000 kcal, and the remaining fibre variables as g/1000 kcal. The participants were divided into quintiles, based on their dietary intake. For the variables with a large proportion of zero-consumers (>25%), i.e., whole grains, cabbage, and juice, the zero-consumers were placed in one group and the remainder of the participants were divided into tertiles.

Leisure-time physical activity

At baseline, participants in the MDCS were requested to record their physical activity habits in the lifestyle questionnaire. Seventeen common physical activities were listed (see Table 2), and the individuals were asked to give the time spent on each activity, separately for each season of the year (spring, summer, autumn, and winter). Space was provided for individuals engaged in an activity not listed in the questionnaire to report this activity. This activity was then recoded to coincide with one of the 17 activities listed with an equivalent MET value (metabolic equivalent task). METs are defined as the estimated energy expenditure and amount of oxygen required for specific activities. For example, sitting quietly for one hour is equal to one MET, and playing tennis for one hour is equal to seven METs (85). One MET is equivalent to an oxygen uptake of 3.5 ml per kg of body weight, or one kcal per kg of body weight per hour. Body weight is not accounted for and therefore everyone is assigned the same MET value for the same activity, regardless of body weight (86).

Activity	MET value	Activity	MET value
Badminton	4.5	Cycling	4.0
Table tennis	4.0	Walking	3.5
Football	7.0	Walking stairs	8.0
Golf	4.5	Dancing	4.5
Running	7.0	Ballroom dancing	5.5
Gymnastics	4.0	Grass cutting	5.5
Orienteering	9.0	Digging	5.0
Swimming	7.0	Gardening	4.0
Tennis	7.0		

Table 2: The 17 activities included in the lifestyle questionnaire, and their MET values. Activities with >10% participants are underlined.

Total leisure-time physical activity was the main exposure in Study V. This was expressed in MET-h/week, and divided into the following intervals: <7.5, 7.5-15, 15-25, 25-50 and >50. This variable was an average of the 17 activities over all four seasons. To obtain MET-h/week, the sum of the MET values for each included activity was multiplied by the time spent on each activity. The intervals for this variable were chosen to reflect different levels of physical activity, while ensuring enough participants in each group to allow for meaningful analyses.

The 17 activities were also explored individually. A composite variable was also created for all the high-intensity physical activities. These activities are those defined as having MET values >6 and include running, swimming, tennis, football, and orienteering (85). Walking in stairs can also be considered a high-intensity activity but was not

included in the composite variable due to the very high rate of stair climbers among the participants and because the speed and energy exerted can vary greatly between individuals. Walking was not included in the analyses for the same reason. A second composite variable was generated for all ball sports and included badminton, table tennis, football, and tennis.

The information gathered at baseline was also compared with the levels reported at the five-year follow-up. To allow comparisons between the two time points, four categories were created for each of the 17 activities, namely: started, stopped, never, and continued. Individuals who did not report participation in an activity at baseline but did so at the five-year follow-up were categorised as 'started', and individuals who did the opposite, i.e., were engaged in an activity at baseline but not at the five-year follow-up were categorised as 'stopped'. Individuals who never took part in an activity were classed as 'never' and those who stated that they were engaged in an activity at both baseline and at the five-year follow-up were classed as 'continued'. This comparison was made for the most common activities, i.e., when >10% of study population participated at baseline (see Table 2), as well as for the composite variable high-intensity physical activity. The date of the five-year follow-up was set as the starting point for the individuals included in these analyses.

Socioeconomic, anthropometric and lifestyle variables

The variables age and sex were determined by the civic registration number of each individual in Studies I, II, III and V. Anthropometric measurements were made at baseline, and each participant's height, weight, and blood pressure after ten minutes of rest were registered. Their body mass index (BMI) was calculated as weight/height^2, and expressed in kg/m^2. Hypertension was defined as using any hypertensive medication, systolic blood pressure ≥130 mmHg, or diastolic blood pressure ≥85 mmHg.

Lifestyle variables were created based on the questionnaire. Regarding alcohol consumption, an individual was considered a zero-consumer if they had not consumed any alcohol during the past year. The remaining individuals were divided into sex-specific quintiles based on their reported consumption in the 7-day food diary. Smoking status was classified as: never, current, or former smoker. The former smokers also reported the time elapsed since cessation of smoking. This information was used to create a smoking score ranging from 0 to 4: 0 = never smoked; 1 = not smoking for 25-51 years; 2 = not smoking for 12-24 years; 3 = not smoking for 1-11 years; and 4 = current smoker, in Studies I and III. In Study II, the number of cigarettes per day for the smokers was assessed instead, resulting in the following quintiles: ≤7, 8-10, 11-15,

16-20 and ≥ 21. The highest educational level attained was categorised as follows: less than nine years, elementary school (9-10 years), upper secondary school (11-13 years), university without a degree, and university degree. Total energy intake was determined based on the dietary assessment, and consisted of intake through diet and supplements, including alcohol and fibre, and was expressed as kcal/day. Studies I and III also included variables related to the cardiovascular medications used by the participants, as reported in the 7-day menu book and the lifestyle questionnaire. The medications included were lipid-lowering medicines, statins, and acetyl salicylic acid for cardiovascular disease.

During the course of the MDCS, there was a change in coding routine in 1994; the time allocated to the diet interview being shortened from 60 to 45 minutes (81). This resulted in the variable 'method' which is included in the statistical model in Studies I-III. The variable 'seasons' accounts for the time of year (spring, summer, autumn, winter) when the baseline data collection was conducted, and is also used in papers I-III. In Study V, the date of baseline data collection and anthropometric measurements was used instead and denoted screening date. Individuals who reported that they had changed their diet in the past, by answering yes to "have you substantially changed your dietary habits in the past?" in the questionnaire, were labelled dietary changers. Potential dietary misreporters were identified by comparing the individually reported intake with their energy expenditure (87). Individuals who reported outside the 95% confidence interval for total energy expenditure were categorised as 'misreporters'. Both dietary changers and misreporters were included in the analyses in Studies I-III.

Endpoint ascertainment

In Studies I, II, III and V the endpoints were obtained by linking the civic registration number of each individual in the MDCS with registers. In studies I, II and III, the Cause of Death Register and the Inpatient and Outpatient Register were used. Information on the first diagnosis of AAA, ruptured AAA, or surgical procedure for AAA was gathered for Studies I and II. For Study III, the relevant endpoints were first diagnosis of PAD or surgical procedures for PAD. The Cause of Death Register includes all deaths in Sweden together with the cause of death as noted on the death certificate. The Inpatient and Outpatient Register logs all hospitalisations as well as procedural and surgical codes. The International Classification of Disease (ICD) versions 8, 9 and 10 were used for both registers in Studies I, II and III, and the surgical codes were based on a Swedish classification system. In Study V, the Cause of Death Register was utilised to ascertain the outcome cardiovascular mortality (CVM). ICD 9 and 10 were used, and the relevant codes were 390-459 and 100-199, respectively.

CVM was required to be listed as the main cause of death to be ascertained as the relevant endpoint.

Validation of diagnoses

The endpoints AAA, PAD and CVM were validated by randomly selecting 100 patients diagnosed with each respective outcome.

The validation for AAA was conducted on 100 of the individuals diagnosed with AAA in 2016. Eighty-two patients were diagnosed with AAA and 18 with ruptured AAA. Two individuals had been simultaneously diagnosed with AAA and ruptured AAA, and therefore 98 remained for the validation. The diagnosis AAA or ruptured AAA was confirmed in 93 out of the 98 patients (95%). The five misdiagnoses were: thoracic aortic aneurysm, common iliac aneurysm, multiple mycotic pseudoaneurysm in the abdominal aorta, chronic type B aortic dissection with secondary thoraco-abdominal aneurysm formation, and lower extremity artery stenosis.

For the diagnosis PAD, the validation showed that out of 100 patients, 69 had chronic limb-threatening ischaemia, 13 had acute limb ischaemia, 15 had intermittent claudication, and one had asymptomatic PAD. Two patients were misdiagnosed due to venous insufficiency. PAD could therefore be confirmed in 98% of cases.

The validation of the diagnosis CVM confirmed the diagnosis in 88 out of 100 patients. The cardiovascular death causes were heart failure (n=26), ischaemic heart disease (n=23), stroke (n=26), ruptured aortic aneurysm (n=5), pulmonary embolism (n=3), hypertension (n=2), ruptured gastroduodenal aneurysm (n=1), aortic dissection, type A (n=1) and aortic valve stenosis (n=1). Six causes of death were unclear and six were due to other causes, namely: pneumonia (n=3), chronic obstructive pulmonary disease (n= 2) and infection of unclear origin (n=1). The diagnosis of CVM could therefore be confirmed in 94% (88/94) of the individuals.

Statistical analysis

The statistical analyses in Studies I, II, III and V were primarily conducted using IBM SPSS (SPSS Inc., Chicago, IL) version 22 (Study I) and version 25 (Studies II, III and V). Rstudio 1.3.959 (Rstudio, Boston, MA, USA) using R 4.02 was used to plot Schoenfeld residuals in Study V.

Descriptive statistics

Papers I, II, III and V present descriptive statistics of the study participants. In Studies I and II, the individuals were divided according to incident AAA and in Study III according to incident PAD. In Paper V, the descriptive statistics are presented according to the five predefined physical activity levels of the included individuals. The descriptive statistics tables in each of these studies include information on socioeconomic and lifestyle factors, and the included variables are given as the mean (±SD) or median (and IQR) for continuous variables, and n (%) for categorical variables.

Survival analysis

Cox proportional hazards regression was performed using different models in Studies I, II, III and V, to obtain the hazard ratios. Studies I and III included three models which were tested with Cox regression, namely: basic, multivariable, and mutually adjusted multivariable. In Studies II and V, the models used were basic and multivariable. Study V also contained an additional model where BMI was added to the multivariable model. In Studies I, II, III and V, the basic model included age and sex and lifestyle factors (i.e., smoking, education level and alcohol intake) were added in the multivariable model. The mutually adjusted models in Studies I and III included the same variables as the multivariable model, but were also adjusted for the components of the dietary index. The variables included in the models were chosen based on their role as potential confounders in the association between exposure and outcome.

Additional analyses

Sensitivity analyses were carried out to assess any potential deviations from the main results in Studies I, II, III and V. In Studies I-III, individuals who had misreported their energy intake (categorised as 'misreporters') and the individuals who reported that

they had changed their diet in the past ('dietary changers') were excluded from the sensitivity analysis. In Study V, two additional analyses were conducted. First, hypertension was included in the analysis and tested in the multivariable model. The second analysis was conducted *post hoc* and assessed the influence on the results of individuals diagnosed with prevalent diabetes at baseline, who were excluded from the main analyses.

The role of smoking was further investigated in Study II by including an interaction term in the model. This interaction term consisted of a cross product of smoking status and the quintiles or tertiles of the dietary variables. In addition, *post hoc* analyses on the key findings were conducted separately for smokers and non-smokers.

The proportional hazards assumption was tested in Study V by plotting Schoenfeld residuals. The variables that violated the proportional hazards assumption were stratified and tested in models to assess the potential impact on the results.

Systematic review and meta-analysis

Paper IV presents a systematic review and meta-analysis published in the Cochrane Database of Systematic Reviews, and therefore adheres to the recommendations and standards outlined in the Cochrane Handbook for Systematic Reviews of Interventions (88). Before initiating the review, a protocol was written and published (89). The review investigated the effects of added sugar on CVD. The methodology employed in this review is explained in detail below.

Inclusion and exclusion criteria

The type of studies eligible for inclusion in the review were randomised controlled trials (RCTs), including cross-over trials. Cluster RCTs were also allowed, but no studies were identified with this design. Published and unpublished data were included as well as trials only reported as abstracts. Studies were required to last at least four weeks between baseline and follow-up, and six months was required for the primary outcomes. For cross-over trials, a minimum wash-out period of two weeks was required to avoid carry-over effects.

This review focused only on the adult population, and it was therefore an inclusion criterion that the included participants were older than 18 years. Since the primary outcome was incident cardiovascular events, trials on individuals already diagnosed as

having CVD were excluded. Studies on individuals with diabetes mellitus were also excluded from this review.

The exposure for the systematic review was high or low added sugar intake. The levels considered to be high or low were defined in the individual studies. Studies focusing on any type of added sugar (e.g., fructose, sucrose, or glucose) or sugar-rich foods or beverages, were included, but studies comparing the same intake level of different types of sugar (i.e., fructose vs. glucose) were excluded. As the aim was to evaluate the effects of added sugar, interventions investigating, for instance, different intake levels of fruit were not included. Nor were trials that encompassed a lifestyle alteration included (i.e., altering both diet and physical activity) to avoid potential confounding. The included trials were those giving dietary advice, those providing the participants with sugar-rich foods and/or beverages, or those modifying the diet. The comparison group was given either a placebo, no advice/supplementation, or was asked to continue their usual diet.

Outcomes

The primary outcomes for the review were:

- incident cardiovascular event (coronary, carotid, cerebral or peripheral arterial disease)
- all-cause mortality

In addition to the primary outcomes, nine secondary outcomes were also included.

- Changes in systolic blood pressure
- Changes in diastolic blood pressure
- Changes in total cholesterol
- Changes in low-density lipoprotein (LDL)-cholesterol
- Changes in high-density lipoprotein (HDL) -cholesterol
- Changes in triglycerides
- Changes in fasting plasma glucose
- Adverse events: gastrointestinal symptoms (such as nausea, abdominal pain, constipation, or diarrhoea)
- Adverse events: impaired dental health (such as dental caries)

If none of these outcomes was reported in a trial, but were deemed relevant for the review in other regards, attempts were made to contact the authors to determine whether the outcomes had been reported but not included in the final report. Studies in which the relevant outcomes were measured but the data not included, or trials in which the outcomes were not reported in a usable format, were described narratively in the results but not included in the meta-analysis.

Search methods and data collection

Relevant trials were identified by systematic searches of the following bibliographic databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library
- MEDLINE
- Embase
- Conference Proceedings Citation Index - Science

The search strategy was developed and run by an information specialist employed by the Cochrane Collaboration. No language restrictions were imposed, and studies were included regardless of their publication status. In addition to the search strategy developed by the Cochrane Collaboration, reference lists of the included trials were manually checked for any additional RCTs that had not been identified in the search.

The entire data collection was conducted independently by two review authors (the author of this thesis and Anna Johansson), and all decisions in the review process were required to be unanimous. If any disagreements occurred, two additional review authors were asked to arbitrate. In total, 17 716 titles and abstracts were screened and categorised as include/not include and 160 of them were assessed in full-text. Justification was required for excluding any of the trials assessed in full-text. Ultimately, 21 trials were included in the systematic review, and 20 were included in the meta-analysis. The complete study flow for the selection of trials can be seen in Figure 9.

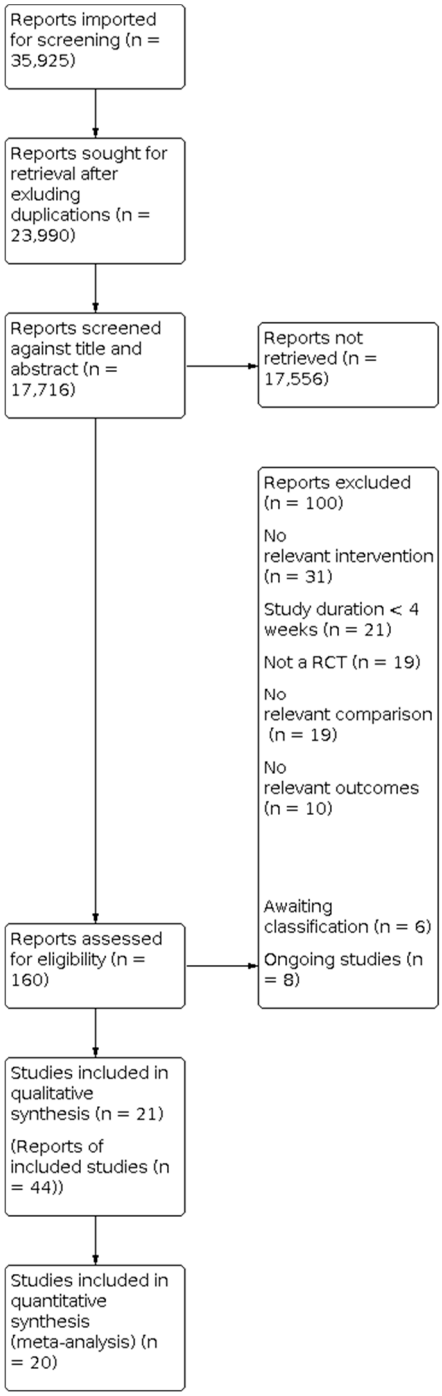


Figure 9: Study flow diagram for study IV

For the 21 studies included, the following data were extracted independently by the two review authors.

- *Methods*: study design, total duration of study, number of study centres and location, study setting, date of study, and wash-out period for cross-over trials.
- *Participants*: number randomised, number lost to follow-up/withdrawn, number analysed, mean age, age range, gender, mean BMI, parameters of metabolic syndrome, other diseases, weight change, compliance with intervention, inclusion criteria, and exclusion criteria. Baseline data on lipids and other characteristics were collected and assessed for imbalance between groups.
- *Interventions*: intervention details, and comparison details in sufficient detail to allow subgroups to be determined.
- *Outcomes*: primary and secondary outcomes (including adverse events) specified and collected, and time points reported.
- *Notes*: sources of trial funding and notable conflicts of interest of trial authors.

Risk of bias assessments

Risk of bias in each included intervention was assessed by studying and reporting the following criteria.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- Other bias.

An included study could be rated, for each risk of bias domain, as high, low, or unclear. For this review, the relevant primary other bias was compliance with the intervention.

For the cross-over trials the following domains were considered, in addition to those listed above:

- Whether the cross-over design was suitable.
- Whether there was a carry-over effect.
- Whether only first-period data were available.
- Incorrect analysis.
- Comparability of results with those from parallel-group trials.

Finally, to minimise the risk of bias when conducting this systematic review, it was conducted in accordance with the previously published protocol (89), and any deviations between the protocol and the review were reported in the review.

Measures of treatment and unit of analysis

The mean difference (MD) and standard error (SE) were used for continuous data. Trials reporting data as standard deviations (SD) were converted to SEs using the Revman calculator. When there were differences in units across trials conversion was made to the unit most used. Trials that only reported the median and interquartile range were narratively described, as insufficient information was provided to allow for conversions to the mean difference. For the trials in which results were reported at several time points, the time point with the longest follow-up was used. For trials including multiple intervention groups, only the highest and the lowest intake groups were included, to avoid splitting the control group.

Heterogeneity

The heterogeneity among the trials was assessed using the I^2 test and by evaluating the P value from the Chi^2 tests. The statistical significance was set at $P<0.05$ and a random-effects model was used when calculating I^2. The I^2 value was interpreted in accordance with the Cochrane Handbook (88), which gives the following guidelines:

0% to 40%: might not be important

30% to 60%: may represent moderate heterogeneity

50% to 90%: may represent substantial heterogeneity

75% to 100%: considerable heterogeneity

If substantial heterogeneity was identified, it was reported, and potential causes were explored by conducting the pre-specified subgroup analyses. Forest plots were also

examined to assess the direction and magnitude of the effects and to identify any potential overlapping 95% CIs.

Subgroup analyses

In addition to the main analyses of the included outcomes, the following subgroup analyses were carried out.

- Isocaloric exchange or ad libitum intake
- Liquid or solid state of added sugar source
- Control in form of starch/refined grains
- Weight change (> 0.5 kg difference in weight change between the two study arms) or no weight change
- Healthy population or high-risk population (metabolic syndrome or obesity, hypertension, dyslipidaemia, and elevated fasting blood glucose levels/pre-diabetes)
- Duration of intervention (more or less than 6 months)
- Industry funded studies or no involvement with industry

Sensitivity analyses

The following sensitivity analyses were conducted:

- Only including studies with a low risk of bias. A study was judged to be at low risk of bias when there was low risk in at least four domains (not including 'other bias'). Randomisation, concealed allocation, and selective outcome reporting were of the greatest concern in this review.
- Excluding cross-over trials.

Certainty of evidence assessment

The certainty of the evidence was assessed using the GRADEpro software (90) together with the GRADEpro handbook (91). This software enabled an assessment of the evidence, based on the following considerations.

- Study limitations
- Consistency of effect
- Indirectness
- Imprecision
- Publication bias

Study limitations refers to the risk of biases identified in the studies. Judgment was based on the collective risk of bias for all studies included, separately for each outcome, and rated as low, unclear, or high. Consistency of effect describes any potential unexplained heterogeneity in the results. This means that heterogeneity was not necessarily a problem, provided it could be explained, for example by differences in populations, interventions, or study methods. This could be tested by conducting relevant subgroup analyses. Indirectness assesses the level of confidence the review authors had that the results showed direct evidence. There were four sources of indirectness: differences in population, differences in interventions, differences in outcome measures (surrogate outcomes), and indirect comparisons. Imprecision existed when the results were imprecise due to few participants and/or few events, causing wide CIs. In other words, it assessed the review authors' confidence in the effect estimates. Finally, publication bias refers to a systematic over- or under-estimation of the beneficial or harmful effects of the topic at hand.

According to the Cochrane recommendations, the number of outcomes that can be assessed is limited, hence not all outcomes could be included in this evaluation. The following outcomes were considered the most relevant and were therefore included in the quality of evidence assessment.

- Cardiovascular event
- All-cause mortality
- Systolic blood pressure
- Total cholesterol
- LDL-cholesterol
- Fasting plasma glucose

The quality of evidence assessment ultimately resulted in a grade that represents how the review authors rated the *overall* quality of evidence for each outcome. The four grades and the definitions are given in Table 3.

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident about the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect

Table 3: Quality of evidence grades obtained from the GRADEpro assessment

Results

Characteristics of the study participants in the MDCS

The baseline demographic and socioeconomic characteristics of the participants in Studies I, II, III and V are presented in Table 4. The baseline dietary intake in Studies I-III is given in Table 5. The study population varies slightly due to different exclusion criteria, but they are similar in other regards.

The majority of individuals diagnosed with AAA, PAD or who died of cardiovascular disease were men, and were slightly older than the individuals who were not diagnosed with these conditions. For AAA, 61% of the individuals were current smokers, compared with 28% in the non-AAA group. BMI, physical activity, and alcohol consumption were similar across the groups. As individuals with prevalent CVD were excluded from the studies, very few individuals who were included reported using statins or acetylsalicylic acid. Individuals who died of CVD had a higher prevalence of hypertension, than those who did not (91% vs. 75%).

Individuals diagnosed with AAA generally consumed less fruit and vegetables than individuals without AAA. They also consumed less fibre and less sucrose than non-AAA individuals. Individuals diagnosed with PAD consumed less fibre than individuals not diagnosed with PAD. Otherwise, no major differences in dietary intake were identified in the PAD subgroup, compared with the control group.

	Study 1		Study II		Study III		Study V	
Variable	**AAA**	**Non-AAA**	**AAA**	**Non-AAA**	**PAD**	**Non-PAD**	**CVM**	**Non-CVM**
N	353	25780	429	25704	1122	24888	2564	23312
Males (%)	260 (73)	9616 (37)	315 (73)	9561 (37)	483 (43.0)	9333 (37.5)	1357 (52.9)	8410 (36.1)
Age (years)	62.1 (9.5)	57.2 (12.9)	60.7 (8.8)	57.8 (7.6)	57.7 (7.2)	57.8 (7.6)	64.0 (6.4)	57.2 (7.4)
BMI (kg/m^2)	25.6 (4.6)	25.2 (4.8)	25.6 (3.9)	26.2 (3.8)	25.8 (3.8)	25.6 (3.9)	26.5 (4.2)	25.5 (3.8)
Current smoker	214 (60.6)	7223 (28)	256 (59.7)	7181 (27.9)	329 (29.3)	7079 (28.4)	836 (32.6)	7717 (33.1)
Leisure-time physical activity								
0-7.5 MET-h/week	51 (14.6)	2394 (9.4)	55 (12.8)	2390 (9.3)	107 (9.5)	2324 (9.3)	264 (10.3)	2170 (9.3)
15-25 MET-h/week	66 (18.9)	5896 (23)	88 (20.5)	5874 (22.9)	258 (23.0)	5685 (22.8)	533 (20.8)	5420 (23.2)
>50 MET-h/week	53 (15.1)	4098 (16)	60 (14)	4091 (15.9)	164 (14.6)	3961 (15.9)	465 (18.1)	3665 (15.7)
Alcohol consumption								
Quintile 1	70 (19.8)	4728 (18.3)	83 (19.3)	4715 (18.3)	217 (19.3)	4561 (18.3)	585 (22.8)	4149 (17.8)
Quintile 3	68 (19.3)	4889 (19)	90 (21)	4867 (18.9)	192 (17.1)	4745 (19.1)	464 (18.1)	4450 (19.1)
Quintile 5	65 (18.4)	4925 (19.1)	81 (18.9)	4909 (19.1)	221 (19.7)	4744 (19.1)	407 (15.9)	4547 (19.5)

Table 4: Demographic and socioeconomic characteristics of the participants in Studies I, II, III and V. Mean (and SD) are shown for the variables age and BMI. N (%) is given for the remainder of the variables.

	Study 1		Study II		Study III	
Diet variable	**AAA**	**Non-AAA**	**AAA**	**Non-AAA**	**PAD**	**Non-PAD**
Saturated fat (E%)	15.75 (5.14)	15.82 (4.73)			16.5 (3.9)	16.2 (3.8)
Polyunsaturated fat (E%)	6.07 (2.15)	5.73 (1.97)			6.0 (1.6)	5.9 (1.6)
Fish and shellfish (g/week)	290.81 (290.87)	276.67 (287.76)			277 (298)	277 (287)
Fibre (g/MJ or E%)	1.87 (0.84)	2.13 (0.78)	1.63 (0.56)	1.81 (0.54)	2.17 (0.6)	2.21 (0.6)
Fruit and vegetables (g/day)	274.25 (197.30)	347.83 (228.72)			355 (228)	347 (229)
Sucrose (E%)	7.76 (5.25)	8.12 (4.21)			8.3 (3.5)	8.6 (3.5)
Vegetables (g/1000 kcal)	53 (15.1)	4098 (16)	60 (14)	4091 (15.9)	164 (14.6)	3961 (15.9)
Fruit and berries (g/1000 kcal)			59.53 (48.20)	74.50 (56.37)		
Juice (g/1000 kcal)			0.03 (25.92)	0.31 (45.07)		
Whole grains (servings/1000 kcal)			0.11 (0.25)	0.15 (0.26)		
Refined grains (servings/1000 kcal)			1.10 (0.68)	1.07 (0.64)		
Potatoes (g/1000 kcal)			58.25 (34.72)	49.59 (35.30)		

Table 5: Baseline diet characteristics of the participants in Studies I-III. Mean (and SD) are given for all variables in the table. Fibre expressed as g/MJ in Studies I and III, and as E% in Study II.

Diet quality index and the risks of AAA and PAD

The diet quality index used in Studies I and III was investigated in relation to the risk of AAA (Paper I) and PAD (Paper III).

Diet quality index score

AAA

No associations were found when comparing the medium and high categories of the diet quality index with the lowest category, in the multivariable model (Figure 10). The P values of the risk per diet index category, i.e., comparing the risk of each category with the preceding one (e.g., high category vs. medium category), were 0.03 and 0.68 in the basic and multivariable model, respectively.

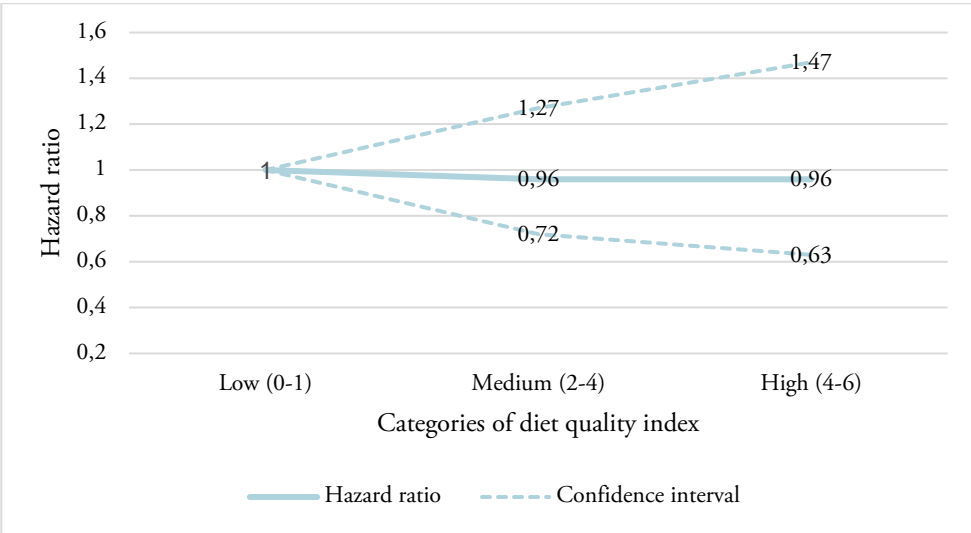


Figure 10: HR and 95% CI for incident AAA by category of the diet quality index, tested in the multivariable model. Adjusted for age, sex, total energy intake, diet assessment method, season, alcohol consumption, physical activity, smoking, education, and BMI.

PAD

An association was found between the diet quality index and the risk of PAD in the basic model, when comparing the high category with the low category; and the association was attenuated in the multivariable model (Figure 11). The risk per diet index category showed an association in the basic model (P=0.009), and an almost statistically significant association in the multivariable model (P=0.06).

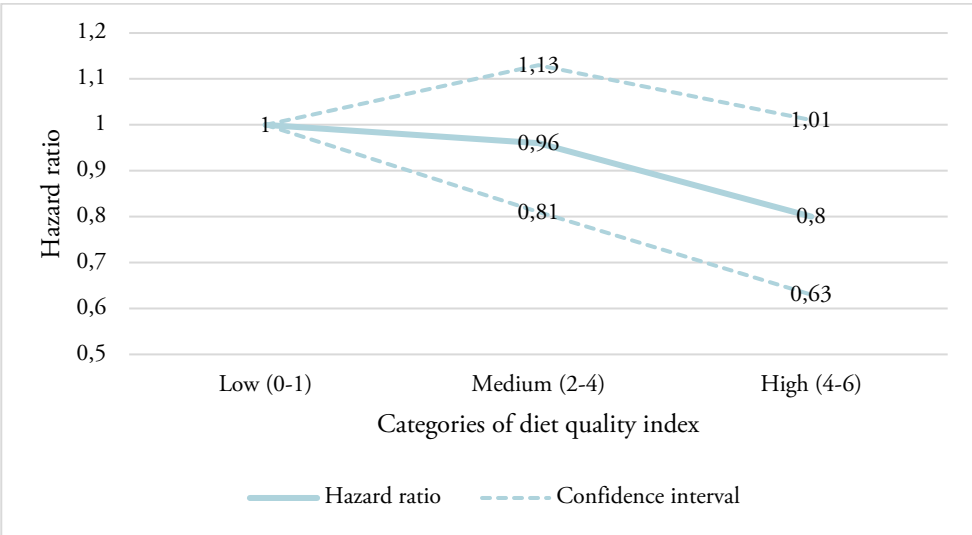


Figure 11: HR and 95% CI for incident PAD by category of the diet quality index, tested in the multivariable model. Adjusted for age, sex, total energy intake, diet assessment method, season, alcohol consumption, physical activity, smoking, education, and BMI.

Adherence to diet quality index components

Table 6 gives the association between adherence to the dietary recommendations included in the diet quality index and the risk of AAA and PAD, in the multivariable and mutually adjusted multivariable models. Adherence to the dietary recommendations for fibre, and fruits and vegetables was associated with a reduced risk of AAA in the basic model; HRs of 0.68 (95% CI 0.53-0.88) and 0.59 (95% CI 0.46-0.76), respectively. Using the multivariable model, a trend was seen for adherence to the recommendations for fruit and vegetables and the risk of AAA (P=0.07).

An association was identified between fibre intake and the risk of PAD in the basic (HR 0.79; 95% CI 0.70-0.91), multivariable (HR 0.83; 95% CI 0.72-0.95), and mutually

adjusted multivariable (HR 0.84; 95% CI 0.72-0.99) models. An association was also found regarding the intake of fruit and vegetables in the basic (HR 0.82; 95% CI 0.72-0.93) and multivariable (HR 0.85; 95% CI 0.74-0.96) models, while the association was lower in the mutually adjusted multivariable model.

	AAA		PAD	
Dietary component	**Non-adherence**	**Adherence**	**Non-adherence**	**Adherence**
Saturated fat	> 14 E%	≤ 14 E%	> 14 E%	≤ 14 E%
Multivariable model	1.00	1.16 (0.92-1.48)	1.00	0.96 (0.84-1.10)
Mutually adjusted multivariable model	1.00	1.24 (0.95-1.61)	1.00	1.06 (0.92-1.23)
Polyunsaturated fat	<5 E% or >10 E%	5-10 E%	<5 E% or >10 E%	5-10 E%
Multivariable model	1.00	1.10 (0.86-1.40)	1.00	1.02 (0.90-1.17)
Mutually adjusted multivariable model	1.00	1.09 (0.86-1.40)	1.00	0.99 (0.87-1.14)
Fish and shellfish	< 300 g/week	≥ 300 g/week	< 300 g/week	≥ 300 g/week
Multivariable model	1.00	0.93 (0.75-1.15)	1.00	0.91 (0.80-1.03)
Mutually adjusted multivariable model	1.00	0.93 (0.75-1.15)	1.00	0.92 (0.81-1.04)
Fibre	< 2.4 g/MJ or >3.6 g/MJ	2.4-3.6 g/MJ	< 2.4 g/MJ or >3.6 g/MJ	2.4-3.6 g/MJ
Multivariable model	1.00	0.94 (0.73-1.22)	1.00	0.83 (0.72-0.95)
Mutually adjusted multivariable model	1.00	0.97 (0.71-1.32)	1.00	0.84 (0.72-0.99)
Fruit and vegetables	< 400 g/day	≥ 400 g/day	< 400 g/day	≥ 400 g/day
Multivariable model	1.00	0.79 (0.61-1.02)	1.00	0.85 (0.74-0.96)
Mutually adjusted multivariable model	1.00	0.78 (0.59-1.03)	1.00	0.91 (0.78-1.05)
Sucrose	> 10 E%	≤ 10 E%	> 10 E%	≤ 10 E%
Multivariable model	1.00	0.97 (0.77-1.23)	1.00	1.07 (0.94-1.23)
Mutually adjusted multivariable model	1.00	0.99 (0.78-1.27)	1.00	1.10 (0.96-1.27)

Table 6: HR and 95% CI for adherence to the diet components and the risk of AAA and PAD. Multivariable model adjusted for age, sex, total energy intake, diet assessment method, season, alcohol consumption, physical activity, smoking, education, and BMI. Mutually adjusted multivariable model adjusted for age, sex, total energy intake, diet assessment method, season, alcohol consumption, physical activity, smoking, education, BMI, and mutual adjustment for the six diet quality index components.

Sensitivity analyses

Sensitivity analyses were carried out in Studies I and III after removing misreporters (n=4799) and dietary changers (n=5623). The association between the diet index score and the risk of AAA or PAD remained virtually the same. The association between the dietary components remained the same for AAA risk. The association between adherence to the recommendation for fish and shellfish and incident PAD was strengthened in the mutually adjusted model (HR 0.84; 95% CI 0.72–0.97) but remained the essentially the same for the other components.

Fibre intake and the risk of AAA

The association between the intake of fibre and plant foods, and AAA was investigated in study II.

Fruit and vegetables

The association between various types of fruits and vegetables and the risk AAA was investigated and tested in several models. Figure 12 shows the risk of AAA according to category of total vegetable intake and total intake of fruit and berries. An association was identified for both vegetables, and fruit and berries. In the multivariable model, the HRs were 0.91 (95% CI 0.84-0.98) and 0.89 (95% CI 0.82-0.96) for vegetables, and fruit and berries and AAA risk, respectively.

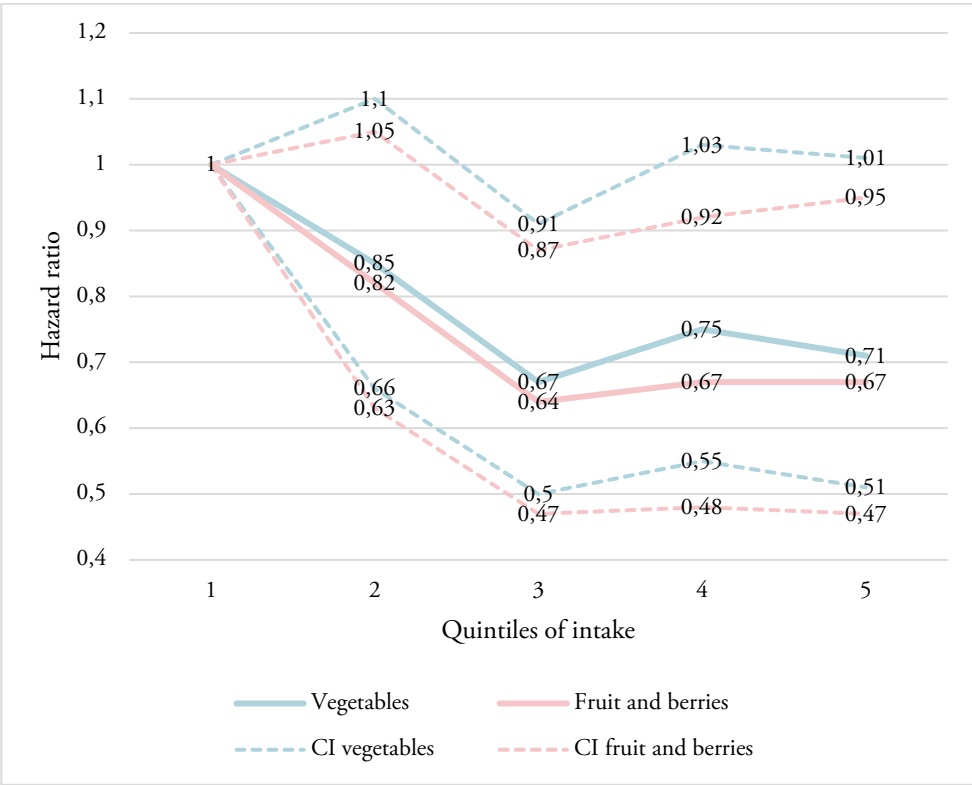


Figure 12: HR and 95% CI for intake of vegetables and fruits and berries in the multivariable model for AAA, in relation to quintiles of dietary components. Adjusted for age, sex, season, method, total energy intake, physical activity, education, alcohol, smoking and BMI

The association between the intake of leaf vegetables and the risk of AAA in and multivariable model is shown in figure 13. The HR for AAA risk was 0.87 (95% CI 0.81-0.94) in the basic model, and 0.88 (95% CI 0.80-0.97) in the multivariable model. No significant associations were identified in the multivariable model for potatoes, root vegetables, carrots, or cabbage.

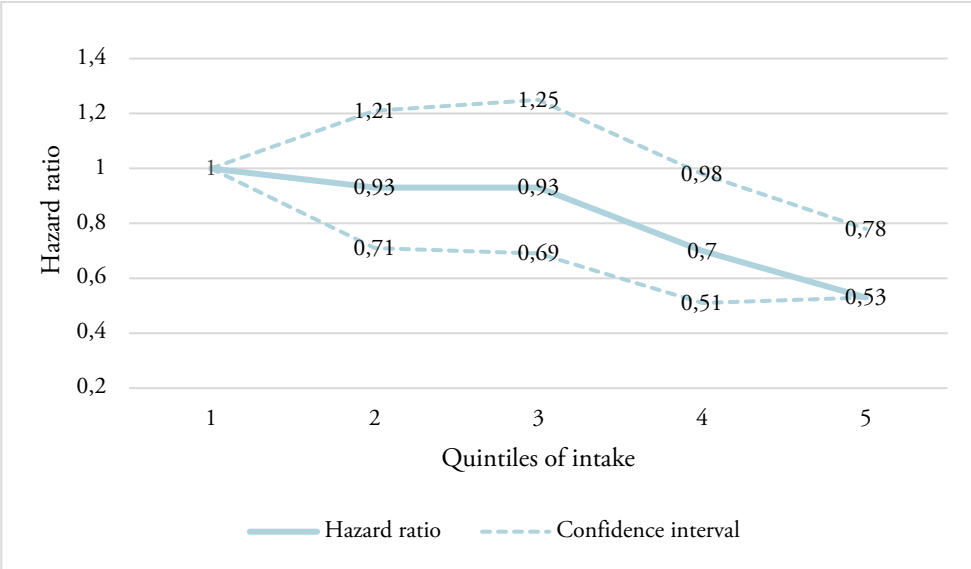


Figure 13: HR and 95% CI for intake of leaf vegetables in the multivariable model for AAA, in relation to quintiles of dietary component. Adjusted for age, sex, season, method, total energy intake, physical activity, education, alcohol, smoking and BMI

When fruits were divided into citrus and non-citrus, the AAA risk was found to be slightly lower for non-citrus fruits than for citrus fruits, with HRs per quintile of 0.87 (95% CI 0.81-0.95) and 0.91 (95% CI 0.85-0.98) in the multivariable model, respectively. The lowest risks were observed in the fourth quintile for non-citrus fruits (HR 0.61 95% CI 0.44-0.84) and in the fifth quintile for citrus fruits (HR 0.68 95% CI 0.49-0.95), when compared with the lowest intake group (first quintile).

Refined and whole grains

No associations were identified between the intake of refined grains and risk of AAA. Fibre intake and the intake of whole grains were associated with reduced AAA risk in the basic model, with HRs of 0.80 (95% CI 0.74-0.86) and 0.88 (95% CI 0.82-0.94), respectively. None of the associations were significant in the multivariable model (Figure 14) but became statistically significant again in the sensitivity analysis excluding misreporters.

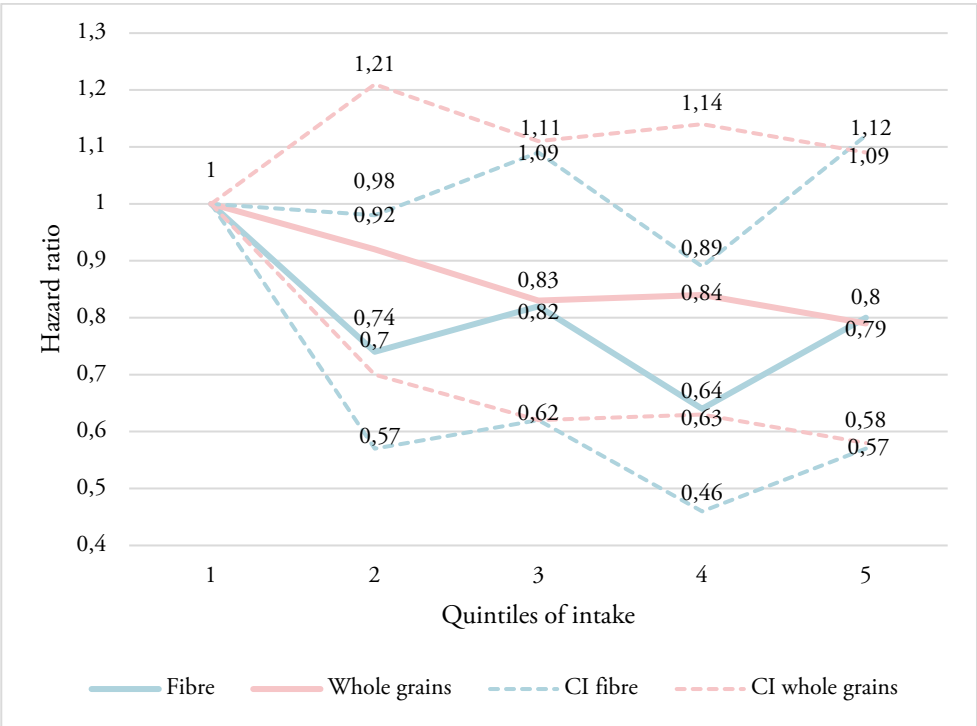


Figure 14: HR and 95% CI for intake of fibre, whole grains, and refined grains in the multivariable model for AAA, in relation to quintiles of dietary components. Adjusted for age, sex, season, method, total energy intake, physical activity, education, alcohol, smoking and BMI

Smoking status

Further analyses regarding smoking status were performed in Study II. Instead of adjusting for smoking status (never, former, or current), adjustments in the multivariable model were made according to number of cigarettes per day. This did not change the results. The analysis was also stratified for smoking status. When only current smokers were included in the analysis, the associations were attenuated for total and leaf vegetables, but remained the same for fruit and berries, citrus fruits, non-citrus fruits, and fibre. When only non-smokers and former smokers were included in the analysis, no associations were found for total vegetables, leaf vegetables, citrus fruits, or fibre. The risk was in principle unchanged for fruit and berries, and non-citrus fruits. No significant interactions were identified in AAA risk between smoking status and leaf vegetables (P=0.19), total vegetables (P=0.29), fruit and berries (P=0.31), fibre (P=0.94), citrus fruits (P=0.43), or non-citrus fruits (P=0.17).

The effects of high and low added sugar intake on CVD

The study presented in Paper IV was performed to investigate the possible role of different levels of added sugar intake in the primary prevention of CVD.

Included studies

Types of studies

In total, 21 studies were included in the systematic review (92-113). One trial (113) did not provide any SDs for the results and could therefore not be included in the meta-analysis. Hence, 20 trials were included in the meta-analysis. Seven were crossover trials and 14 were parallel group RCTs. The year of publication of the studies ranged from 1972 to 2021, and the majority were published in the 2000s. Six studies had been conducted in the US, five in the UK, two each in Denmark, Switzerland, Norway, and Mexico and one in New Zealand and one in South Africa. Twelve of the included studies were two-arm trials, five were three-arm trials, three were four-arm trials, and one a six-arm trial. Table 7 provides information on the trials included and the study characteristics.

Study population

The total study population for all the trials included was 1110, the mean study population per trial was 53, and the study populations ranged in size from 13 (92, 97) to 231 (98). In general, the study population was described as healthy (92, 103, 106, 111-113) or overweight or obese (93, 97-101, 104, 105, 107). One trial required the participants to be at increased CVD risk (110). Two trials focused on individuals with a specific diagnosis: polycystic ovary syndrome (96) and non-alcoholic fatty liver disease (108). It was also required in some trials that the participants had a habitually high SSB consumption (93, 94, 102, 109).

Title	Authors	Country and publication year	Design and duration	Reported outcomes
Effects of high and low sugar diets on cardiovascular disease risk factors.	Ahmad, A, Isherwood, C, Umpleby, M et al.	UK 2021	Crossover, 12 weeks x2, wash-out 4 weeks	SBP, DBP, triglycerides, total-c, HDL-c, LDL-c, FPG
Effect of eucaloric high- and low-sucrose diets with identical macronutrient profile on insulin resistance and vascular risk	Black, R N, Spence, M, McMahon, R O et al.	UK 2006	Crossover, 6 weeks x2, wash-out 4 weeks	SBP, DBP, total-c, HDL-c, LDL-c, FPG
Sugar- and artificially sweetened beverages and intrahepatic fat	Campos, V, Despland, C, Brandejsky, V et al.	Switzerland 2015	Parallel group RCT, 12 weeks	SBP, DBP, total-c, LDL-c, triglycerides, FPG
Differential effects of sugar-sweetened, artificially sweetened, and unsweetened beverages on taste preference but not CVD risk factors in a 12-month RCT	Ebbeling, C B, Feldman, H A, Steltz, S K et al.	USA 2019	Parallel group RCT, 12 months	SBP, DBP, HDL-c, LDL-c, FPG
Fructose- and sucrose- but not glucose sweetened beverages promote hepatic de novo lipogenesis	Geidl-Flueck, B, Hochuli, M, Nemeth, A et al.	Switzerland 2021	Parallel group RCP, 7 weeks	SBP, DBP
Fructose content of low-calorie diets: Effect on cardiometabolic risk factors in obese women with polycystic ovarian syndrome	Johnson, L K, Holven, K B, Nordstrand, N et al.	Norway 2015	Parallel group RCT, 8 weeks	SBP, DBP, total-c, HDL-c, LDL-c, triglycerides, FPG
Comparison of 5% versus 15% sucrose intakes as part of a eucaloric diet in overweight and obese subjects: effects on insulin sensitivity, glucose metabolism, vascular compliance, body composition and lipid profile.	Lewis, A S, McCourt, H J, Ennis, C N et al.	UK 2013	Crossover, 6 weeks x2, wash-out 4 weeks	SBP, DBP, total-c, HDL-c, LDL-c, FPG

The effects of fructose containing sugars on weight, body composition and cardiometabolic risk factors when consumed at up to the 90th percentile population consumption level for fructose	Lowndes, J, Sinnett, S, Yu, Z et al.	USA 2014	Parallel group RCT, 10 weeks	SBP, DBP, total-c, HDL-c, LDL-c, triglycerides, FPG
The effect of normally consumed amounts of sucrose or high fructose corn syrup on lipid profiles, body composition and related parameters in overweight/ obese subjects	Lowndes, J, Sinnett, S, Pardo, S et al.	USA 2014	Parallel group RCT, 10 weeks	SBP, DBP, total-c, HDL-c, LDL-c, triglycerides, FPG
A pilot study on the impact of a low fructose diet and allopurinol on clinic blood pressure among overweight and prehypertensive subjects	Madero, M, Rodriguez Castellanos, F E, Jalal, D et al.	Mexico 2015	Parallel group RCT, 4 weeks	SBP, DBP, total-c, triglycerides
Sucrose-sweetened beverages increase fat storage in the liver, muscle, and visceral fat depot	Maersk, M, Belza, A, Stodkilde-Jorgensen, H et al.	Denmark 2012	Parallel group RCT, 6 months	Total-c, LDL-c, triglycerides, FPG
Sugar-sweetened product consumption alters glucose homeostasis compared with dairy product consumption in men and women at risk of type 2 diabetes mellitus	Maki, K C, Nieman, K M, Schild, A L et al.	USA 2015	Crossover, 6 weeks x2, wash-out 2 weeks	Total-c, HDL-c, LDL-c, triglycerides, FPG
Effects on serum-lipids in normal men of reducing dietary sucrose or starch for five months	Mann, J I, Hendricks, D A, Truswell, A S et al.	South Africa 1970	Parallel group RCT, 22 weeks	No outcomes included in the systematic review
Energy compensation following consumption of sugar-reduced products	Markey, O, Le Jeune, J, Lovegrove, J A	UK 2016	Crossover, 8 weeks x2, wash-out 4 weeks	SBP, DBP total c, HDL-c, LDL-c, triglycerides, FPG

Effects of sugar-sweetened and sugar-free cocoa on endothelial function in overweight adults.	Njike, V Y, Faridi, Z, Shuval, K et al.	USA 2011	Crossover, 6 weeks x3, wash-out 4 weeks	SBP, DBP, total-c, HDL-c, LDL-c, triglycerides, FPG
Increased postprandial glycaemia, insulinemia, and lipidemia after 10 weeks' sucrose-rich diet compared to an artificially sweetened diet	Raben, A, Moller, B K, Flint, A et al.	Denmark 2002	Parallel group RCT, 10 weeks	SBP, DBP, total-c, HDL-c, triglycerides, FPG
Changes in nutrient and calorie intake, adipose mass, triglycerides and TNF-alpha concentrations after non-caloric sweetener intake	Sanchez-Delgado, M, Estrada, JA, Paredes-Cervantes, V et al.	Mexico 2021	Parallel group RCT, 6 weeks	Total-c, triglycerides, FPG
The effect of reduced extrinsic sucrose intake on plasma triglyceride levels	Smith, J B, Niven, B E, Mann, J I.	New Zealand 1996	Parallel group RCT, 9 months	Total-c, LDL-c, triglycerides
Metabolic and behavioral effects of a high-sucrose diet during weight loss.	Surwit, R S, Feinglos, M N, McCaskill, C C et al.	USA 1997	Parallel group RCT, 6 weeks	SBP, DBP, total-c, HDL-c, LDL-c, triglycerides, FPG
A diet low in sugar reduces the production of atherogenic lipoproteins in men with high liver fat	Umpleby, M, Shojaee-Moradie, F, Fielding, B et al.	UK 2015	Crossover, 12 weeks x2, wash-out 4 weeks	Total-c, HDL-c, LDL-c, FPG
A randomized control trial for reduction of caloric and non-caloric sweetened beverages in young adults: effects in weight, body composition and blood pressure.	Vazquez-Duran, M, Orea-Tejeda, A, Castillo-Martinez, L et al.	Mexico 2016	Parallel group RCT, 6 months	SBP, DBP

Table 7: Trials included and study characteristics of study IV. SBP=systsolic blood pressure, DBP=diastolic blood pressure, total-c=total cholesterol HDL-c =HDL-cholesterol, LDL-c=LDL-cholesterol, FPG=fasting plasma glucose

Description of interventions

The different types of interventions and controls included in the systematic review are shown in Figure 15. The most common study interventions were to compare the effects of high and low intake of sucrose, as a percentage of the total daily energy intake, as well as comparing SSBs with unsweetened or artificially sweetened beverages. Eight trials used an ad-libitum diet, and the remaining trials described the dietary exchange as isocaloric.

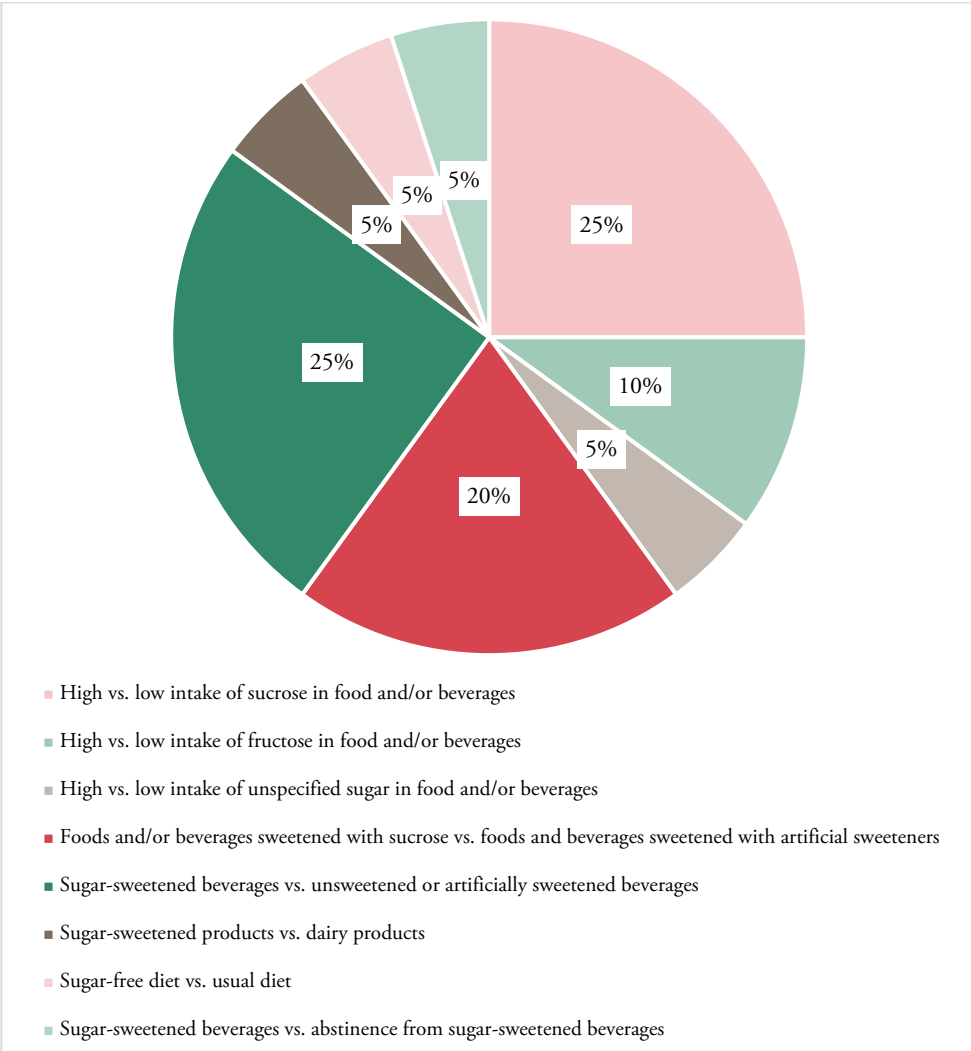


Figure 15: Types of interventions and controls included in the meta-analysis in Study IV

Included outcomes

None of the included studies reported on the primary outcomes, cardiovascular events, and all-cause mortality. At least ten different trials reported on each secondary outcome, a prerequisite according to the previously published protocol, which allowed for analysis of all secondary outcomes. One trial did not report the SDs for the reported outcomes and could thus not be included in the meta-analysis, but was only reported narratively (113). One study reported on dental health, which was included as a potential adverse event (101).

Risk of bias

The risk of bias for each included trial was assessed in seven domains. Figure 16 shows the summative risk of bias for all trials. All studies assessed compliance with the intervention by, for instance, interviews throughout the study or by requesting the participants to return empty packages of beverages to the study site. All crossover trials had a suitable study design and an adequate wash-out period. Eight trials were not blinded, primarily because the trialists stated that blinding was not possible due to the nature of the intervention, for instance, when the intervention group and the control group were given different products. Eleven trials reported on the randomisation sequence generation in sufficient detail and accounted for the randomisation methods used. Eight trials reported the number of individuals lost to follow-up, and reasons for attrition, and had similar drop-out rates in the intervention groups. Four studies did not meet these criteria and were rated at a high risk of attrition bias. Trials were rated at an unclear risk of bias when it was not possible for the review authors to assess the domains based on the published report, as was the case for all trials in at least some domains. Five trials were rated as having an overall low risk of bias (100, 103, 104, 109, 111), meaning that these trials were rated as low risk of bias in at least four domains (not including 'other bias').

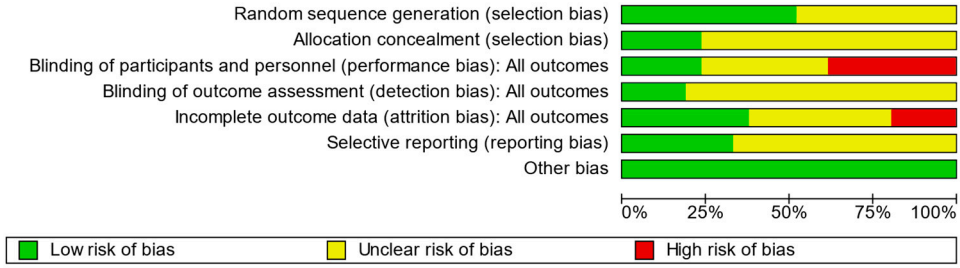


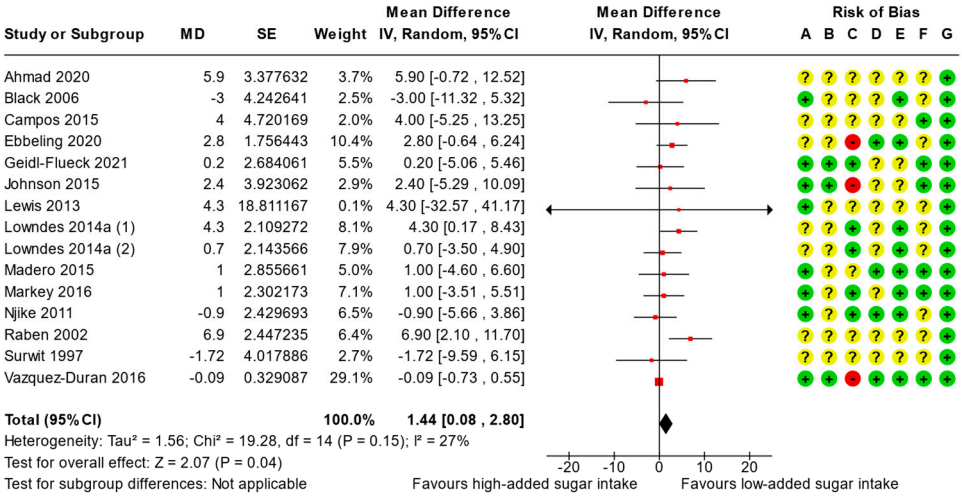
Figure 16: Risk of bias in the trials included in Study IV. Based on the review authors' judgement of each risk of bias domain as percentage across all included trials

Effect of interventions

No trials reported on the primary outcomes cardiovascular event and all-cause mortality. Detailed results for blood pressure and blood lipids are given below. For fasting plasma glucose, no difference in effect was observed between the comparison groups (MD 0.06, 95% CI -0.01-0.13; I^2=26%; 14 studies; 720 participants; low certainty of evidence).

Blood pressure

A difference in effect between the comparison groups was observed for both systolic blood pressure (MD 1.44, 95% 0.08-2.80; I^2 = 27%; 14 studies; 873 participants; low certainty of evidence) and diastolic blood pressure (MD 1.52, 95% CI 0.67-2.37; I^2 = 0%; 13 studies; 873 participants), both favouring a low added sugar intake, as can be seen in Figures 17 and 18, respectively.



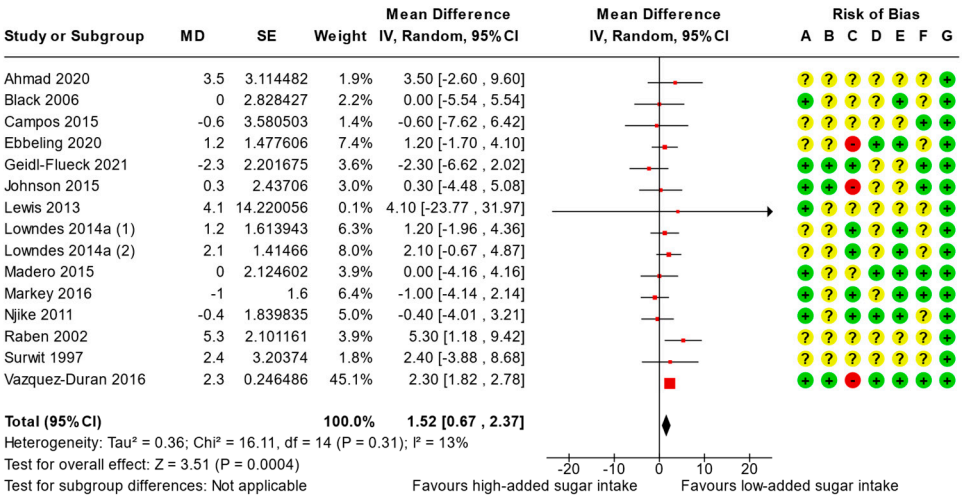
Footnotes

(1) Shows the two arms of the intervention that compares high and low sucrose intake.
(2) Shows the two arms of the intervention that compares high and low HFCS intake.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 17: Effect of high vs. low added sugar consumption for the outcome systolic blood pressure



Footnotes

(1) Shows the two arms of the intervention that compares high and low sucrose intake.
(2) Shows the two arms of the intervention that compares high and low HFCS intake.

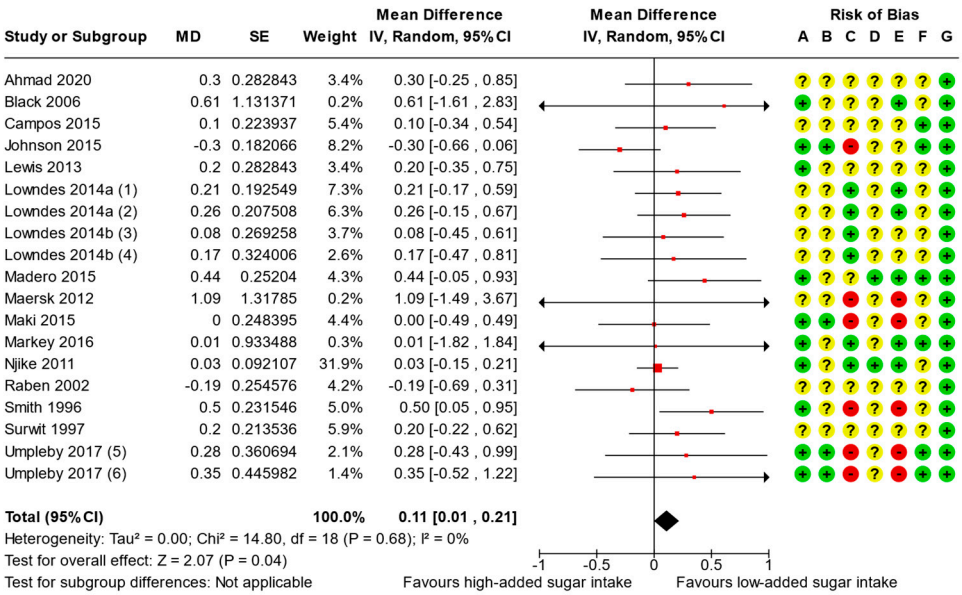
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 18: Effect of high vs. low added sugar consumption on the outcome diastolic blood pressure

Blood lipids

A difference in effect between the comparison groups was observed for total cholesterol (MD 0.11, 95% CI 0.01-0.21; I^2 = 0%; 16 studies; 763 participants; low certainty of evidence), favouring a low added sugar intake (Figure 19). HDL-cholesterol (MD 0.01, 95% CI -0.02-0.04; I^2 = 0%; 16 studies; 817 participants; low certainty of evidence) and LDL-cholesterol (MD 0.01, 95% CI -0.08-0.10; I^2 = 20%; 12 studies; 712 participants; low certainty of evidence) were also analysed separately, showing no difference in effect between the comparison groups for either outcome. The results for triglyceride levels showed a difference in effect between the comparison groups (MD 0.10, 95% CI 0.03-0.17; I^2 = 3%; 14 studies; 725 participants), favouring a low added sugar intake, as can be seen from Figure 20.



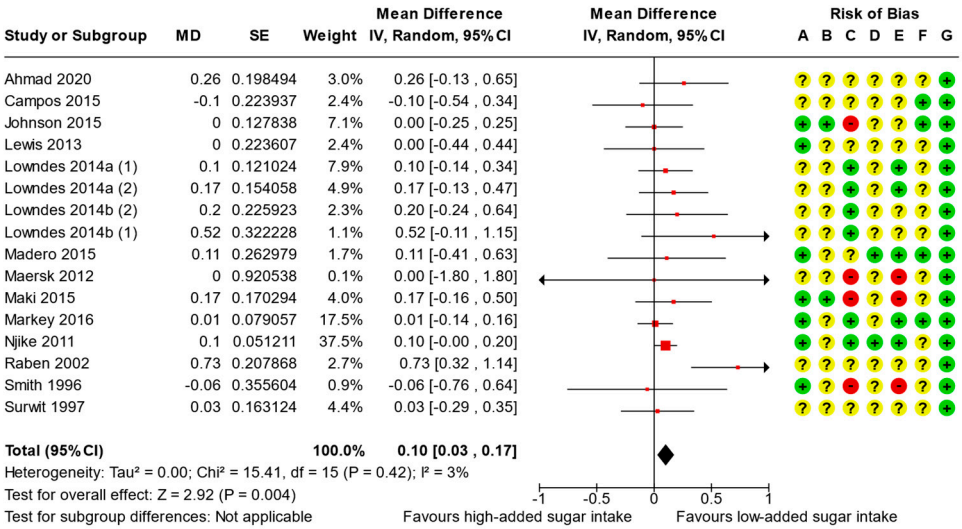
Footnotes

(1) Shows the two arms of the intervention that compares high and low HFCS intake
(2) Shows the two arms of the intervention that compares high and low sucrose intake
(3) Shows the two arms of the intervention that compares high and low sucrose intake.
(4) Shows the two arms of the intervention that compares high and low HFCS intake.
(5) Includes only individuals not diagnosed with NAFLD, the controls.
(6) Includes only individuals diagnosed with NAFLD.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 19: Effect of high vs. low added sugar consumption on the outcome total cholesterol



Footnotes

(1) Shows the two arms of the intervention that compares high and low HFCS intake.
(2) Shows the two arms of the intervention that compares high and low sucrose intake.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 20: Effect of high vs. low added sugar consumption on the outcome triglycerides

Subgroup and sensitivity analyses

In addition to the main analysis, seven subgroup analyses and two sensitivity analyses were carried out on all secondary outcomes. No differences were observed between the subgroups in the subgroup analyses regarding isocaloric or ad libitum, solid and liquid or liquid state, healthy or high-risk population or industry funding or no involvement. The remaining analyses and the results obtained are summarised below.

- Trials in which there was a >0.5 kg difference in weight change between the comparison arms were separated from those in which there was no difference in weight change between the arms. A difference in effect was observed for diastolic blood pressure, suggesting that high and low added sugar intake have different effects on diastolic blood pressure depending on weight change.
- Trials were divided according to duration (< or ≥ 6 months). A difference in effect depending on the study duration was observed on diastolic blood pressure, where the longer studies had higher effect of a low added sugar intake, suggesting that the effect might depend on the study duration.
- Including only trials with an overall low risk of bias score (n=5) in a sensitivity analysis did not affect the effect estimate for any outcomes.
- Excluding the crossover trials (n=7) in a sensitivity analysis did not influence the effect estimate for any outcomes.

Leisure-time physical activity and the risk of CVM

In Study V, leisure-time physical activity was investigated in relation to its association with the risk of CVM.

Total leisure-time physical activity

The relationship between total leisure-time physical activity and the risk of CVM according to the multivariable model is shown in Figure 21. The lowest risk was observed in the category 15-25 MET-h/week (HR 0.80; 95% CI 0.69-0.93), compared with the lowest category. When BMI was added to the multivariable model, the results were mitigated, but remained significant for the category 15-25 MET-h/week (HR 0.84; 95% CI 0.72-0.97).

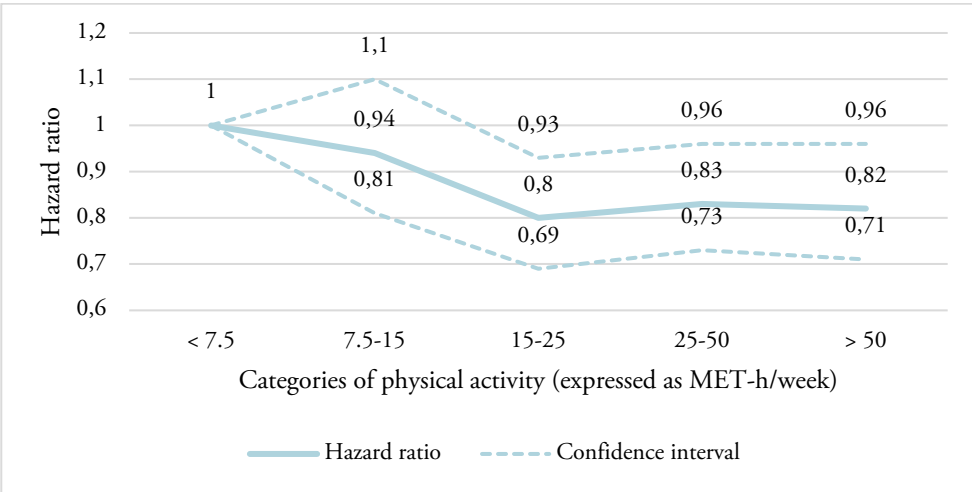


Figure 21: HRs and 95% Cis for categories of leisure-time physical activity and the risk of cardiovascular mortality, in the multivariable model. Adjusted for age, sex, screening date, education, smoking status, alcohol, diet index, and total energy intake

The effect of total leisure-time physical activity was also analysed separately for men and women in the multivariable model, showing no difference (HR per category for women 0.97, 95% CI 0.92-1.02 and HR per category for men 0.98, 95% CI 0.94-1.02).

Specific activities

The 17 specific activities were tested in the four statistical models, and the results are given in Table 8. Individuals participating in tennis, golf, running, gymnastics, cycling, dancing, grass cutting, digging, or gardening had a lower risk of CVM than individuals not participating in those specific activities, in the multivariable model. The largest risk reduction was observed for running: HR 0.64 (95% CI 0.53-0.77) according to the multivariable model, when comparing runners with non-runners. Adding BMI to the multivariable model led to attenuated results for gymnastics and virtually unchanged results for the other activities. The activities were also mutually adjusted for each other and remained significant for tennis, golf, running, cycling, and grass cutting.

Activity	Basic model	Multivariable model	Mutually adjusted model
Orienteering	0.36 (0.13-0.95)	0.43 (0.16-1.16)	0.51 (0.19-1.37)
Walking up stairs	0.92 (0.85-0.99)	0.95 (0.87-1.02)	0.98 (0.91-1.07)
High intensity physical activity	0.75 (0.68-0.83)	0.82 (0.74-0.90)	
Tennis	0.62 (0.47-0.82)	0.67 (0.50-0.89)	0.73 (0.54-0.97)
Running	0.56 (0.47-0.68)	0.64 (0.53-0.77)	0.71 (0.59-0.86)
Football	0.93 (0.57-1.50)	0.94 (0.58-1.52)	1.03 (0.64-1.68)
Swimming	0.86 (0.77-0.95)	0.91 (0.82-1.02)	0.97 (0.87-1.08)
Ball sports	0.73 (0.61-0.87)	0.78 (0.65-0.93)	
Ballroom dancing	0.90 (0.78-1.04)	0.90 (0.78-1.03)	0.96 (0.84-1.11)
Grass cutting	0.75 (0.69-0.82)	0.80 (0.73-0.88)	0.87 (0.78-0.96)
Digging	0.83 (0.75-0.91)	0.86 (0.78-0.95)	0.98 (0.88-1.10)
Badminton	0.77 (0.57-1.03)	0.81 (0.60-1.09)	0.92 (0.68-1.25)
Folk dancing	0.78 (0.63-0.97)	0.76 (0.61-0.95)	0.81 (0.65-1.01)
Golf	0.63 (0.53-0.77)	0.72 (0.59-0.87)	0.74 (0.61-0.90)
Cycling	0.78 (0.72-0.84)	0.84 (0.77-0.90)	0.90 (0.83-0.98)
Gardening	0.76 (0.70-0.82)	0.82 (0.76-0.89)	0.91 (0.83-1.00)
Gymnastics	0.79 (0.72-0.88)	0.87 (0.79-0.97)	0.98 (0.88-1.10)
Table tennis	0.75 (0.49-1.14)	0.79 (0.51-1.19)	0.83 (0.54-1.26)
Walking	0.83 (0.75-0.92)	0.91 (0.82-1.01)	0.94 (0.84-1.05)

Table 8: HRs and 95% CIs for participation in different activities and the risk of cardiovascular mortality. Basic model adjusted for age, sex and screening date. Multivariable model adjusted for age, sex, screening date, education, smoking status, alcohol, diet index and total energy intake. Multivariable model including BMI adjusted for age, sex, screening date, education, smoking status, alcohol, diet quality index, total energy intake, and BMI

The most common activities (>10% participating) were divided into tertiles, with a separate category for non-participants (Table 9). According to the multivariable model, the greatest risk reductions were observed in the first tertile for running (HR 0.60; 95% CI 0.43-0.84) and the summary variable high-intensity physical activity (HR 0.81; 95% CI 0.71-0.92), when compared with the groups of participants not engaged in running or high-intensity physical activity. Adding BMI to the multivariable model did not affect the results.

Leisure-time physical activity after five years

Changes in physical activity after five years can be found in Table 10. The greatest risk reductions, compared with individuals who never exercised, were observed for individuals categorised as 'continued' for high-intensity physical activity and gymnastics, individuals categorised as 'started' for running and swimming, and both the 'started' and 'continued' individuals for cycling. Information from the five-year follow-up was missing for 6513 individuals and the follow-up time ranged from three to eight years.

Additional analyses

Additional analyses were conducted in which hypertension was added to the multivariable model including BMI, and the results remained virtually unchanged. Including prevalent diabetes at baseline in the multivariable model resulted in unchanged effect estimates.

	No activity	1st tertile	2nd tertile	3rd tertile	Trend (per category)
High-intensity physical activity					
Mean MET-h/week	0	2.29	6.53	18.25	
Mean hours/week	0	0.33	0.93	2.57	
Multivariable model	1.00	0.81 (0.71-0.92)	0.82 (0.69-0.97)	0.82 (0.69-0.97)	0.92 (0.87-0.96)
Running					
Mean MET-h/week	0	2.25	5.73	16.05	
Mean hours/week	0	0.32	0.82	2.29	
Multivariable model	1.00	0.60 (0.43-0.84)	0.63 (0.45-0.88)	0.68 (0.51-0.90)	0.84 (0.77-0.91)
Swimming					
Mean MET-h/week	0	1.22	3.68	10.88	
Mean hours/week	0	0.17	0.53	1.55	
Multivariable model	1.00	0.84 (0.70-0.999)	0.90 (0.76-1.05)	1.03 (0.86-1.22)	0.98 (0.93-1.03)
Cycling					
Mean MET-h/week	0	2.28	7.50	19.80	
Mean hours/week	0	0.57	1.87	4.95	
Multivariable model	1.00	0.77 (0.69-0.87)	0.83 (0.74-0.92)	0.90 (0.81-1.01)	0.96 (0.92-0.99)
Gymnastics					
Mean MET-h/week	0	2.26	3.98	8.54	
Mean hours/week	0	0.57	0.99	2.13	
Multivariable model	1.00	0.89 (0.78-1.03)	0.76 (0.59-0.97)	0.90 (0.76-1.08)	0.94 (0.89-0.99)

Table 9: HRs and 95% CI for the most common activities (≥10% participating) and high-intensity leisure-time physical activity divided into tertiles. Multivariable model adjusted for age, sex, screening date, education, smoking status, alcohol, diet index and total energy intake.

	Basic model	Multivariable model
High-intensity exercise		
Never	1.00	1.00
Stopped	0.90 (0.79-1.01)	0.93 (0.82-1.05)
Started	0.57 (0.33-0.98)	0.56 (0.32-0.97)
Continued	0.44 (0.33-0.60)	0.49 (0.36-0.66)
Running		
Never	1.00	1.00
Stopped	0.76 (0.58-0.99)	0.80 (0.62-1.05)
Started	0.36 (0.17-0.76)	0.37 (0.17-0.77)
Continued	0.41 (0.27-0.61)	0.45 (0.30-0.68)
Swimming		
Never	1.00	1.00
Stopped	0.96 (0.81-1.13)	0.99 (0.84-1.17)
Started	0.74 (0.58-0.94)	0.76 (0.60-0.97)
Continued	0.85 (0.71-1.02)	0.89 (0.74-1.07)
Cycling		
Never	1.00	1.00
Stopped	0.94 (0.82-1.09)	0.98 (0.85-1.13)
Started	0.79 (0.63-0.99)	0.80 (0.64-1.00)
Continued	0.75 (0.67-0.84)	0.78 (0.71-0.90)
Gymnastics		
Never	1.00	1.00
Stopped	0.93 (0.78-1.11)	0.98 (0.82-1.17)
Started	0.96 (0.79-1.16)	1.02 (0.84-1.24)
Continued	0.71 (0.59-0.85)	0.77 (0.64-0.92)

Table 10: HRs and 95% CIs for the risk of CVM in those reporting changes in leisure-time physical activity after five years for high-intensity activity and the most common activities. Basic model adjusted for age, sex and screening date. Multivariable model adjusted for age, sex, screening date, education, smoking status, alcohol, diet index and total energy intake.

Discussion

The main findings of the work presented in this thesis will be discussed and interpreted first with special attention on putting the results into the context of previous research. Methodological considerations will then be discussed in relation to the study designs employed. Discussions of the study design, biases and errors, quality of evidence and misclassifications, for example, will give an in-depth understanding of the methodological strengths and weaknesses of the studies as well as identifying the aspects that are important to consider in future research.

Discussion and interpretation of main findings

The findings presented in Papers I and III will be discussed first, with the focus on the role of a healthy diet for the prevention of AAA and PAD. Secondly, the role of fibre in the prevention of AAA will be discussed (Paper II). Thirdly, the lack of research on the potential impact of different intake levels of added sugar on CVD will be discussed, and the findings presented in Paper IV interpreted. Finally, the effects of leisure-time physical activity on CVM will be discussed, based on the results presented in Paper V.

Healthy diet for the prevention of AAA and PAD

Studies I and III explored the associations between a healthy diet and the risk of AAA and PAD, respectively. Associations were found between the diet quality index and AAA, and the index and PAD, when adjusting for age and sex, but the associations became attenuated as further adjustments were made. Analyses of the components of the index showed that adherence to the dietary recommendations for fruit and vegetable intake was associated with a decreased risk of both AAA and PAD. Adhering to the recommendations for fibre intake was also associated with a reduced risk of PAD and, to a lesser extent, AAA.

A high-quality diet, rich in fruit, vegetables, and nuts, has been associated with reduced AAA risk in a large retrospective cohort study conducted in the US (114). In a study

on two large Swedish cohorts (n=81 705), an anti-inflammatory diet index was developed and assessed in relation to AAA risk. The index score was based on a high intake of foods with anti-inflammatory potential (e.g., fruit and vegetables, tea, wholegrain bread, and nuts) and a low intake of foods with pro-inflammatory potential (e.g., read meat, soft drinks, and chips). The results of that study showed that a diet rich in anti-inflammatory foods reduced the risk of AAA, and in particular the risk of rupture (115). Another study conducted on the same two cohorts also found that following a Mediterranean diet was associated with a reduced risk of AAA among smokers (116). The Mediterranean diet is rich in fruit, vegetables, and fish while the intake of red meat is limited.

Fruit and vegetable intake in relation to AAA risk has been explored previously. In a Swedish cohort study including 80 446 individuals, it was concluded that the group with the highest fruit intake (>2 servings/day) had a 25% reduced risk of incident AAA, compared with the group lowest intake (<0.7 servings/day). No association was found for vegetable intake (117). Fruit and vegetable intake were assessed by using a 96-item food frequency questionnaire at baseline. In the present work (Paper I), the diet was assessed not only using a food frequency questionnaire, but the participants also filled in a 7-day menu book and participated in an interview. The difference in diet assessment methods between these two studies might explain the difference in the results for vegetable intake and risk of AAA. Nonetheless, a systematic review, including Paper II and two other studies (117, 118), showed that it was primarily fruit, and not vegetables, that drives the association with AAA risk (119). No previous research could be found on any associations between fibre intake and AAA. The lack of research on fibre and its role in AAA development warranted further exploration and was therefore thoroughly investigated in Study II.

Following a high-quality diet, based on the Alternate Healthy Eating Index, has previously been associated with a reduced risk of inflammation and PAD (120). Moreover, following the Mediterranean diet has been shown to be associated with a reduced risk of PAD in the PREDIMED study (121, 122). Similarly, a systematic review investigating the role of nutrition in PAD development revealed that a high intake of fibre, vitamins and following the Mediterranean diet had a beneficial effect on the risk of PAD, disease progression and disease outcomes (123).

The association between fruit and vegetable intake and PAD reported in Paper III is not corroborated by some previous research (124-126). This might, in part, be explained by differences in the study populations, as two of these previous studies included only men (125, 126). However, other previous research has identified an association between a high intake of fruit and vegetables and reduced risk of PAD (127, 128). An association was established in the present work between a high fibre intake

and reduced PAD risk (Paper III), in agreement with a previously conducted cross-sectional study on PAD patients, where a high intake of fibre was found to be associated with reduced leg pain and increased walking ability (129). An association between a high intake of cereal fibre and reduced PAD risk in men has also been reported previously (126).

Intake of fibre and plant foods and the reduced risk of AAA

The study presented in Paper II showed an association between the intake of plant foods and fibre-rich products, and a reduced risk of developing AAA in the MDCS. An association between the intake of whole grains and reduced AAA risk was also established in a sensitivity analysis in which dietary changers and misreporters were excluded. These results are in line with the findings of another study conducted in the MDCS identifying an association between intake of whole grains and reduced CVD, defined as myocardial infarction and stroke (130). These results are similar to those from a study conducted in the US investigating components of the "Dietary Approaches to Stop Hypertension" diet, where it was found that individuals with a high intake of whole grains had a lower risk of developing AAA (118).

Subgroups of vegetables and fruits were also investigated in this work (Paper II), showing an association between leaf vegetables and reduced AAA risk. No previous research investigating this potential association could be found, but it has been suggested that inorganic nitrate, common in green leafy vegetables, can protect against cardiovascular risk factors, i.e., hypertension and arterial stiffness (131). Regarding fruit intake, it has been suggested that it is not the type of fruit that is important regarding CVD prevention, but rather a high overall intake of a wide variety of fruits that matters (132). In line with this statement, the analysis of subgroups of fruits and vegetables in Study II showed similar risk scores for non-citrus and citrus fruits, suggesting that the protective component in fruits is a nutritional component present in both citrus and non-citrus fruits. One plausible explanation of these findings is that fruits and vegetables are rich in antioxidants, such as quercetin and polyphenol, believed to reduce oxidative stress in the aortic wall, hence reducing the risk of developing AAA. The anti-inflammatory properties of fruits and vegetables can impact the clinical presence of AAA as well as the pathogenesis. Examples of the association between inflammation and AAA are increased plasma C-reactive protein levels and increased concentration of inflammatory cells, such as macrophages and lymphocytes, in the aortic wall (133). Drinking tea also appears to decrease the risk of AAA, further supporting the notion that antioxidants are important in reducing the risk of AAA (134). Like fruits and vegetables, tea is rich in antioxidants, primarily flavonoids.

Study II also explored the role of smoking in the association between fibre intake and AAA. An association was established between intake of vegetables, in particular leaf vegetables, and reduced AAA risk in smokers while no association was found between fruit intake and AAA risk. However, an association was found between fruit intake and reduced AAA risk in non-smokers, while no association between vegetable intake and AAA risk was found. These deviations from the main results presented in Paper II might be explained by the stratification of the study participants into smokers and non-smokers, leading to smaller study samples. Different baseline characteristics between smokers and non-smokers might also provide some explanation of the results. However, excluding current smokers from the analysis did not affect the results in other, similar studies (117, 118), suggesting that the results in Paper II might not be transferable to other study populations. One plausible explanation for the effects of smoking reported in paper II is that smoke, nicotine, and tobacco products increase the aortic dimension and induces matrix metalloproteinase through various molecular mechanisms. One or more components of fruit and vegetables might interrupt some of the molecular pathways of matrix metalloproteinases and thus hindering the development of AAA (135).

As the pathogenesis of AAA is not yet fully understood, it is difficult to determine how dietary components reduce the risk of AAA formation and progression. It is plausible that the individuals who reported a high intake of fibre and plant foods also had a healthier lifestyle in general as has been illustrated in studies evaluating various lifestyle factors and AAA risk (114, 136), as well as in research on other outcomes, such as diverticulitis (137).

A lack of research on the effect of added sugar intake on CVD

The results presented in paper IV highlight the lack of RCTs on the effects of added sugar intake on CVD. However, observational studies have been conducted on the topic. According to a report published by the EFSA in 2022, comprising all available research on the topic, it is not possible to ascertain whether there is a positive relationship between the intake of added sugar and the risk of CVD based on the current body of evidence (40). For instance, no association could be established between added sugar and CVD in a cohort study comprising 353 751 middle-aged individuals followed for up to 13 years (138). The association between added sugar intake and CVD has also been investigated in the MDCS, and it was concluded that the association varies between added sugar intake and different CVDs, and also between different sources of added sugar and CVD (139). A high intake of SSBs has been associated with an increased risk of CVD in several prospective cohort studies (140-

143). The EFSA report on dietary sugars supports this claim and states that there is, with high level of certainty, a causal relationship between SSB intake and the risk of CVD (40). Therefore, observational data suggest that SSBs are associated with an increased risk of CVD and its related risk factors, while there is less conclusive evidence regarding total added sugar intake and CVD risk (144).

Although no association could be identified between added sugar intake and CVD (Paper IV), trials on added sugar and risk factors for CVD were identified and analysed. The results of the systematic review and meta-analysis showed that a low intake of added sugar was associated with lower diastolic blood pressure, total cholesterol, and triglycerides, although the quality of evidence was generally considered low. The EFSA report on dietary sugars has similarly identified, with moderate certainty, an association between added sugar and risk of dyslipidaemia, based on evidence from both RCTs and prospective cohort studies. According to this report, the evidence of a positive association between added sugar intake and hypertension is less conclusive, and the existing body of evidence of low certainty (40).

Elevated cholesterol levels are believed to induce atherosclerosis (145), and atherosclerosis is responsible for the development of a significant proportion of CVDs (50). Increased blood pressure is one of the strongest risk factors for CVD and is generally the first treatment target for CVD (146). Hence, although it was not possible to conclude that added sugar played a role in the prevention of CVD (Paper IV), a low added sugar intake appears to have led to improved status of intermediators to CVDs, such as lower cholesterol levels and lower blood pressure.

It is important to address the role of body weight when discussing added sugar and CVD risk. Sugar-rich foods and beverages are generally considered palatable (147), while still being less satiating than fibre-rich products (148). Therefore, a high intake of sugar-rich products can lead to over-consumption, resulting in weight gain. It was concluded in a previously conducted systematic review that SSB intake is a determinant of body weight among free-living individuals on *ad libitum* diets (149). However, it has also been suggested that reducing sugar intake will only have a modest effect on obesity (149). A subgroup analysis was conducted in the present work aimed at addressing this issue. The trials were separated according to the difference in mean weight change between the study arms (>0.5 kg vs. no weight change) and there appeared to be difference in effect for diastolic blood pressure, depending on weight change, but not for any of the other outcomes studied (Paper IV).

In addition to body weight, it has been suggested that a high sugar intake can lead to decreased insulin sensitivity (150) and can promote low-grade inflammation (150-152). However, not all previous research agrees with these findings (92, 97, 101). It is

therefore difficult to ascertain whether the effects of added sugar intake result from the sugar itself or from an accumulation of adipose tissue and hyperlipidaemia.

High-intensity physical activities and CVM

It was concluded that total leisure-time physical activity as well as several activities classified as moderately and highly intense were associated with a reduced risk of CVM (Paper V). Previously conducted systematic reviews on this topic corroborates these findings (153, 154). The association between physical activity and CVM was primarily driven by a few high-intensity activities, in particular running. Previous research on the role of running in CVM prevention is inconsistent (155, 156). The results in Paper V showed that when the runners were divided into tertiles, with the non-runners in a separate group, the greatest risk reduction was seen in the first tertile, compared with non-runners. A previous systematic review on the same topic reported a similar finding (156). After the runners were divided into quintiles, the greatest risk reduction was observed for individuals in the first quintile, and a slight U-trend was observed in the association between running and CVM. The individuals in the first quintile generally ran 1-2 times a week for <51 minutes per week. This finding suggests that it is not necessary to engage in extreme events such as marathons to achieve the maximum health benefits of running (156). Additionally, it has been suggested that individuals engaging in extreme physical activities run a higher risk of atrial fibrillation (157), myocardial fibrosis (158), and, infrequently, sudden arrhythmogenic death (159). Similarly, a systematic review, of 15 cohort studies, investigating the association between daily number of steps and all-cause mortality showed that the optimal step count per day was 8000-10 000 for individuals aged <60 years, and the risk of all-cause mortality did not continue to decrease above this but rather increased slightly (160).

The results for the summary variable high-intensity physical activity, which included all activities with a MET factor >6, showed a similar pattern to that for running. In general, the activities that fell into this category were associated with a reduced risk of CVM, as has been reported elsewhere (161). The individuals in the first tertile had a marginally lower risk of CVM than tertiles two and three, compared with non-participants of high-intensity physical activity. The individuals in the first tertile engaged in high-intensity physical activities for approximately 30 minutes per week, suggesting that the health benefits of high-intensity physical activity do not increase with frequency and that the most important factor is the intensity of the exercise, not the duration.

The status of many cardiovascular risk factors is improved by physical activity. LDL-cholesterol, blood pressure, and C-reactive protein levels are some of the significant

intermediaries in the development of CVD that are improved by physical activity (162-166). In addition, physical activity reduces body weight and promotes a healthy weight distribution and, by extension, reduces the risk of CVD, given that obesity is a major risk factor (167, 168).

Methodological considerations

Several factors must be considered regarding the two study designs applied in this work: cohort study and systematic review and meta-analysis.

Study design

Traditionally, types of study design have been divided in a pyramid-like manner, as shown in Figure 22, where the highest quality of evidence is believed to be obtained from systematic reviews (169). This image shows a broad generalisation of study designs and is not always applicable in practice. In some cases, it might not be ethical to conduct an RCT and a cohort study design is therefore more appropriate (170). In new, ground-breaking research, or research on rare diseases or outcomes, there may not be a sufficient number of trials to conduct a systematic review, and the highest quality of evidence can then be provided through expert opinions (169). It has been suggested that there has recently been an upsurge in the number of systematic reviews being published, leading to redundant and contradictory results. For example, between 2007 and 2014, 185 meta-analyses were published on the use of antidepressants to treat depression, many of which were sponsored by pharmaceutical companies or carried out by authors with ties to the industry (171). This brings into question whether a systematic review should exclusively be the preferred target in evidence-based medicine and whether the highest quality of evidence can always be attained with this study design.

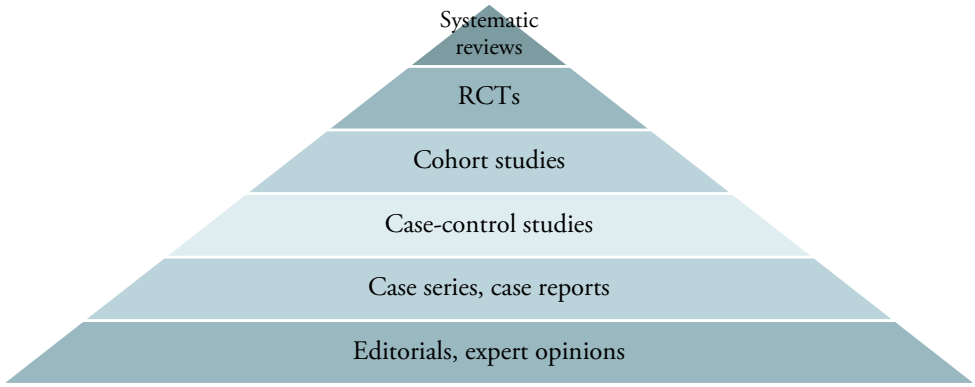


Figure 22: Hierarchy of evidence according to study design (169)

The longitudinal, observational study design of the MDCS is a major strength as it enables evaluation of the relationship between exposures and outcomes over time. The most common criticism of observational study designs, such as cohort studies, is that no causal inference can be established due to the non-randomised structure (172). As the name implies, observational studies are not designed to control the environment of the study participants, in contrast to RCTs, rather the intention is to observe the relationship between exposure and outcome in a natural setting. This allows for larger study populations and longer follow-up times, and observational studies are generally considered less expensive than RCTs. In the MDCS, endpoint data were obtained from national health registers. This resulted in almost complete follow-up of the participants for a period of approximately 20 years.

Most of the baseline data were collected by self-report. Erroneous reporting can affect the results, and lead to inaccurate conclusions. Sensitivity analyses were therefore conducted in which misreporters were excluded from the analyses, in order to address this issue. Additionally, suspected over-reporters of physical activity (>50 hours of physical activity/week) were excluded from the analyses (Paper V). It is also possible that the study participants in the MDCS changed their dietary patterns after the baseline data collection. However, it has been shown in a cohort study on middle-aged individuals attempting weight reduction, that over 70% of the individuals still maintained the same diet after 24 months (173). Moreover, dietary changers were also excluded from the study population in a sensitivity analysis, to elucidate the potential effect on the results of individuals who had previously stated that they had changed their diet. The value of conducting sensitivity analyses was highlighted in Paper II, where excluding misreporters and dietary changers led to a significant association

between the intake of whole grains and reduced AAA risk, an association not revealed in the main analysis.

One way to counteract potential problems associated with self-reported data is to incorporate biomarkers in the study design. Biomarkers have the advantage of being objective, and are therefore not subject to misreporting. In addition, biomarkers are useful in the prevention of diseases as they allow for the identification of individuals with risk factors or subclinical disease. For example, haemoglobin A1C is a biomarker frequently used to identify and monitor individuals with pre-diabetes and diabetes mellitus, as it indicates hyperglycaemia for several weeks preceding the test (174, 175). Based on the findings of the MDCS it has been suggested that elevated levels of the amino acid ergothioneine are associated with a reduced risk of future coronary artery disease and CVM, hence showing potential as a possible biomarker (176). There are also suitable biomarkers for dietary intake, for example, fructose and sucrose in urine (177). Urinary sugars have potential as biomarkers, and can be used as a complement to self-reported data, as demonstrated in the Malmö Offspring Study (178). Numerous biomarkers for fruit and vegetable intake have also been suggested, and include plasma vitamin C and serum carotenoids (179). New technologies such as proteomics, metabolomics and genomics offer ground-breaking possibilities to identify new biomarkers. Nonetheless, it is still an arduous process to identify and validate new biomarkers and although biomarkers can generally be applied on population level, large individual variations may exist (175).

The systematic review and meta-analysis presented in Paper IV followed the Cochrane methodology, as described in the methods chapter of this thesis. The main advantage of a systematic review is that the current state of knowledge on a particular topic is synthesised. Potential knowledge gaps and methodological concerns are identified, which help guide future research in new directions (180, 181). The results of systematic reviews are often included in the scientific evidence when new guidelines are developed or when new treatments are introduced (88). Synthesising the current evidence on a topic is not without challenges and it is a laborious and time-consuming undertaking. Different kinds of bias may also rise in all stages of a systematic review and must be addressed adequately. Another challenge in a systematic review is that it may be difficult to combine the results of many different interventions, and in some cases even impossible. This was a challenge in Study IV, as some of the interventions included differed in design and study population from others. One way of dealing with different interventions is to conduct subgroup analyses to investigate whether there are any major differences that could potentially affect the results. Being aware of potential heterogeneity between the trials is also crucial when interpreting the results of a systematic review.

Study populations

The large study population is a strength in the studies related to the MDCS. The study population was also middle-aged at baseline, which is beneficial when studying CVDs as the risk increases with age. However, the participation rate in the MDCS was 40%, which can be considered relatively low, and could potentially affect the external validity of the study (83). The overrepresentation of women in the MDCS is also a potential concern as the diagnoses studied in the present work primarily affect men. Furthermore, the individuals who agree to participate in a cohort study are generally healthier than those who decline, creating selection bias. In a study comparing those who participated in the MDCS with those who did not, it was found that the cancer prevalence and mortality among the participants was lower than the non-participants (79). However, a similar study comparing participants with non-participants in the Danish National Birth Cohort found that selection bias was not of major concern and that the possible impact of this on the investigated exposure-outcome relationships was limited (182).

The study population included in the systematic review (Paper IV) consisted mainly of healthy or overweight individuals from high-income countries, and more than half of the included trials were conducted in Anglo-Saxon countries. The consumption of products with added sugar varies considerably throughout the world (44), and the results of Paper IV may not be applicable, for example, in low- and middle-income countries. In addition, the mean age of the total study population in this review was 39 years, and it can be argued that when studying risk factors for CVD a slightly older study population would have been preferable.

Biases and errors

The level of significance in the studies described in this thesis was set at 95%. The significance level indicates the risk of a type I error, i.e., false positive results. If there are no confounders, systematic errors or biases, a 95% significance level means that in 100 independent observations that all are true, five will be inaccurately rejected (183). Although it has been argued that the significance level should be higher in order to reduce the risk of type 1 errors in research (184), the vast majority of studies still apply a 95% significance level (185).

A potential weakness of Studies I and II is the relatively low number of individuals with incident AAA, a result of AAA being a relatively uncommon condition. This could potentially cause type 2 statistical errors, i.e., false negative results (183). Larger sample sizes, leading to more individuals with AAA, is one method of counteracting type 2

statistical errors, as this would increase the statistical power of the analyses. There are, however, obvious problems with this solution, as it is not possible to increase the study population once baseline data collection has already taken place (as with the MDCS) nor might it be possible in ongoing studies due to time or budget restraints.

The prospective nature of the MDCS meant that the study participants were not at risk of recall bias, but recorded their lifestyle and dietary habits in real time, which is a methodological strength of all studies utilizing data from the MDCS. Recall bias is a significant risk in retrospective epidemiological research and can generate systematic errors and inaccurate results (186).

Prior to the systematic review (Paper IV), a study protocol was published (89). This ensured that no *post hoc* alterations were made in the analyses and that the study design remained true to its original purpose, increasing credibility. Moreover, the rigorous search strategy applied together with no restrictions on language or publication year, generated a comprehensive and wide-ranging search result. Although it is not impossible that some studies were missed in the search, it is not likely. Moreover, the screening process conducted independently by two review authors, which further minimised the risk that pertinent studies were missed. All data extraction and assessments of risk of bias were also conducted independently by the same two review authors.

The in-depth assessment of risk of bias conducted in Study IV is a significant strength. All trials were scrutinised and assessed according to risk of bias domains. This reduces the risk that studies of poor quality were given unwarranted weight in the meta-analysis. The risk of bias tool used in Cochrane reviews was developed by a team of experts, including statisticians and epidemiologists. The process was thorough and rigorous and resulted in the seven risk of bias domains included in Study IV. The results of a meta-analysis can be biased, partly due to potentially biased results of the included trials, but applying the comprehensive risk of bias tool minimises this risk. In addition, the tool is believed to increase transparency in the review process as all decisions made by the review authors are presented and justified in the final review (187).

Precision and quality of evidence

The MDCS was designed to measure fibre intake and fibre content. This means that rigorous data were collected on fibre, which allowed for in-depth analyses (Paper II). The participants were, for example, asked to register what type of bread they ate, making it possible to determine exactly how much fibre the participants consumed. Moreover, the baseline study collection methodology has been validated showing lower

levels of misreporting than other, similar, data collection methods. Although misreporting the dietary intake was not a major concern in the MDCS, it is important to bear in mind that the intake of certain food products, for example potatoes and milk products, were overreported by some of the study participants. Men tended to overestimate more than women, in particular regarding the intake of fruit, potatoes, high-fat meat and total fat intake (188).

A significant weakness of Study IV is the absence of trials reporting cardiovascular events. Although analyses could be carried out on the secondary, intermediary outcomes, no association could be established between added sugar and CVD. Moreover, the quality of evidence in Paper IV was rated as low, meaning that there is little confidence in the effect estimate. This rating was based on the risk of bias assessments, where many domains of the trials were rated as 'unclear', the variability between interventions and populations across trials, and the fact that only surrogate outcomes were reported in the trials. An attempt was made to only include the trials with an overall low risk of bias in a sensitivity analysis. But seeing as only five trials fulfilled this criterion, the results from this analysis should be interpreted cautiously.

In Study V, the endpoint CVM was broad and encompassed many diagnoses, with varying aetiology and risk factors. For instance, CVM was ascertained by ICD codes, which include for instance venous thromboembolism (189), a very different diagnosis from coronary or cerebral atherosclerotic disease. It was therefore reassuring that the validation of 100 random participants in Study V showed that only 3.4% had pulmonary embolism and that the vast majority died of cardio-cerebral causes. Nonetheless, the lack of specific cause of death diagnoses in Study V could have affected the precision of the results. However, the study design allowed for comprehensive evaluation of leisure-time physical activities and the broad endpoint was not considered to be a major concern.

A strength of Study V was the five-year follow-up, which allowed for evaluation of the long-term physical activity habits of the study participants. However, one third of the participants did not record their physical activity habits after five years, leading to reduced statistical power. This meant that some of the groups (started, continued, stopped, never) were very small, affecting the trustworthiness of these results. The fact that one-third of individuals were lost to follow-up can partially be explained by some participants moving abroad or dying in the interval between baseline and the five-year follow-up.

Only leisure-time physical activity was considered in Study V, and not any other type of physical activity, such as occupational physical activity. It is possible that other domains of physical activity should also be considered and that not including these in

the analyses might affect the results. However, it has been shown that the greatest health benefit is seen from leisure-time physical activity and this domain is therefore the most important one (190). Another study in the MDCS, investigating different domains of physical activity in association with type 2 diabetes, revealed that the strongest association was between leisure-time physical activity and decreased risk of diabetes, but also that there was a linear association between domestic physical activity and risk of developing diabetes. No association was found between occupational physical activity and diabetes risk (191).

Confounders

Confounders can cause considerable problems in epidemiological research and must therefore be taken into account. A long-standing definition of a confounder is a pre-exposure variable that is associated with both the exposure and the outcome, and which affects the relationship between these (192). Age, sex and socioeconomic factors are common confounding variables in epidemiological research (1). Adjusting for potential confounders during the statistical modelling can, to some extent, reduce the risk of other extraneous factors impacting the results. Age, sex and various socioeconomic factors are therefore usually included in the statistical models and adjusted for, to ensure that these do not confound the association between exposure and outcome (1). However, unknown confounders can never be ruled out, but the risk of unidentified confounders affecting the results can be reduced by conducting sensitivity analyses (193). Common confounders were considered in Studies I, II, III, and V, and adjusted for in the various statistical models. Sensitivity analyses were also conducted where, for example, hypertension status was included in the model.

Misclassification

The study design used at baseline in the MDCS has been validated and has higher validity than other similar methodologies, as well as lower rates of misreporting (188). In a study on a random subsample of the MDCS, physical activity was either measured by the lifestyle questionnaire or by an accelerometer. The results showed moderate correlations between the results reported in the questionnaire and those measured by the accelerometer ($r=0.35$ for men and $r=0.24$ for women) (194), suggesting that the level of physical activity reported by the participants in the MDCS is mostly accurate and the level of misclassification relatively low.

The diagnoses included in Studies I, II, III, and V were validated using a randomly selected sample of 100 individuals for each diagnosis. AAA was confirmed in 95%,

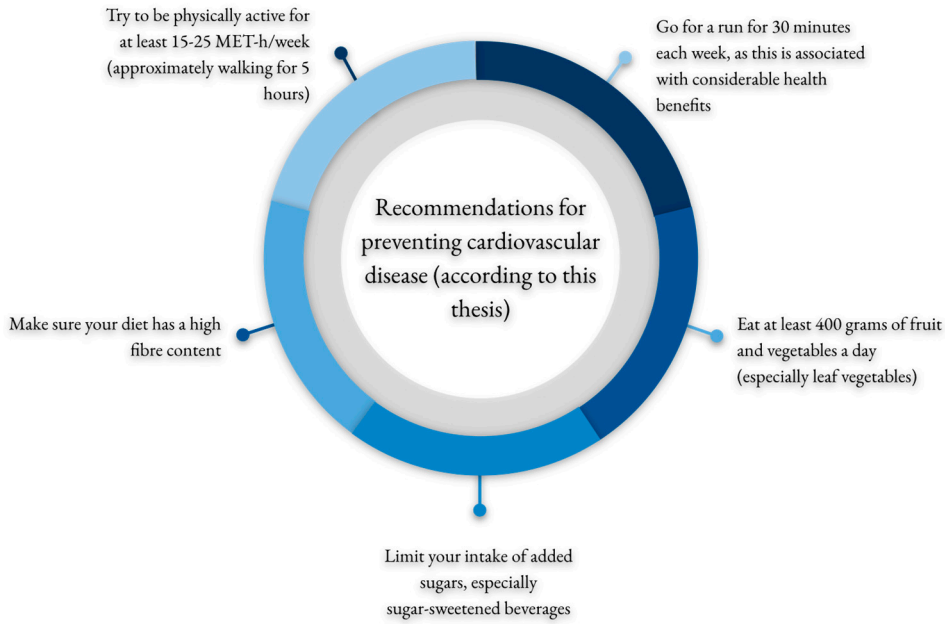
PAD in 98%, and CVM in 94% of the individuals. Validation was performed by scrutinizing post-mortem reports and patient records. The results of the validation show that relatively few individuals were misdiagnosed, which is a strength of these studies. No ultrasound examinations were conducted at baseline to ensure that the participants did not have asymptomatic, small AAA. Hence, some individuals with asymptomatic AAA at baseline might have been erroneously included in the study.

Conclusions

The importance of a healthy lifestyle in avoiding disease and promoting longevity has long been recognised. This doctoral thesis has highlighted the role of various dietary components and physical activities in preventing CVD and has added knowledge to the existing body of evidence on CVD prevention. The overall conclusion of this work is that adhering to the international or national recommendations for dietary intake and physical activity reduces the risk of developing CVD later in life.

The following main conclusions of this work are given below, in relation to the specific aims stated at the beginning of this thesis.

- An intake exceeding the recommendation of >400 g of fruit and vegetables daily reduced the risk of AAA and PAD. The results also suggest that adhering to the recommendation for fibre intake (2.4-3.6 g/MJ) reduced the risk of PAD, and to a lesser extent the risk of AAA.
- An association was found between a high intake of fibre, whole grains, fruit, and vegetables and reduced risk of AAA. More detailed analysis of separate kinds of fruits and vegetables showed an association between a high intake of leaf vegetables and reduced AAA risk.
- No RCTs could be found investigating the role of added sugar in the primary prevention of CVD. A low intake of added sugar decreased diastolic blood pressure, systolic blood pressure, total cholesterol, and triglycerides, compared to a high intake, but the effect was modest and the quality of evidence generally low.
- Individuals engaging in 15-25 MET-h/week of total leisure-time physical activity had the lowest risk of CVM. Engaging in high-intensity physical activity was associated with a reduced risk of CVM. Running was the specific activity associated with the greatest reduction in risk.



Recommendations regarding diet and exercise, based on the results of this research.

Future perspectives

Despite its many benefits, a major challenge associated with epidemiological research is the primarily self-reported nature of the data collection. This is especially true regarding lifestyle factors, such as diet and physical activity, which are often self-reported. Measures can, and often are, taken to avoid this potential pitfall, for example, by applying several data collection tools and by validating the data in different ways, for instance, utilizing biomarkers. Nonetheless, in research it is impossible to be absolutely certain that the study participants are following the study protocol and are reporting their lifestyle habits accurately. It is unlikely that this problem will ever be completely eliminated but measures can be taken to at least minimise the risk of misreporting. For instance, during baseline data collection in the MDCS, several methods were applied during the dietary assessments to ensure that the reported dietary intake was as accurate as possible. It is also important that studies aim to collect diet data at multiple timepoints, to account for everyday changes in dietary intake.

Mendelian randomisation is an increasingly used statistical method for establishing whether an identified association in an observational study is causal. In mendelian randomisation studies, a genetic variant affecting a risk factor needs to be identified, such as the ABCA1 gene which affect cholesterol levels, and used as a proxy for the exposure. If certain conditions are met (e.g., the genetic variant is associated with the risk factor and not associated with any confounders) this method reduces the risk of confounding as well as reverse causation and can lead to conclusions on the causality between an exposure and an outcome (195).

The measurement of physical activity also remains a challenge. Like diet, physical activity is a complex human behaviour with day-to-day variations that must be considered. The different methods available for measuring physical activity have strengths and limitations (86). The use of accelerometers in physical activity research has increased rapidly in recent years. Accelerometers provide many benefits in research as they are small, non-invasive, measure bodily activity frequently, and are not based on self-reported data. However, some of the problems associated with accelerometers are that they might not accurately detect low-impact exercise, especially in the case of wrist-worn devices, and they are unable to detect what kind of physical exercise is being

undertaken (196). In addition, the financial cost of accelerometers may present a problem when undertaking large-scale, epidemiological research. Other devices used to measure physical activity include pedometers and heart rate monitors, but these have similar strengths and limitations to those of accelerometers (86). The best method currently available may well be self-reporting where the participants specify what type of activity they are engaged in, in combination with an unbiased tool such as an accelerometer.

Another emerging trend for measuring and promoting physical activity and a healthy diet is to use smartphone apps, sometimes referred to as "mobile health" or "mHealth" (197, 198). The benefits of mHealth include easy access, at least in countries where most individuals own a smartphone, low cost as many apps are free of charge, and the fact that these apps are generally considered easy to use (199, 200). The vast amount of data collected by apps could be used to conduct large-scale research on trends in physical activity and dietary patterns in a natural environment, providing a valuable complement in controlled trials. However, this kind of "big data" or "mega data" is generally not publicly available, and its use would be associated with problems related to individual anonymity and integrity (201). However, if these issues could be overcome in the future, new opportunities for conducting research on a large scale would further improve our understanding of physical activity and diet and their role in public health.

Regarding the role of added sugar in the prevention of CVD, future trials must be longer to allow for a more accurate evaluation of cardiometabolic outcomes. Longer trials are also needed to allow CVD to develop, as this may take many years. However, this would be associated with some drawbacks as RCTs are generally expensive and participant compliance may decrease with time, a problem relevant for most RCTs, and not only those focusing on diet and CVD. It is also important to bear in mind that although associations were identified between added sugar intake and blood pressure and blood lipid levels, the quality of evidence was low, and the results should thus be interpreted with caution (Paper IV). Therefore, future studies must be carefully designed, and the data and methodology reported in sufficient detail to allow for a comprehensive assessment of the risk of bias.

The gap between research and everyday practice can also pose problems and it is worrying that the findings of research sometimes do not extend beyond academia. This gap can, in part, be explained by research interventions being too narrow in scope, too complex, costly, and possibly not meeting the needs of the community (202). Cochrane reviews have the potential to act as a bridge between research and practice, and the findings of such systematic reviews frequently form the basis for new guidelines and recommendations (203). Cochrane reviews also aim to make their content more

accessible outside academia by including a plain language summary. In addition, the peer review process includes reviewers not only from academia, but also a consumer reviewer. Even though Cochrane reviews are currently not made open access until 12 months after publication, the ambition is to provide immediate open access by 2025 (204).

Historically, academic publishing has been dominated by a few publishers (e.g., Elsevier and SAGE), where the papers are only accessible by paid subscription, making research findings less accessible and publishing costs steep (205). The open access movement aims to enable all academic publications to be openly available to everyone. Today, one third of all peer-reviewed journals are open access, and everything suggests that this number will continue to increase in the future (206). The increasing demand on open-access has generated many new journals, most of whom are legitimate but some that can be defined as "predatory journals" or "pseudo-journals" with, for example, questionable peer-review processes and unreasonable costs (207). Publications presenting negative or null results are more likely to be published in predatory journals, given the bias in academic publishing towards mainly publishing papers presenting statistically significant results (207, 208). In the future, publishing open access will most likely be the self-evident choice for most researchers, which will hopefully make research findings more accessible to all.

Most research is conducted in, and by authors from, middle- and high-income countries (209, 210), but it is vital for the global health that other settings are not forgotten. It has been shown that simply changing the setting of a research abstract from a low- to a high-income country results in the research being deemed more relevant, and the evidence is rated as stronger, due to the unconscious bias of the research community (211). The wave of non-communicable diseases is also reaching lower income countries (212), and the challenges facing these countries must thus be addressed. All the RCTs included in the systematic review (Paper IV) were from middle- and high-income countries. It is then important to ask whether these results are transferrable to all settings, and what measures can be taken to ensure that none are forgotten. Tackling these issues will not be easy, but it is essential that high-quality research is also carried out in less affluent settings, especially as non-communicable diseases and their often-modifiable causes continue to spread throughout the world.

Identifying the ideal lifestyle that provides optimal health benefits has been the subject of much research in the past, and will continue to be in the future. This doctoral thesis has, in the author's humble opinion, added another small piece to that puzzle.

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