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Physical Activity, Visceral Adipose Tissue, and Cardiovascular Disease in Older Adults

- Associations and Effects

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"The true scientist is always skeptical, always curious, and always willing to change their mind in the face of evolving evidence."

Brad Schoenfeld

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Abstract

BACKGROUND: Cardiovascular disease (CVD) poses a substantial public health burden and is the leading cause of mortality in older adults. With the population aging rapidly, interventions aimed at improving modifiable risk factors for CVD, such as physical inactivity and visceral obesity, could play an important role in reducing its burden, provided they are proven effective.

PURPOSE AND AIMS: The overall purpose of this thesis was to create a deeper understanding of the links between physical activity, visceral adipose tissue (VAT), and CVD in older adults, by studying it from both an observational and an interventional perspective. The specific aims were to investigate the associations of objectively measured physical activity and VAT with the risk of CVD and all-cause mortality, to investigate the effect of structured physical activity (exercise) on VAT, and to review the effects of exercise on CVD and all-cause mortality based on evidence from randomized controlled trials (RCTs).

METHODS: This thesis comprised two prospective cohort studies, one RCT, and one narrative review of evidence from RCTs. The cohort studies included about 3,300 men and women aged 70 years with baseline data on physical activity and VAT mass, as obtained using accelerometry and dual-energy X-ray absorptiometry, respectively. Cases of stroke, myocardial infarction, and all-cause mortality during follow-up were collected from Swedish nationwide registers. The RCT included 77 men and women aged 70 years with visceral obesity who were randomly allocated to either 10 weeks of supervised vigorous-intensity exercise or to no exercise, with VAT mass measured before and after the intervention. In the review, evidence from published RCTs and meta-analyses of RCTs reporting on the effects of exercise on CVD (N=19,162) and all-cause mortality (N=37,443) in general older adults and in individuals with chronic conditions (such as obesity, type 2 diabetes, and preexisting CVD) were reviewed.

MAIN FINDINGS: In the cohort studies, greater amounts of physical activity of any intensity, but especially that of moderate to vigorous intensity, were associated with lower risk of stroke, myocardial infarction, and all-cause mortality. Conversely, greater VAT mass was associated with higher risk of stroke or myocardial infarction. In the RCT, short-term vigorous-intensity exercise seemed to decrease VAT mass slightly, but the effect was not statistically significant. Finally, the review showed that there is currently no convincing evidence from RCTs that exercise effectively reduces the risk of CVD or all-cause mortality, which stands in sharp contrast to the strong associations typically reported in observational studies. The reasons for the conflicting findings are likely complex and multifactorial. In the RCTs, a lack of statistical power could

partly explain why no effects have been detected in the general population of older adults, but it is unlikely to explain the null findings in clinical populations, as some of these trials, including meta-analyses of such trials, have been large. Other potential explanations could be a ceiling effect due to the inclusion of participants who were healthier and more physically active than the general population, or that an effect of exercise was masked by the use of effective medications such as antihypertensives and lipid-lowering agents. On the other hand, observational studies have likely overestimated the benefits of physical activity, because these studies are vulnerable to selection bias, reverse causation, and unmeasured confounding, such as from heritable influences.

CONCLUSIONS AND IMPLICATIONS: Despite strong associations, the protective effect of physical activity as a single intervention against CVD and all-cause mortality in older adults is probably not as substantial as is commonly presumed. To uncover the true role of physical activity in preventing CVD, further high-quality trials would be valuable. However, because these trials are very difficult and resource demanding, they should be complemented by innovative observational studies that seek to strengthen causal inference through addressing sources of bias and confounding that are often incompletely accounted for in conventional observational studies. This could include a variety of methodologies, such as utilizing negative control outcomes, instrumental variables, sibling comparisons, and other genetically informed designs. As the aging population continues to grow, it becomes increasingly important to take these scientific steps in order to provide a more definitive answer to the question of the extent to which physical activity alone can reduce the risk of CVD.

Abbreviations

BMI	Body mass index
CI	Confidence interval
CVD	Cardiovascular disease
DXA	Dual-energy X-ray absorptiometry
HAI	Healthy Ageing Initiative
HIIT	High-intensity interval training
HR	Hazard ratio
LPA	Light-intensity physical activity
MET	Metabolic equivalent of task
MICT	Moderate-intensity continuous training
MPA	Moderate-intensity physical activity
MVPA	Moderate-to-vigorous physical activity
SMD	Standardized mean difference
SNP	Single-nucleotide polymorphism
VAT	Visceral adipose tissue
VPA	Vigorous-intensity physical activity
WHO	World Health Organization

Enkel sammanfattning på svenska

Bakgrund till avhandlingen

Sjukdomar i hjärtat och blodkärlen, ofta benämnt som kardiovaskulära sjukdomar (CVD), är fortfarande den främsta orsaken till att människor avlider, såväl globalt som i Sverige. Stroke och hjärtinfarkt är de typer av CVD som orsakar de flesta av dödsfallen, och det är framför allt personer 65 år och äldre som drabbas. Samtidigt blir vi allt fler äldre i samhället, vilket föranleder ett behov av effektiva förebyggande åtgärder.

En uppsjö av observationsstudier har visat på starka *samband* mellan brist på fysisk aktivitet, det vill säga rörelse, samt att ha mycket visceralt fett, det vill säga fett lagrat djup inne i buken kring de inre organen, och ökad risk för CVD och förtida död hos personer i medelåldern. I merparten av studierna har fysisk aktivitet och visceralt fett dock mätts med subjektiva eller indirekta metoder, vilka är mindre tillförlitliga än objektiva metoder. Därtill har relativt få studier fokuserat på äldre personer. Samtidigt bygger det mesta av kunskapen kring fysisk aktivitet för att förebygga CVD på just resultat från observationsstudier, som till exempel kohortstudier. I en kohortstudie mäts graden av fysisk aktivitet hos individerna i en utvald grupp vanligtvis vid ett enstaka tillfälle. Exempelvis frågar man individerna hur aktiva de anser sig vara, eller så mäter man aktiviteten med en rörelsemätare under några dagar. Därefter följer (observerar) man deltagarna framåt i tiden, till exempel med hjälp av hälsodataregister, för att se vilka som drabbas av sjukdom. Slutligen undersöker man om det föreligger något samband mellan aktivitetsnivån vid start av studien och risken för sjukdom under uppföljningstiden. I den statistiska analysen försöker man samtidigt kontrollera för underliggande skillnader mellan mer och mindre fysiskt aktiva individer som skulle kunna tänkas förklara eventuella samband. Med andra ord försöker man skapa jämförbara grupper. Detta är dock svårt att göra i tillräckligt noggrann och detaljerad utsträckning, samtidigt som faktum kvarstår att det inte är den faktiska *effekten* av ökad fysisk aktivitet som testas. Detta görs bäst genom det som kallas randomiserade kontrollerade studier (RCTs). I dessa studier lottas personer slumpmässigt till att antingen få ökad fysisk aktivitet eller att inte få det. Man kommer på så vis till rätta med problemet med ojämförbara grupper, och kan på ett mer tillförlitligt sätt besvara frågan ifall ökad aktivitet minskar risken för CVD. Utifrån detta kan man alltså fråga sig hur väl de starka samband som ofta ses i observationsstudier överensstämmer med de effekter som visas i RCTs.

Vad var syftet?

Det övergripande syftet med avhandlingen var att skapa en djupare förståelse för samband och effekter rörande fysisk aktivitet, visceralt fett, och CVD hos äldre personer. Detta gjordes genom fyra delarbeten, var och ett med ett specifikt syfte:

1. Undersöka sambandet mellan objektivt uppmätt fysisk aktivitet och risken att drabbas av stroke, hjärtinfarkt eller att avlida.

2. Undersöka sambandet mellan objektivt uppmätt visceralt fett och risken att drabbas av stroke, hjärtinfarkt eller att avlida.

3. Utvärdera effekten av strukturerad fysisk aktivitet (träning) på visceralt fett.

4. Granska RCTs som utvärderat effekten av träning på risken för CVD och förtida död.

Hur gick studierna till?

De två första delarbetena var kohortstudier bestående av cirka 3,300 personer som alla genomgått objektiv mätning av fysisk aktivitet och visceralt fett vid 70 års ålder. Med hjälp av nationella hälsodataregister följdes deltagarna framåt i tiden under ett antal år för att spåra vilka som drabbades av en stroke, hjärtinfarkt, eller avled. Därefter analyserades sambanden mellan mängden fysisk aktivitet och visceralt fett som deltagarna hade i relation till risken att senare drabbas av något av utfallen. Det tredje delarbetet var en RCT som testade effekten av träning på visceralt fett under 10 veckor. Här lottades slumpmässigt 77 personer, som alla var 70 år gamla och hade mycket visceralt fett, till en av två grupper. I den ena gruppen, kontrollgruppen, fick deltagarna instruktionen att leva som vanligt. I den andra gruppen, interventionsgruppen, blev deltagarna erbjudna 10 veckors övervakad, intensiv träning. Mängden visceralt fett hos samtliga deltagare mättes före studiens start och sedan efter 10 veckor, då grupperna jämfördes. Det fjärde delarbetet var en litteraturstudie där vi granskade publicerade RCTs och meta-analyser av RCTs som testat effekten av träning på CVD (drygt 19,000 deltagare) och död (drygt 37,000 deltagare) hos generella äldre personer och hos personer med kronisk sjukdom (som till exempel personer med övervikt, typ 2 diabetes, eller tidigare CVD).

Vad visade resultaten?

1. Ju mer fysiskt aktiva som deltagarna var desto lägre var risken för stroke, hjärtinfarkt eller död under uppföljningstiden. All aktivitet oavsett intensitet verkade fördelaktig, men ju intensivare desto bättre.

2. Ju mer visceralt fett som deltagarna hade desto högre var risken för stroke eller hjärtinfarkt under uppföljningstiden.

3. Kortvarig intensiv träning verkade minska mängden visceralt fett något, men effekten var liten och inte statistiskt säkerställd.

4. De RCTs som hittills genomförts har inte visat att träning tydligt minskar risken för CVD eller död. Förklaringarna till de motstridiga resultaten mellan observationsstudierna och de randomiserade studierna bedömdes vara komplexa och flera till antalet. I RCTs skulle avsaknaden av effekt hos den generella äldre befolkningen delvis kunna bero på att dessa studier var små och hade begränsad statistisk styrka. Däremot förefaller det osannolikt att låg statistisk styrka var den begränsande faktorn gällande avsaknaden av effekt hos kliniska populationer, då dessa studier ofta var större. Andra möjliga förklaringar skulle kunna vara det faktum att deltagarna i studierna kan ha varit alltför friska och fysiskt aktiva redan från start vilket gjort att en takeffekt uppstått, eller att effekten av just träningen maskerades eftersom studierna inkluderade personer som ofta tar läkemedel som visat sig effektiva för att minska risken för CVD. Å andra sidan har observationsstudier sannolikt överskattat fördelarna av fysisk aktivitet på grund av olika metodologiska brister samt underliggande skillnader mellan fysiskt aktiva och fysiskt inaktiva personer som inte tagits hänsyn till, exempelvis genetiska skillnader.

Vilka är slutsatserna?

Trots starka *samband*, så är *effekten* av fysisk aktivitet som enskild insats för att förebygga CVD och förtida död hos äldre personer förmodligen inte så stor som den ofta antas vara. Framöver behövs fler högkvalitativa RCTs som undersöker betydelsen av fysisk aktivitet för att förebygga CVD. Då dessa studier tar lång tid, och dessutom är svåra och resurskrävande, bör de kompletteras med olika typer av innovativa observationsstudier som är utformade för att adressera de brister som traditionella observationsstudier ofta har. I takt med att andelen äldre i befolkningen ökar blir det allt viktigare att vi på så vis höjer ribban och ambitionsnivån inom forskningsområdet för att på sikt, baserat på starkare evidens, kunna ge mer tillförlitliga svar på frågan i vilken utsträckning som fysisk aktivitet för sig självt är effektivt för att förebygga CVD.

Original papers

Paper I

Ballin M, Nordström P, Niklasson J, Nordström A. Associations of Objectively Measured Physical Activity and Sedentary Time with the Risk of Stroke, Myocardial Infarction or All-Cause Mortality in 70-Year-Old Men and Women: A Prospective Cohort Study. *Sports Med*. 2021;51(2):339-349.

Paper II

Ballin M, Nordström P, Niklasson J, Nordström A. Associations of Visceral Adipose Tissue and Skeletal Muscle Density with Incident Stroke, Myocardial Infarction, and All-Cause Mortality in Community-Dwelling 70-Year-Old Individuals: A Prospective Cohort Study. *J Am Heart Assoc*. 2021;10(9):e020065.

Paper III

Ballin M, Lundberg E, Sörlén N, Nordström P, Hult A, Nordström A. Effects of Interval Training on Visceral Adipose Tissue in Centrally Obese 70-Year-Old Individuals: A Randomized Controlled Trial. *J Am Geriatr Soc*. 2019;67(8):1625-1631.

Paper IV

Ballin M, Nordström P. Does exercise prevent major non-communicable disease and premature mortality? A critical review based on results from randomized controlled trials. *J Intern Med*. 2021;290(6):1112-1129.

Introduction

Population aging

The increased life expectancy of mankind is one of the greatest public health accomplishments of the last century. Countless advancements and developments across virtually all sectors of society have resulted in a continuous growth of the older population. In 2019, 9% of the global population, equal to 700 million people, were aged 65 years or older, which is more than a fourfold increase since the 1960s.[1] Similarly, life expectancy among individuals aged 70 years or older has increased by about two years during the last three decades.[2] Moreover, there does not seem to be a decrease in sight, with recent projections indicating that by 2050, there will be at least 1.5 billion people aged 65 years or older.[1] In Sweden, the proportion of older people is larger, where individuals over the age of 65 constitute one fifth of the population, and this number is also expected to grow.[3]

The upside of these demographic changes is that more people will have the possibility of living a long and meaningful life while contributing to society. Nevertheless, challenges remain, such as an increasing need to promote healthy aging and prevent diseases that primarily affect older people. According to the World Health Organization (WHO),[4] every person should have the opportunity to live a long and healthy life and enjoy a healthy aging. This is also specified in the United Nations Agenda 2030 for Sustainable Development, and for instance the sustainable development goal number III, which reads "Ensure healthy lives and promote well-being for all at all ages".[5] Given the demographic shift towards an older population, which will likely impact not only individuals but also most sectors of society, including healthcare services, the WHO has declared 2021-2030 as the Decade of Healthy Aging.[6] This initiative, which is part of the WHO Global strategy on aging and health, envisions a world in which all people can live long and healthy lives. The initiative includes an action plan aiming to improve the lives of older people, their relatives and the communities in which they live.[6] To achieve this, focusing on prevention of age and lifestyle-related diseases in both research and clinical practice is one of many important factors.

Cardiovascular disease

From a biological perspective, aging is characterized by numerous progressive changes in physiological systems, the accrual of molecular and cellular damage, decreases in physiological reserves, impaired function, and increased vulnerability to disease and mortality.[7,8] As many of these changes are related to cardiovascular health, such as arterial thickening and stiffening, endothelial dysfunction, oxidative stress, chronic low-grade inflammation, and insulin resistance, old age is the primary risk factor for cardiovascular disease (CVD).[9,10] As an umbrella term, CVD includes several subtypes of diseases involving the heart and blood vessels such as ischemic heart disease, cerebrovascular disease, peripheral artery disease, heart failure and arrythmias.[11]

Apart from biological deteriorations, aging is also characterized by behavioral changes, which depending on the direction they are altered in, may act either to exacerbate or counteract cardiovascular aging.[10] This suggests that although aging per se is inevitable, behavioral factors may be of interest from a CVD prevention perspective given their modifiable nature. Altogether, interactions between cardiovascular aging, hereditary factors, and unfavorable changes in lifestyle behaviors and modifiable risk factors, likely explain why CVD is one of the most common group of chronic diseases among older adults.[9] The present thesis focuses primarily on the two types of CVD which are most harmful, namely stroke and myocardial infarction, which fall under the subcategories of cerebrovascular disease and ischemic heart disease.

Epidemiology

The Global Burden of Disease is the most comprehensive epidemiological study of global trends in health, including surveillance of CVD. Data from this study show that CVD remains the leading cause of global mortality and among the leading causes of disability.[12] In 2019, there was an estimated 523 million prevalent cases and around 18.6 million CVD-related deaths, of which 85% were due to stroke and ischemic heart disease, together representing nearly one third of global mortality.[13] Stroke and ischemic heart disease are also the leading causes of mortality in older adults specifically.[2]

In Sweden, the incidence of and mortality from CVD has declined gradually during the past decades but remains the leading cause of death,[14] imposing a significant burden both on an individual and population level. In 2020, the incidence of myocardial infarction was 290 per 100,000 individuals, with a mortality rate of 60 per 100,000.[15] The numbers for stroke were 340 and 76 per 100,000, respectively.[16] About 80% of these cases occur among individuals aged 65 or over, with a higher burden among men than among women, especially for myocardial infarction.[15,16] Besides the burden that these diseases cause for

individuals and their relatives, their financial burden amount to an estimated yearly sum of at least 63 billion Swedish Krona, equal to 9% of the total annual healthcare costs.[17]

Stroke

Stroke is characterized as a neurological deficit attributed to an acute focal injury of the central nervous system by a vascular cause,[18] and is caused by reduced blood flow to areas in the brain following cerebral artery blockage or bleeding. It is often recognized by a sudden onset of motor, sensory, or cognitive problems such as speaking problems, local paralysis (for example of the face and upper and lower extremities), or vision impairment. In 1970, the WHO defined stroke as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer, or leading to death, with no apparent cause other than of vascular origin".[19] While this earlier definition focused mainly on clinical symptoms, the American Heart Association in 2013 suggested an updated and broader definition. Here, stroke was defined as "brain, spinal cord, or retinal cell death attributable to ischemia, based on pathological, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; or clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms persisting $\geq$24 hours or until death, and other etiologies excluded".[18] Thus, diagnosis of stroke is established through a clinical examination together with the use of imaging techniques, primarily computed tomography. Other imaging techniques such as magnetic resonance imaging, ultrasound, electrocardiography, and echocardiography, may also be part of the stroke examination.

There are generally two main types of strokes: ischemic and hemorrhagic. Ischemic stroke (cerebral infarction) is the most common type of stroke, accounting for around 87% of all cases.[20] In an ischemic stroke, a cerebral artery is blocked by an occlusive thrombus, which is a blood clot that obstructs the supply of oxygen-rich blood to the brain. While most ischemic strokes can be attributed to atherosclerosis (see definition below), another common cause is cardioembolism, which occurs when a blood clot formed in the heart, often due to atrial fibrillation, travels to a cerebral blood vessel where it gets stuck. The remaining 13% of strokes are classified as hemorrhagic strokes, which in turn are divided into intracerebral (10% of cases) and subarachnoid hemorrhage (3% of cases).[20] Intracerebral hemorrhages are typically caused by rupture of an aneurysm, which is a weakened and enlarged area of a blood vessel. A subarachnoid hemorrhage occurs when blood leaks into the subarachnoid space. This is often the cause of arteriovenous malformation, which means that there is an abnormal formation of blood vessels in the brain, which are weaker and more susceptible to burst.

Myocardial infarction

Myocardial infarction is defined as myocardial cell death caused by prolonged ischemia.[21] It can occur following rupture of a lipid-rich and inflammatory atherosclerotic plaque in a coronary artery which triggers a cascade of reactions and coagulation pathways leading to the formation of an occlusive thrombus. This causes acute myocardial ischemia which in turn may permanently damage the myocardium, with complications such as arrythmias, heart failure and cardiac arrest. Acute myocardial infarction includes the presence of acute myocardial injury detected by abnormal cardiac biomarkers and evidence of acute myocardial ischemia. The diagnosis is made upon detection of elevated levels of cardiac troponin in addition to evidence of myocardial ischemia. The latter can be determined either clinically in terms of typical symptoms such as persistent pain or discomfort in the chest, pain that radiates to the upper extremities such as the arms and jaw, feelings of nausea, dyspnea, and lightheadedness, or through changes and pathological findings from electrocardiogram readings. Imaging techniques can also be used to assess whether there is evidence of new loss of viable myocardium, abnormalities in regional wall motion, or a coronary thrombus.

Atherosclerosis

As briefly stated above, stroke and myocardial infarction are most often the result of atherosclerosis. This is a multifactorial, inflammatory disease, and the clinical manifestations typically include major cardiovascular events such as stroke or myocardial infarction.[22] For a long time, atherosclerosis has been considered an age-related degenerative disease with a continuous progression throughout life, although more recent views suggest that atherosclerosis might evolve episodically during life, being more pronounced at certain phases and which may regress based on measures taken.[23] Atherosclerosis is often asymptomatic for a long period of time, and the prevalence of silent coronary artery atherosclerosis in the general Swedish population may be as high as 40% or more.[24]

Atherosclerosis is largely driven by inflammation and involves hardening of the arteries and the deposition and buildup of low-density lipoprotein cholesterol and other substances in the artery wall in the form of plaques. As the plaque grows, it narrows the vessel lumen, which then causes ischemia as blood flow and oxygen supply to the tissue become restricted. Plaques may gradually progress and become more severe in terms of characteristics and stability. Eventually they could rupture, leading to the formation of a thrombus. The thrombus may either reside at the site of the plaque or detach and travel further down the circulation, also known as thromboembolism. Eventually, the embolus reaches a vessel that is too narrow for it to pass, where it gets stuck. As a result, blood supply to the affected tissue is cut off, leading to acute ischemia and eventually tissue necrosis.

The exact pathway from initiation of atherosclerosis to plaque progression and a final endpoint such as stroke or myocardial infarction is complex and multifactorial. However, the deposition of low-density lipoprotein cholesterol, together with endothelial dysfunction, inflammation, and migration of smooth muscle cells, are some of the well-established key factors. Endothelial cells form the endothelium; a layer that lines the interior of the blood vessels, which separates the circulating blood in the lumen from the artery wall. The endothelium has many important functions in relation to preserving cardiovascular health and homeostasis. Key features include its vasodilatory, antioxidative, anti-inflammatory and antithrombotic effects, as well as its ability to inhibit smooth muscle cell proliferation and migration and excessive adhesion of leukocytes and platelets. In the state of endothelial dysfunction, these functions act in the opposite direction, causing reduced vasodilation, increased inflammation and being prothrombotic.

Factors which may contribute to endothelial dysfunction include aging, smoking, type 2 diabetes, hypertension, dyslipidemia, visceral obesity, and physical inactivity.[25-29] These factors share the common ground of being associated with increased oxidative stress, damaging the endothelium, and thereby facilitating for low-density lipoprotein cholesterol to make its way into the intima. Consequently, production of pro-inflammatory cytokines and growth factor are increased, and endothelial dysfunction is aggravated. This leads to increased expression for adhesion molecules that recruit leukocytes and monocytes to the atherosclerotic lesion, where they enter the intima and become activated. Consequently, production of pro-inflammatory cytokines increases, which further damages the endothelium. Monocytes also differentiate into macrophages and grow into foam cells as they engulf the low-density lipoprotein cholesterol. A potentially protective player in this sense could be high-density lipoprotein cholesterol, which is believed to have an antiatherogenic effect through its "reverse cholesterol transport", promoting the removal of cholesterol from macrophages and reversing plaque progression.

The formation and growth of the foam cells is essentially known as the fatty streak, which is the first clear visible sign of atherosclerosis. Besides the role of dysfunctional endothelial cells and inflammatory factors described above, growth factors are also released, causing adjacent vascular smooth muscle cells to migrate into the intima where they synthesize collagen-rich materials and form a fibrous cap surrounding the fatty streak, thus formatting a plaque. Pro-inflammatory factors may act to destabilize the plaque through inhibiting the collagen synthesis of the smooth muscle cells. In addition, the foam cells, which are growing as they engulf more and more of the low-density lipoprotein cholesterol, may eventually die from apoptosis or necrosis, releasing their content and creating a lipid-rich necrotic core with a thin fibrous cap, which is

characteristic for the progress towards a plaque that is prone to rupture. Eventually, this unstable, lipid-rich plaque and its fibrous cap surrounding it may rupture, and through a cascade of events it leads to the formation of a thrombus, which ultimately may result in a stroke or myocardial infarction. Plaque rupture is the most common cause of thrombosis, although a thrombus may also be formed without the rupture of a plaque, which is known as plaque erosion, although the mechanisms behind this are less understood.[30]

Relevance of modifiable risk factors

Despite a strong age gradient in risk, not everyone will experience a stroke or myocardial infarction. The heritability of stroke and myocardial infarction has been estimated to about 40%,[31,32] but the ultimate cause of disease outcome is probably the result of interactions between genetic, environmental, socioeconomic, and modifiable (behavioral and lifestyle-related) risk factors.

Well-known attempts to estimate the role of modifiable risk factors in CVD include for example the INTERHEART and INTERSTROKE. In these two case-control studies, the associations of modifiable risk factors with myocardial infarction and stroke were examined in 13,000 and 15,000 cases from 52 and 32 countries, respectively.[33,34] The results suggested that 90% of the population attributable risk of myocardial infarction and stroke was linked to the presence of 9 to 10 modifiable risk factors.[33,34] Broadly similar results were reported in the prospective PURE study, where the associations of modifiable risk factors with incident CVD and mortality was investigated in more than 155,000 individuals from 21 countries. Here, 79% of incident myocardial infarction, 65% of incident stroke, and 75% of all-cause mortality was associated with the presence of 12 modifiable risk factors.[35] The relevance of modifiable risk factors has also been observed in older adults specifically. In an individual participant data meta-analysis of more than 257,000 individuals from 18 cohort studies, there was an association between the number of modifiable risk factors present and risk of CVD even through 80 years of age.[36] Similarly, in the Framingham Heart Study, the absence of modifiable risk factors were associated with reduced risk of CVD in older people.[37] Taken together, these associations, assuming they are causal, would imply that it is never too late to prevent CVD. In this thesis, the specific modifiable risk factors which are in focus are physical activity and visceral adiposity, both covered in the next chapters. As already acknowledged, however, many other modifiable risk factors have also been identified, including for example hypertension, type 2 diabetes, dyslipidemia, smoking, and unhealthy diet.[35]

Stagnating decline in cardiovascular disease burden

The reason for the long-observed decrease in CVD incidence and mortality in many countries, including Sweden, is probably multifactorial and may include factors such as decreased smoking prevalence, enhanced primary- and secondary prevention and better treatment.[38-41] However, in recent years the rate of decline in CVD seems to have slowed in high-income countries, and there has even been an increase in some countries.[38,42,43]

These trends might partly relate to trends in modifiable risk factors, where rates of hypertension, hyperglycemia, and obesity have increased during the last three decades, during which mortality attributable to obesity also increased.[44,45] Similarly, rising obesity rates may have attenuated the previously observed reductions in cardiovascular mortality, which could have been larger if the obesity epidemic had been contained.[46] If these modifiable risk factors continue to worsen, this might curtail further improvements in CVD burden in the future.[12,47] For example, a recent study from Scotland found an increasing incidence of stroke and myocardial infarction during a 25-year period that appeared to be attributable to changes in the rates of obesity and diabetes.[48] Therefore, it would seem likely that tackling these factors will be important to counteract an increased burden from CVD.[49] It is also worth highlighting that trends in modifiable risk factors may have experienced further worsening during the recent COVID-19 pandemic, partly as a consequence of unfavorable behavioral changes that occurred due to social restrictions and lockdowns.[50,51]

Apart from negative trends in modifiable risk factors, population aging is probably another contributor to trends in CVD burden. It has been estimated that the growth of the older population during the last three decades has coincided with an increase in the total number of deaths from primarily stroke and ischemic heart disease in more than 150 countries.[52] It has also been projected that population aging might henceforth be accompanied by increased disability, prevalence, and deaths due to CVD.[13] This would likely have an impact on healthcare services and resources, and already today CVDs amount to an overwhelming economic burden.[53,54] Based on the demographic shift, coupled with the negative trends in modifiable risk factors, there seems to be a strong case for why prevention of CVD in older people is imperative to prevent unnecessary suffering and premature death, as well as to minimize complications within healthcare services. An important piece of the puzzle is therefore to characterize modifiable risk factors in older people, both in terms of their influence on CVD risk as well as their susceptibility to change through targeted interventions.

Obesity

Obesity is a chronic disease defined as excessive fat accumulation that may impair health.[55] It is the result of sustained imbalance between energy intake and energy expenditure that has a multifactorial etiology including genetic, environmental, psychological, social, and behavioral factors.[55] Obesity is diagnosed using the body mass index (BMI), calculated as an individual's body weight in kilograms divided by height in meters squared (kg/m^2), where a BMI of 30 or above is classified as obesity.[55] Because the BMI is easily assessed it is the standard approach in clinical practice and in large-scale epidemiological studies. However, as will be discussed later, its appropriateness in older adults is debatable.

In 1997, the WHO declared obesity as a global epidemic with negative impacts on public health,[56] but it took until 2021 before the European Commission officially defined obesity as a chronic relapsing disease which in turn acts as a gateway to other non-communicable diseases.[57] To live with a high BMI and excess adiposity is strongly associated with increased risk of CVD and premature death,[55,58-62] causing an estimated 4.7 million global deaths every year,[63] and 14% of all deaths in Europe.[62]

The WHO has stated that halting the rising obesity rates is key in CVD prevention.[64] However, the question remains as to whether or not we are on the right track to achieve this. In 2016, there were an estimated two billion people (39%) worldwide living with overweight and 650 million (13%) living with obesity.[55,58] This corresponded to a dramatic rise since 1975,[65,66] which is thought to primarily be due to changes in people's diets.[67] In Europe, the prevalence is even higher where 59% have overweight and 23% obesity, increasing by 138% since 1975.[68] Henceforth, it is projected that by 2030 the prevalence of obesity will have risen to 18% globally and about 30% in Europe.[69] By consequence of this tsunami-like rise in obesity, a majority of the world's inhabitants are now living in countries where more people are estimated to be dying from overweight than of underweight,[55] and in Europe there is not a single country on track to halt the rise in obesity.[68] In Sweden, trends in obesity between 1995 and 2017 were explored in a study of almost 0.5 million individuals. During this time, the obesity prevalence increased by 86%, with an estimated overall obesity prevalence of 17% in 2017.[70] The prevalence increased especially in older people, where 20% of older adults were estimated to have obesity in 2017.[70]

Besides implications for individual health, obesity also poses a financial burden for society at large. In Sweden, the Public Health Agency estimated 70 billion Swedish Krona worth of total annual economic expenses attributable to obesity.[71] The Swedish Institute for Health Economics reported a more conservative, although still high, estimate of 25 billion Swedish Krona.[72]

Body fat distribution in aging and the "obesity paradox"

Despite being easy to use and commonly used in clinical practice and for large-scale data collection, the BMI has several limitations. One is that the BMI does not distinguish between fat mass and muscle mass. Another is that it provides no information about regional body fat distribution. This is important given that both the amount of total body fat and fat stored at specific locations in the body can vary considerably between individuals with the same BMI.[56] In normal-weight individuals, the use of BMI can lead to underestimation of adiposity,[73] and in turn, misclassification of cardiometabolic risk.[74] Importantly, among individuals with a similar amount of total adiposity there could be a variation in risk factor profiles due to differences in regional body fat distribution.[75]

Using the BMI as a measure of adiposity may have particular limitations when applied to older adults. As people age, their height decreases which could cause an increase in BMI. Some have therefore proposed age-specific BMI thresholds as a means of better determining cardiometabolic risk compared with standard thresholds.[76] Another limitation relates to the fact that the aging process is also characterized by certain changes in body composition and body fat distribution, which are not adequately captured by BMI. With aging there is a loss of muscle mass, while fat mass continues to accumulate, and preferentially so in the abdominal region.[77] These changes may also occur in the absence of a concurrent change in BMI.[77] Taken together, this suggests that relying on the BMI when studying or assessing older adults could potentially mask substantial variations in body fat distribution.

In this context, the so called "obesity paradox" in aging is worth discussing.[78] This term stems from the somewhat counterintuitive finding in some epidemiological studies, where a high BMI in old age has been deemed protective.[78] This might suggest either that obesity should not be the target of interventions in older people, alternatively, that the usefulness of BMI, especially the general BMI thresholds, are inappropriate for older people. There is an ongoing debate as to what extent the obesity paradox represents a causal association or whether it is due to confounding and other methodological problems.[79] For example, the association may be an artifact due to selection bias, reverse causation, and other confounding factors such as old age, smoking, comorbidity, unintentional weight loss, low cardiorespiratory fitness, low muscle mass, socioeconomic status, and failing to account for body fat distribution.[61,78-80] On the other hand, some might argue that the association is age dependent, where a biological explanation to the finding could be that higher BMI is a marker of better nutritional status in very old people.[81]

Visceral obesity

Definition and prevalence

The idea that assessment of body fat distribution might be preferable for an adequate prediction of obesity-related health outcomes was brought forward in the late 1940s and 1950s by Jean Vague. As a pioneer in the field of body fat distribution and cardiometabolic health, Vague discovered that an obesity phenotype characterized by excess fat in the central parts of the body, rather than fat stored more peripherally, was associated with atherosclerosis and diabetes.[82,83] Despite this observation, many years passed before his idea received broad attention in the scientific community, spurring an increase in epidemiological and experimental research related to the heterogeneity of obesity, and the link between abdominal fat and cardiovascular health.

Eventually, the WHO recognized that having an excessive amount of abdominal fat can be particularly detrimental for health.[56] This condition is commonly referred to as abdominal, central, or visceral obesity, and it is characterized by excessive storage of fat known as visceral adipose tissue (VAT) in the abdominal cavity, surrounding the intra-abdominal organs. Historically, adipose tissue has been viewed as a passive organ with the sole purpose of energy storage. Today, however, adipose tissue and especially VAT is considered a highly endocrine and metabolically active organ with implications for cardiometabolic health. The WHO defines visceral obesity using cut-off values for anthropometric indexes, namely waist circumference and waist-to-hip ratio,[84] which are commonly viewed as surrogates for VAT. For men, the cut-off is a waist circumference >94 cm (increased risk) or >102 cm (substantially increased risk), or a waist-to-hip ratio $\geq$0.90.[84] For women, the cut-off is a waist circumference >80 cm or >88 cm, or a waist-to-hip ratio $\geq$85.[84]

The first systematic review of the global prevalence of visceral obesity was published in 2020. Based on 288 population-based studies including more than 13 million participants, the global prevalence of visceral obesity defined by waist circumference was estimated to 41.5%.[85] The prevalence increased from 31.3% in the 1990s to 48.3% in the mid-2010s, with a particularly high prevalence among older people and in high-income countries.[85] Similarly, a Norwegian population-based study investigated the trends in objectively measured VAT mass between 2001 and 2016, observing an increase among both older men and women.[86]

Storage and determinants

The accumulation of excess fat mass results from a prolonged period of positive energy balance, where energy intake exceeds energy expenditure, often due to excessive food intake and insufficient physical activity. Free fatty acids and

glycerol are, with the assistance of lipoprotein lipase, stored as triglycerides in adipocytes. The primary site of storage is subcutaneous adipose tissue, which accounts for about 80% of total body fat, while VAT generally represents 10% to 20% of the total.[87] Typically, the ability of subcutaneous adipose tissue to expand and store fat during positive energy balance occurs through adipogenesis and hyperplasia of preadipocytes. However, adipogenesis in subcutaneous adipose tissue may become exceeded or impaired in association with aging.[88] As a result, existing adipocytes preferentially undergo hypertrophy and there is an increased accumulation of VAT, which also leads to an associated lipid spillover resulting in lipotoxicity, which means storage of fat in non-adipose tissue organs such as the heart, liver, and muscle, known as ectopic fat.[89,90]

Two common observations regarding accumulation of VAT relate to sex and age. In general, men store about twice the amount of VAT mass compared with women, and VAT mass increases with age.[91] Although the exact reasons are incompletely understood, it has been suggested that men preferentially accumulate fat in the visceral region because of a greater number of adipocytes in that region compared to women, and that sex hormones may be involved.[92] In men, the age-related increase in VAT may be linked to the decrease in testosterone, whereas in women, estrogen may explain why fat is mostly stored in gluteal femoral regions before menopause, and consequently, why accumulation of VAT increases at a faster rate after menopause.[92-94] Furthermore, age-related reductions in physical activity, energy expenditure, and resting metabolic rate, as well as a dysfunctional lipid metabolism, are probably also involved.[77,94] There are also factors beyond sex and age which may influence VAT accumulation, such as chronic stress. Overactivation of the sympathetic nervous system leads to elevated cortisol levels, which in turn may promote VAT accumulation through increased activation of lipoprotein lipase in adipose tissue.[95]

Most notably, however, is the contribution of genetic factors. After accounting for age and sex, heritability estimates of BMI in heterogenous populations reach about 40% to 50%, with slightly higher estimates for VAT.[96] These data show that genetic predisposition to both overall and visceral obesity is substantial. Genetic factors also impact individual change in VAT mass in response to interventions. Proof-of-concept twin studies have shown that changes in VAT mass following long-term overfeeding or exercise can vary much more between twin pairs than within pairs, with a 6 to 12-fold difference observed.[97,98] Collectively, genetic factors play an important role in both the predisposition to visceral obesity as well as the degree of change following an intervention. However, it should be emphasized that these are group-level based estimates and do not imply the risk of obesity for a specific individual. It has also been shown that even individuals

with a high genetic risk of obesity can benefit from lifestyle interventions including physical activity and exercise.[99,100]

Measuring visceral adipose tissue

Although anthropometric measures are cheap and easy to use, they are unable to accurately distinguish between abdominal subcutaneous adipose tissue and VAT,[101] and might better reflect total adiposity.[102] Importantly, at a given level of total adiposity, VAT may vary up to threefold.[103] Therefore, imaging techniques are important for assessment of body composition, especially among older adults given the age-related changes in terms of reduced muscle mass and increased propensity towards VAT accumulation.[104] The gold standard method for accurately quantifying VAT is computed tomography and magnetic resonance imaging.[101] These methods include either high exposure to radiation, or high cost and long scan times. An alternative method is dual-energy X-ray absorptiometry (DXA). A whole-body DXA scan usually takes no longer than 10 minutes and the radiation dose is much lower compared with computed tomography.[105] The DXA technology works by sending X-ray beams at two energy levels through the body, which are attenuated differently depending on the density of the tissue. While originally developed for the assessment of bone mineral content, it also measures soft tissue divided into lean body mass and fat mass. Additionally, software has been developed that uses algorithms to estimate VAT mass using DXA, which has been validated to the gold standard methods.[106] Because of its lower cost, shorter scan time, and negligible radiation dose, the DXA has become increasingly popular both in research and clinical practice.

Influence on cardiovascular disease and all-cause mortality

Vague's work in the 1940s and 1950s stayed unsupported until the 1980s, when his findings eventually received support.[107] Fast forward to today, and there is an extensive line of epidemiological evidence suggesting that excess VAT, independent of total adiposity, is a key conduit through which excess adiposity links with CVD and premature death in the general adult population.[107]

Most studies have employed anthropometric surrogates for VAT, with results across large case-control studies, prospective cohort studies and subsequent meta-analyses consistently showing associations with increased risk of CVD and mortality, independent of and beyond BMI.[34,108-114] For the outcome of CVD, the association has been confirmed in studies using objective measures of VAT. In the Framingham Heart Study, comprising 3,086 middle-aged individuals, greater VAT, independent of BMI, was associated with 44% increased risk of incident CVD during five years of follow-up.[115] There was a trend towards a sex-specific interaction, where greater VAT was associated with 66% increased risk in men but there was no association in women.[115] Additionally, VAT outperformed BMI

and waist circumference in terms of CVD risk prediction.[115] Moreover, in the Multi-Ethnic Study of Atherosclerosis, comprising 1,910 individuals aged 45 to 84 years, participants in the highest tertile of VAT, independent of BMI, had 73% increased risk of incident CVD during about nine years of follow-up, but no sex differences were observed.[116] Another smaller study comprising 972 middle-aged individuals followed for an average of nine years also showed that greater VAT, but neither BMI nor waist circumference, was associated with 20% increased risk of incident CVD.[117] These findings can be contrasted to earlier comparative evaluations of adiposity measures for CVD risk prediction, which suggested similar contribution from all anthropometric indexes.[118]

The fact that VAT appears to be a primary and independent measure of adiposity explaining the link with increased CVD risk was further illustrated in a recent study, where excess VAT was associated with increased risk of CVD in middle-aged individuals also among those with low amount of liver fat.[119] A causal relationship between VAT and CVD is further supported by mendelian randomization studies which have shown that genetically predicted VAT is associated with 30% to 50% increased risk of stroke, 50% to 80% increased risk of myocardial infarction, and reduced longevity.[120-123] Thus, a vast body of evidence currently indicates that objective measures of VAT are important for establishing a valid and accurate link between adiposity and CVD outcomes in adult populations.

Despite the findings outlined above, the role of visceral obesity in CVD in older people remains incompletely understood. It has even been deemed controversial by some, mainly due to a lack of studies conducted in representative samples of older people including objective assessment of VAT.[112] Consequently, it has not yet been possible to firmly establish the role of VAT in CVD, preferably through a meta-analysis. By the time that the studies upon which the present thesis is based were conducted, there had to my knowledge been two previous cohort studies investigating the association of VAT with incident CVD in older adults. In the Health ABC Study, Nicklas et al. measured body composition including VAT using computed tomography in 2,503 individuals aged 70 to 79 years from the US.[124] During an average of about five years of follow-up, greater VAT mass as measured using computed tomography was associated with 24% increased risk of myocardial infarction.[124] The association appeared to differ between the sexes, where an association was observed in women but not in men.[124] This study was later followed up by a study based on the Outcomes of Sleep Disorders in Older Men Study, where Schousboe et al. found no association between greater DXA-measured VAT mass and incident CVD in 2,899 US men with a mean age of 76 years during an average follow-up of about eight years.[125]

Although these two studies suggested an increased risk of CVD from excess VAT in older women but not in men, the overall body evidence regarding VAT and CVD in older adults, including potential sex differences, is clearly limited and insufficient to draw firm conclusions from. In these previous studies, possible explanations for the lack of observed association in older men might include different types of selection biases, an issue that is frequently occurring in geriatric epidemiology.[126] For example, in the study by Nicklas et al., VAT mass did not differ significantly between men and women,[124] despite that men generally have around twice the amount of VAT compared with women.[91] This could mean that men with the greatest amount of excess VAT had already suffered associated cardiovascular complications earlier in life, including death, making them ineligible for the study and thereby introducing selection bias. Similarly, the study by Schousboe et al. included an even older population, which may further increase the risk of selection bias, where the included participants may have been predisposed to live up to an old age while unhealthier individuals died prior to being eligible for the study. In this context it is worth mentioning that the relevance of metabolic risk factors, such as obesity, has been found weaker in the oldest old as compared with the younger old[127]. While it could also be hypothesized that the detrimental role of VAT in old age may differ between age groups, it is possible that it simply reflects a selection bias. Collectively, based on the scarcity of data, investigation of the association of VAT with CVD in older adults warrants further attention, as was also highlighted in a recent review.[112]

In terms of all-cause mortality, large-scale data based on anthropometric indexes indicate that visceral obesity could be a risk factor in old age. In a meta-analysis of 58,000 individuals aged 65 to 74 years, normal-weight individuals with the highest waist circumference had about 70% increased risk of all-cause mortality during five years of follow-up, as compared with normal-weight individuals with the lowest waist circumference.[128] Furthermore, a cohort study of 130,000 individuals aged 60 to 69 years showed that normal-weight individuals with an elevated waist-to-hip ratio had a higher risk of all-cause mortality during an average follow-up of eight years, as compared with normal-weight individuals with the lowest waist-to-hip ratio.[129]

However, only a few individual studies in older people have used imaging techniques to measure VAT. One study investigated the association of VAT with all-cause mortality in 1,000 Koreans with a mean age of 76 years. The results showed a quite counterintuitive finding, where greater VAT mass, as measured using computed tomography, was associated with lower risk of all-cause mortality during an average of about five years of follow-up.[130] However, certain covariates of interest were lacking, such as socioeconomic factors and medical history. In a similar study of 5,000 Icelanders with a mean age of about 76 years, greater VAT mass, as measured using computed tomography, was associated with

increased risk of all-cause mortality in women but not in men, during an average of eight years of follow-up.[131] In contrast, in a study of 839 Brazilians aged 65 years or older, greater DXA-measured VAT mass was associated with increased all-cause mortality in men but not women during an average follow-up of four years.[132] Finally, in a longitudinal analysis of the Health ABC Study, the association between 5-year changes in VAT mass, as measured using computed tomography, and all-cause mortality was investigated in 1,803 individuals with a mean age of 78 at the beginning of the follow-up.[133] During an average of 12 years of follow-up, around half of the population died, and greater VAT mass was not associated with higher mortality in either men or women.[133] Collectively, evidence for an association between VAT and mortality in older adults is inconsistent and incompletely understood, and the conflicting results may be affected by varying age, health status, length of follow-up, as well as confounding and bias as outlined previously. Importantly, these studies mainly comprised older adults of older age compared to the aforementioned studies using anthropometric indexes, which is an important difference to bear in mind when interpreting the literature.

Pathophysiology

The potential mechanisms through which excess VAT may lead to a cardiovascular event or death have been extensively reviewed.[87,89-92,103,134-137] Much appears to revolve around metabolic disturbances and inflammation. For example, lipolytic responsiveness is higher in VAT than in subcutaneous adipose tissue, and VAT is also less sensitive to the anti-lipolytic effects of insulin, consequently leading to a high release of free fatty acids into the circulation. High levels of plasma free fatty acids are also linked with insulin resistance, oxidative stress, and endothelial dysfunction. VAT is also characterized by its pro-inflammatory profile, particularly in terms of its high infiltration of macrophages and release of pro-inflammatory adipokines such as interleukin-6 and tumor necrosis factor-alpha. These adipokines may be involved in a variety of detrimental processes, including their negative effects on insulin sensitivity and contribution to endothelial dysfunction. For instance, the release of pro-inflammatory adipokines stimulates the expression of adhesion molecules on the surface of the endothelial cells, increasing oxidative stress and impairing endothelium-dependent vasodilation. Furthermore, because VAT venous blood is drained through the portal vein, it exposes the liver directly to the VAT-exaggerated release of free fatty acids and pro-inflammatory adipokines, which may promote hepatic insulin resistance as well as the synthesis and release of very-low-density lipoproteins to the blood stream.

Excess VAT may also exert atherothrombotic effects through its association with higher levels of plasminogen activator inhibitor type 1, a key regulator in the fibrinolytic process. VAT may also exert several direct and indirect detrimental

effects on the myocardium, which may contribute to myocardial injury, hypertrophy, remodeling, and heart failure. Together, there are several plausible ways in which excess VAT contributes to atherosclerosis, CVD, and death. Interestingly, several of these highlighted detrimental effects related to excess VAT may also accelerate pathological aging processes on multiple levels, such as cellular senescence and inflammation.[138] On a further note, excess VAT is associated also with ectopic fat storage such as skeletal muscle adiposity,[135] which just like VAT seems to increase with age[77] and also its pathophysiological characteristics appear similar to those of VAT in many aspects.[107,139] It remains unclear whether the association of VAT with CVD is independent of other fat depots such as skeletal muscle adiposity.[135]

Physical activity

Definitions

Physical activity is defined as any bodily movement produced by skeletal muscle that causes an increase in energy expenditure.[140] As such, physical activity is a broad term that includes all modalities, intensities, and domains (occupational, transportation, household, and leisure). Exercise, on the other hand, is a subset of physical activity which is defined as a planned, structured and repetitive physical activity with the aim of improving or maintaining physical fitness components.[140]

Because oxygen consumption increases in parallel with the intensity of physical activity, the absolute intensity or rate of energy expenditure is often expressed in metabolic equivalent of tasks (METs).[141] One MET is equivalent to the energy expenditure during quiet sitting and the value most used to define this is 3.5 ml O_2/kg/min.[141] The absolute intensity of physical activity can thus be expressed as multiples of the resting metabolic rate. Light-intensity physical activity (LPA) is characterized by METs of 1.6-2.9 and includes activities such as lighter household work and casual walking. Moderate-intensity physical activity (MPA), such as brisk walking, swimming, and bicycling is characterized by METs of 3.0-5.9. Vigorous-intensity physical activity (VPA), which is characterized by METs of $\geq$6.0, may include jogging, running, brisk uphill walking, circuit training and sports activities. MPA and VPA are often expressed as a single entity known as moderate-to-vigorous physical activity (MVPA), characterized by METs $\geq$3.0.

Sedentary behavior can also be determined using METs. In 2017, the Sedentary Behavior Research Network published a terminological consensus statement to attempt to establish a common and accepted definition of sedentary behavior. They concluded that the most frequently adapted definition is the one where sedentary behavior is defined as any waking behavior characterized by an energy

expenditure ≤1.5 METs while in a seated or reclining position.[142] It is critical to distinguish sedentary behavior from physical inactivity, also known as insufficient physical activity, which refers to individuals who perform physical activity at levels below the current recommendations.[142]

As stated, physical activity intensity defined according to METs is a measure of absolute intensity which likely differs according to factors such as sex, age, and fitness level.[141,143] Thus, there are also relative measures of intensity that are commonly used especially in exercise interventions such as percentage of maximum aerobic capacity or scales that assess the rate of perceived exertion.[141]

Collecting data on physical activity

Data on people's physical activity can be collected in different ways depending on which components that are of interest (frequency, duration, intensity, modality, or domain). Historically, most studies have used methods where individuals report their physical activity, in terms of questionnaires and diaries.[141] Such methods are suitable for collecting data on domain- and modality-specific physical activity, such as vigorous exercise, which is by design easier for an individual to recall as opposed to spontaneous or sporadic activity.[141] Self-reported measurements may also be chosen due to the low cost and the possibility for large-scale data collection.[141]

There are also a variety of objective methods available for assessing physical activity.[141] Most notably, the recent decades have been characterized by an exponential increase in the number of studies incorporating motion sensors, primarily accelerometers, to measure physical activity and sedentary behavior and examine their associations with health outcomes.[144] Yet, it should be noted that these types of studies still represent a minority.[145]

An accelerometer is a small wearable device placed at a fixed body location, such as the hip or wrist, where it measures external body movements.[141,146] Depending on the device and the protocol used, the accelerometer measures the amplitude and frequency of accelerations in either the vertical axis (uniaxial) or in the vertical, medio-lateral, and antero-posterior axes (triaxial).[141] By using micro-electromechanical technology, mechanical movements are converted into electronical signals, which after filtering and data processing are transformed into what is known as "counts".[141,146] Using computer software, a data processing criterion, and established count-thresholds that correspond to different physical activity intensities, the raw accelerometer counts can then be used to classify the intensity of the physical activity.[141]

Compared to self-report methods, accelerometers have several advantages such as allowing for measurement of the total amount of physical activity, regardless of which domain it is accumulated in.[144] Accelerometers also minimize biases due to recall and social desirability, which are known limitations of self-report methods.[147] They also allow for a more accurate measurement of LPA and sedentary time, both of which are difficult to adequately self-report.[141,144] This is particularly relevant in geriatric research because older adults spend most of their awake time being sedentary or performing LPA.[148] Further, the imprecision of self-reported as compared with accelerometer-based measurements may potentially bias the associations between physical activity and health outcomes.[149] However, it should be noted that accelerometers are not free from limitations. For example, it cannot capture activities such as cycling and stair climbing, and an if placed on the lower extremities it does not capture upper-body activities. Also, accelerometers cannot account for external load, such as when lifting weights, carrying groceries, or walking with a backpack.

Guidelines and recommendations

In the 1970s, the first guidelines related to physical activity were published by the American College of Sports Medicine and the American Heart Association.[150,151] These guidelines were mainly aimed at improving physical fitness and performance, and the recommendations were to perform 20 minutes of rather vigorous aerobic exercise at least three times per week. However, as new evidence emerged, the recommendations were redeveloped. The 1990s saw a paradigm shift away from the performance-focused exercise towards a broad public health perspective, with an emphasis on promotion of all forms of MVPA to reduce the risk of chronic diseases.[152] Throughout these years, guidelines and recommendations have been endorsed and established by multiple influential organizations and authorities such as the National Institutes of Health, the Centers for Disease Control and Prevention, and the WHO. In 2020, the most recently updated global guidelines were published by the WHO under the slogan "Every Move Counts" , with the title 'WHO Guidelines on Physical Activity and Sedentary Behavior'.[153] These guidelines include specific recommendations on physical activity and sedentary behavior for children, adults, older adults, and special target populations such as people living with chronic diseases, people living with disabilities, and pregnant women.[153]

Specifically, the guidelines include a strong recommendation for older adults aged 65 or over to engage in at least 150 to 300 minutes per week of MPA, or at least 75 to 150 minutes per week of VPA, or an equivalent combination of both. On at least three days per week, this physical activity should comprise multicomponent activity that focuses on improving strength, balance, and endurance. Older adults are also recommended to perform muscle-strengthening

activities at least twice per week. The importance of personalization and individual progression is emphasized, where older adults are encouraged to gradually increase the frequency, intensity, and volume of physical activity according to their individual ability and capacity.

The guidelines also states that even among older adults who are not currently meeting these recommendations, doing some physical activity is better than doing none. The statement that every minute counts, and that physical activity does not have to be accumulated in prolonged bouts, is an updated feature of the 2020 guidelines. This was revised based on new evidence showing that all physical activity, regardless of how it is accumulated, is associated with health benefits,[154] which was also subsequently shown for the outcome of mortality.[155] This is in contrast to the 2010 guidelines which only considered 10-minute bouts of physical activity.[156] Even though the guidelines now recognize the importance of all physical activity, more research has been requested specifically on the role of LPA.[153,157]

Furthermore, the 2020 guidelines for the first time include recommendations on sedentary behavior. Older adults are recommended to limit their time spent sedentary and interrupt periods of sedentary behavior with physical activity of any intensity, including LPA. The guidelines also highlight the interrelation between physical activity and sedentary behavior, concluding that the former may be used to offset some of the risks from the latter. This boils down to a recommendation that in order to further reduce the potentially detrimental effects linked to sedentary behavior, older adults are recommended to perform an amount of MVPA above the levels of the recommendations. Nevertheless, the WHO deemed the evidence to be insufficient to provide specific quantitative recommendations regarding certain thresholds of sedentary behavior and that additional research on the interactions between physical activity and sedentary behaviors in relation to health outcomes are needed.

Prevalence

Historically, people have been required to be more physically active in their day to day lives than they are today, where technological advancements have reduced this need. In addition, longitudinal data suggest that the rising obesity rates have contributed to the decline in physical activity.[158] As a result of the decline in physical activity, Kohl et al. published a seminal paper in 2012, in which they argued that physical inactivity should be viewed as a pandemic.[159] Estimations based on self-reported physical activity indicate that 5% to 6% of the global burden from CVD and 7% to 9% of premature mortality may be attributable to physical inactivity.[160] While the absolute burden is greater in low-income countries, the relative burden of CVD and mortality associated with physical

inactivity is twice as high in high-income countries.[161] Meanwhile, others have estimated that the current prevalence of self-reported physical activity in the global population may avert about four million deaths per year,[162] although an additional 0.5 to 1.3 million people's lives would be further spared by reducing physical inactivity by an additional 10% to 25%.[160] However, these estimations should be cautiously interpreted as they assume causality based on estimations from observational data.

Besides mortality and disease burden, physical inactivity has been estimated to pose substantial economic burden, with conservative estimates of at least $53 billion annually for healthcare systems as well as $13 billion due to productivity loss.[163] Reducing physical inactivity has therefore become one of the prioritized targets of the WHO Global Action Plan for Prevention and Control of Non-communicable Diseases, which states that physical inactivity needs to be reduced by at least 10% by 2025.[64] This target was later extended to a 15% reduction by 2030 in the WHO Global Action Plan for Physical Activity.[164]

In 2012, the global prevalence of physical inactivity was estimated based on self-reported data from 122 countries.[165] The results showed that an estimated 31% of the global adult population was physically inactive, with a higher prevalence in older age groups.[165] In Europe and America, the prevalence of physical inactivity in people aged 60 years or older was 50% and 60%, respectively.[165] Four years later, an updated analysis which included 146 countries estimated that 23% of the adult population was insufficiently active, although this apparent improvement was attributed to discrepancies in how physical inactivity was defined in the two studies rather than an actual increase in physical activity.[166]

In 2018, the most recent and comprehensive evidence on the global prevalence of physical inactivity was published. The study investigated trends in physical inactivity between 2001 and 2016 based on self-reported data from 1.9 million individuals across 168 countries, including twice as many surveys as previous estimates.[167] The results showed that overall, about a quarter of the global population remained insufficiently active during this time period.[167] However, in high-income western countries, the prevalence increased from 30.9% in 2001 to 36.8% in 2016.[167] Similarly, in Sweden, the Public Health Agency estimated the prevalence of physical inactivity in 2021 to 33% in the total adult population, and 42% in older adults.[168] It is likely that self-reported estimates such as these are underestimated. For example, pooling of accelerometer-data from four European countries estimated the physical inactivity prevalence to 72%.[169] Moreover, while a US study reported a decreased prevalence of self-reported physical inactivity and an increased adherence to physical activity guidelines between 1998 and 2018,[170] a meta-analysis based on device-measured physical activity reported that

levels of physical activity in developed countries trended downwards between 1995 and 2017.[171]

In terms of sedentary behavior surveillance, it is only during the recent years that studies in this juvenile area of research have begun to flourish. Based on self-reported data, it was estimated that adults and older adults are sedentary for on average 5 to 6 hours per day.[172-174] Again, recent pooling- and meta-analyses of accelerometer-based data indicate that this estimate is probably underestimated. In these studies, the average sedentary time in middle-aged and older adults ranged from 8.5 to 10.5 hours per day,[169,175] with higher estimates among older adults.[176] Moreover, 80% were sedentary for at least 7.5 hours per day and 20% were sedentary for at least 10 hours per day.[169] Regarding time trends, a US study reported that self-reported sitting time increased slightly between 2001 and 2018, although with a decrease in the last four to five years.[177] Collectively, although device-based data on trends in physical activity and sedentary behavior are limited and difficult to interpret, the overall body evidence indicate that estimates of insufficient activity and prolonged sedentary time remain at a rather high level. By implication, achieving the targets set out by the WHO Global Action Plan for Physical Activity remains a challenge,[164] especially for older adults.

Patterns and determinants

As people age, their physical activity, especially that of higher intensity, tends to decline. This is partly due to age-induced deteriorations in physiological systems, which over time lead to declines in physical function and capacity.[178] Consequently, among older adults, sedentary time constitutes most of the awake time and physical activity is mostly performed at a light intensity.

Accelerometer-based estimates suggest that older adults are sedentary for about 60% to 80% of their awake time, while about 19% to 36%% is spent as LPA, and only 1% to 4% is spent as MVPA.[174,175,179-181] The variations could be influenced by different choices and criteria of how to process accelerometry-data.[182] Yet, beyond methodological discrepancies, variations are expected given that aging is a very heterogenous process characterized by distinct variability in health status, behaviors, and characteristics.

There are several factors that may influence physical activity levels. In general, factors such as older age, female sex, overweight, poor health, low self-efficacy towards physical activity, low education, and lack of accessibility to physical activity-friendly environments, correlate negatively with physical activity levels.[183] In older people specifically, positive correlates of sedentary time include older age, smoking, male sex, living alone, high education, overweight or obesity, polypharmacy, poor health, and impaired physical function.[179,180,184] Similarly,

these factors are negative correlates of MVPA, except for level of education, where low education is a negative correlate, as well as sex, where male sex is a positive correlate.[179,180,185] Moreover, genetic predisposition plays an important role. In twin studies, the heritability of accelerometer-measured energy expenditure and MVPA have been estimated to about 50%, while the heritability of sedentary time ranges from 31% to 56%.[186,187] Similarly, the heritability of exercise participation has been estimated to between 48% to 71%[188] and appears to be moderately to highly stable across the lifespan,[189] largely due to genetic factors.[190] These findings emphasize the importance of recognizing the significant influence of genetic factors in determining people's level of physical activity and sedentary behavior, and caution against oversimplifying them as just a matter of personal choice.

Influence on cardiovascular disease and all-cause mortality

The field of physical activity and cardiovascular health was spearheaded by Jeremy Morris and Ralph Paffenbarger Jr., whose influence as pioneers in this discipline have been widely acknowledged. The work they conducted between the 1950s and 1980s, linking physical activity with lower risk of CVD,[191-193] is considered landmark studies within physical activity and health epidemiology, and eventually spurred an exponential increase in research in this area.[145]

Today, evidence from a large number of reviews, meta-analyses and pooled analyses, all based on observational studies, show that greater amounts of MVPA are strongly associated with lower risk of incident CVD and all-cause mortality, and emerging evidence highlights sedentary behavior as a detrimental risk factor.[153,157] Most of these studies have typically been based on self-reported data. For example, Moore et al. and Arem et al. showed that compared with individuals reporting no MVPA, people reporting some MVPA but below the amount recommended by guidelines, had 20% lower risk of all-cause mortality, while those reporting one to two times the recommended amount had 30% lower risk.[194,195] A maximum risk reduction of around 40% was observed for those reporting more than three times the recommendation.[194,195] As such, there was no lower limit required to observe benefits, as the steepest decline in risk was seen for individuals who reported doing just a small amount of MVPA.[194,195] Similar results have been seen in older populations specifically.[196]

As for CVD, meta-analyses of observational studies have shown that people reporting physical activity at the lower limit of the guidelines had 14% to 17% reduced risk of incident CVD,[197,198] with a maximum observed risk reduction of 25%.[197-199] Similar results were reported by Lear et al. in a cohort study of 130,000 individuals,[200] and by Kyu et al. in a meta-analysis of more than 50 cohort studies.[201] This meta-analysis also found a similar trajectory as previously

reported for all-cause mortality, where most of the benefits seemed to occur at the lower end of the physical activity spectra.[201] In terms of sedentary behavior, meta-analyses based on self-reported data have shown that the most sedentary individuals have 22% to 27% increased risk of all-cause mortality and 14% increased risk of CVD, as compared with the least sedentary individuals.[202-205]

The rapid growth in the number of studies using accelerometers in recent years has deepened and extended our previous knowledge, while opening doors to previously undiscovered and important aspects of investigation. One area that has received special interest is LPA. In a meta-analysis of eight cohort studies comprising 36,000 middle-aged and older individuals, Ekelund et al. found a curvilinear association between greater amounts of accelerometer-measured physical activity, including both LPA, MVPA and total physical activity, and lower all-cause mortality during a median follow-up of six years.[206] The observed maximal risk reduction was 60% to 70%, which is much higher compared to previous estimates based on self-report.[206] This finding was later corroborated by Strain et al. in a cohort study including nearly 100,000 individuals.[207] Similar results were found in another meta-analysis of 15 cohort studies comprising more than 140,000 middle-aged and older individuals, in which there were no restrictions to the specific device used to measure physical activity. The results showed that participants in the highest category of objectively measured LPA, MVPA and total physical activity had 40%, 56% and 67% lower risk of all-cause mortality respectively during follow-up.[208]

Regarding CVD, Ramakrishnan et al. investigated the associations between accelerometer-measured physical activity and CVD in 90,000 individuals during a median follow-up of five years.[209] They found an inverse, linear relationship between physical activity and incident CVD, where the most active individuals, whether divided according to MPA, VPA, or total physical activity, had about 40% lower risk of incident CVD.[209] In terms of potential benefits from LPA, studies of adults and older adults have found greater amounts of LPA to be favorably associated with some cardiovascular risk factors,[210-212] although studies with cardiovascular endpoints have been fewer and with inconsistent results. In a study by LaCroix et al. comprising 5,800 older women followed for an average of three and a half years, participants with the most LPA had 22% lower risk of a composite CVD endpoint compared with those with the least amount of LPA.[213] Additionally, a 1-hour/day increment was associated with 8% lower risk.[213] Similarly, LaMonte et al. reported a lower risk of cardiovascular mortality from greater LPA in a study of older women.[214] In contrast, there have been other studies of both middle-aged and older adults which did not observe significant associations between greater amounts of LPA and lower risk of incident CVD or cardiovascular mortality.[215-218]

Clearly, the field has advanced quickly, with emerging evidence suggesting that not only MVPA, but also LPA might be relevant for CVD prevention. Still, quantitative recommendations of LPA have yet to be incorporated into formal guidelines, hence more studies have been requested.[153,157] Any potential benefits from LPA may be of particular importance to older adults who either have difficulties to reach a high intensity in their daily physical activities, or who lack the willingness to partake in structured high-intensity exercise. This would perhaps be particularly relevant to many older adults who often spend a lot of time sedentary and mainly perform LPA.

However, regardless of whether LPA has certain benefits to offer, the beneficial associations of MVPA remain, and recent evidence suggest that continuing to promote physical activity of at least moderate intensity is important. For example, recent cohort studies based on accelerometer-measured physical activity found that for a given volume of total physical activity, performing a higher proportion of MVPA was associated with greater benefits with respect to CVD and mortality.[207,219] Epidemiological data on the benefits associated with VPA are sparser, although Wang et al. found that among individuals with the same amount of self-reported MVPA, those with a higher proportion of VPA had lower risk of all-cause mortality.[220] Similarly, two cohort studies based on accelerometer-measured physical activity found that very small amounts of VPA were associated with lower risk of incident CVD, as well as all-cause and cardiovascular mortality, even when performed in very short bouts.[221,222]

Can physical activity compensate for sedentary behavior?

Similar as with physical activity, the point estimates for accelerometer-measured sedentary time also appear higher compared to self-reported estimates. In the meta-analysis by Ekelund et al., the most sedentary individuals had more than twofold higher risk of all-cause mortality compared with the least sedentary individuals.[206] A similar pattern appears to apply to the outcome of CVD. For instance, while keeping in mind the 14% increased risk observed for self-reported sedentary time, a cohort study of 5,600 older women found that the most sedentary women had around 50% higher risk of incident CVD compared with the least sedentary women, and every 1-hour/day increment in sedentary time was associated with 12% increase in risk.[223] While this evidence indicates that sedentary time is a risk factor for both mortality and CVD, evidence regarding the latter is sparser.

An interesting question raised in recent years is whether physical activity can compensate for sedentary behavior. In a meta-analysis of data from more than one million individuals, Ekelund et al. found no association between self-reported sitting time (8 hours per day or more) and all-cause mortality among those who

reported 60 to 75 minutes of daily MVPA,[203] implying that high levels of physical activity may be practiced as a way to offset the health risks associated with sedentary behavior. Similarly, in a study of more than 149,000 individuals, Stamatakis et al. found that greater self-reported sitting time was associated with all-cause and cardiovascular mortality only among those who reported MVPA below the amount recommended by guidelines.[224] Later, Ekelund et al. performed a new meta-analysis restricted to accelerometer-based studies. The results showed that while there was an association between sedentary time and all-cause mortality among participants with the least amount of MVPA, there was no such association among individuals performing around 30 to 40 minutes of daily MVPA.[175] Thus, a threshold that is almost half of that reported in their previous meta-analysis. Together, these findings indicate that among people where sedentary time constitutes a considerable proportion of total awake time, such as among older adults, the detrimental effects of prolonged sedentary behavior on mortality risk might be mitigated through MVPA. Whether these observations apply to other outcomes of interest, such as CVD is unclear. For example, one previous study of older women found no statistically significant interaction between sedentary time and MVPA in relation to incident CVD.[223]

In sum, although there has been an exponential increase in physical activity research during the last decades, there is a need to prioritize research in older adults because this segment of the population is rapidly growing while remaining understudied. In fact, a systematic review estimated that less than 10% of all publications have been conducted in people aged 60 years or over.[145] Questions of particular interest revolve around the potential beneficial associations of LPA, and whether physical activity can mitigate the risks associated with prolonged sedentary time, with a special need for objectively measured data. Another critical question to ask is whether associations of physical activity with CVD and mortality can be presumed to be causal, since they are based on observational data. One way to explore this would be to scrutinize the findings from current randomized controlled trials (RCTs) that have investigated the effect of physical activity on clinical CVD endpoints and mortality.

Proposed protective mechanisms

A single bout of physical activity initiates thousands of molecular changes throughout most systems in the human body.[225] Consequently, several mechanistic pathways through which physical activity and exercise might have beneficial effects with respect to atherosclerotic CVD and mortality have been proposed. This includes improvements in traditional risk factors such as cardiorespiratory fitness, blood pressure, blood glucose, and blood lipids, as a result of various cardiac, vascular, and skeletal muscle adaptations.[226]

Physical activity may also induce beneficial adaptations in nontraditional risk factors and through mechanisms not commonly assessed in large-scale observational studies. For example, physical activity can have favorable effects on the fibrinolytic process through lowering the levels of plasma fibrinogen and plasminogen activator inhibitor-1 while increasing the activity of tissue-type plasminogen activator.[227] It may also decrease blood viscosity[228] and platelet adhesion,[229] improve atherosclerotic plaque characteristics and reduce plaque burden,[230] and reduce oxidative stress.[231] There are also a vast number of other effects, as highlighted in several state-of-the-art reviews, such as reduced systemic inflammation, reduced arterial and myocardial stiffness, improved autonomic function, increased angiogenesis, increased mitochondrial density, improved insulin sensitivity, and increased release of anti-inflammatory myokines.[230,232-234]

Mechanisms exclusive to sedentary behavior have been studied to a lesser extent, but among those mentioned are for example detrimental effects on blood flow, shear stress, skeletal muscle mass, insulin sensitivity, mitochondrial capacity, and endothelial function, as well as increased oxidative stress and inflammation.[235,236] Consequently, interrupting prolonged sedentary behavior might counteract some of the negative effects. For example, meta-analyses have shown that interrupting sedentary behavior with physical activity of any intensity reduces postprandial glucose, insulin and triglycerides,[211,237] although higher intensity may yield better effects.[238] Moreover, LPA has been associated with lower subclinical atherosclerosis,[239] and meta-analyses show that interrupting sedentary behavior with LPA could improve vascular function and have anti-inflammatory and anti-oxidative effects.[240,241] In animal models, physical inactivity has been shown to suppress skeletal muscle lipoprotein lipase activity, meaning that uptake of fat to skeletal muscle is impaired. The same study found that low-intensity walking reversed these alterations in lipoprotein lipase activity, suggesting preliminary benefits of LPA in relation to lipid metabolism.[242]

Effect on visceral adipose tissue

The evidence outlined above suggest several potential mechanisms through which increased physical activity might reduce CVD. Another factor that is relevant to this discussion and central to this thesis is how physical activity and exercise might decrease VAT. Traditionally, physical activity and exercise has been viewed as an important component in the treatment of obesity,[243] with current guidelines recommending at least 250 minutes per week of MVPA.[244,245] However, the paradigm is changing. Today, it is suggested that individuals with obesity should be prescribed tailored physical activity and exercise not with the primary intention of achieving weight loss, but rather to target and improve important cardiometabolic risk factors, such as VAT, which may be possible even

in absence of weight loss.[243] In conjunction with the emerging evidence on the harms of excess VAT in relation to CVD, there has been a growing interest in understanding to what extent exercise could decrease VAT, and in turn, potentially the risk of CVD.

In 2001, Ross & Janssen reviewed the evidence and concluded that although short-term aerobic exercise interventions seemed to induce weight loss that was associated with decreased VAT, the overall evidence was limited and insufficient to draw conclusions on the dose-response relationship.[246] A few years later, a systematic review by Kay & Singh concluded that aerobic exercise interventions may lead to statistically significant reductions in VAT in absence of weight loss, but that evidence regarding the influence of intervention duration, intensity and modality was lacking.[247] Shortly afterwards, Ohkawara et al. performed a systematic review of the dose-response relationship between exercise volume and VAT reduction and found that a volume corresponding to the lower limit of the physical activity guidelines elicited significant effects in absence of weight loss among individuals with obesity.[248] Still, the number of studies were relatively few, and the authors emphasized the need for additional high-quality trials also for determining the influence of moderating factors.

As the number of trials increased, several meta-analyses were conducted in the following decade. Ismail et al. performed a meta-analysis of the impact of exercise modalities on VAT in individuals with overweight and obesity (N=2,415).[249] They found that aerobic exercise significantly decreased VAT compared with control groups (standardized mean difference [SMD], -0.4), and with a trend towards a superior effect for aerobic exercise compared with resistance exercise.[249] Yet, they did not assess the influence of exercise intensity. This was revisited by Vissers et al. who performed the first meta-analysis of the effect of exercise in absence of caloric restriction on VAT in individuals with overweight and obesity (N=852). They found that exercise in the absence of dietary restrictions resulted in a significant decrease in VAT (SMD = -0.5), and that exercise of moderate (SMD = -0.5) and high intensity (SMD = -0.6) was effective, but not that of light intensity.[250] Aerobic exercise induced greater effects than resistance exercise, whereas there was insufficient evidence regarding the effect of combined training.[250]

As the field continued to evolve and more evidence emerged, the meta-analyses became more comprehensive and sophisticated. Verheggen et al. performed a meta-analysis of the independent and comparative effects of hypocaloric diet or aerobic exercise on VAT in individuals with overweight and obesity (N=4,815).[251] Both diet (SMD = -0.6) and exercise (SMD = -0.5) led to a significant decrease in VAT compared with control groups. However, whereas the effects of diet on VAT were strongly related to the amount of weight loss (r^2=0.74), this relationship was

modest after exercise (r^2=0.45).[251] Interestingly, although dietary interventions caused greater weight loss, exercise tended to have greater effects on VAT. In the absence of weight loss, exercise decreased VAT by at least 6.1%, whereas dietary interventions without weight loss decreased VAT by merely 1.1%.[251] These results suggested that although both diet and exercise may each decrease VAT, exercise-induced effects appear greater and can be achieved even in absence of weight loss. Similar conclusions were drawn based on the results of a recent meta-analysis, showing that exercise significantly decreased VAT in individuals with overweight or obesity as compared with control groups (SMD = -0.3), and moreover, that the dose-response effect was superior (SMD = -0.2) compared with caloric restriction.[252]

Based on the findings outlined above, it became clear that aerobic exercise was beneficial for decreasing VAT in adult populations with overweight or obesity. At the same time, emerging evidence suggested certain superior effects on cardiovascular health from aerobic exercise performed at a higher intensity but in shorter bouts compared with continuous training at a moderate intensity.[253,254] Wewege et al. performed a meta-analysis of the effects of high-intensity interval training (HIIT) vs. moderate-intensity continuous training (MICT) on body composition in adults with overweight or obesity (N=424).[255] There was no difference in effects between the two modalities, but participants performing HIIT spent 40% less time on training, favoring it as a time-efficient strategy.[255] However, there were too few studies to evaluate the effects on VAT. Shortly after this, a meta-analysis by Maillard et al. evaluated the effects of HIIT compared with control groups on VAT in adults.[256] They found a small (SMD = -0.2) but significant effect of HIIT on VAT as compared with control groups, but given the paucity of data they concluded that studies investigating how characteristics such as sex and age could modify the effects were needed.[256] This study was followed-up by a network meta-analysis where the authors evaluated the effects of HIIT on anthropometric indexes as well as VAT in individuals with overweight and obesity, as compared with control groups or those performing MICT. Only three studies where VAT had been measured were included, and the results showed a small but significant effect when compared with control groups, but superiority compared with MICT, thus corroborating previous results.[257] Again, no studies including older adults specifically were included.

Collectively, studies during the past two decades have deepened our understanding of exercise and visceral obesity. As a result, a few key findings, principles, and knowledge gaps have been identified. First, short-term effects usually fall within the range of small-to-moderate. Second, effects may be achieved from exercise alone, regardless of weight loss or dietary modification. Third, it seems as if a large volume of exercise is not required to achieve an effect, although aerobic-based exercise of at least moderate-to-vigorous intensity

appears preferable. Fourth, modern and popular forms of vigorous aerobic exercise, such as interval training, seem to yield effects of similar magnitude compared with the traditional approach in terms of continuous exercise (assuming that energy expenditure is matched), but with the advantage that interval training is less time consuming.[258]

Nevertheless, several questions remain unanswered. For example, it is unclear what would be the most effective exercise dosage for decreasing VAT. It has also been argued that although interval training seems to produce comparable effects to continuous training, its feasibility and acceptability requires further delineation in high-risk populations.[259] Older people remain underrepresented in studies meaning that it is uncertain to what extent previously observed effects can be extrapolated to older populations in general, and in those with visceral obesity in particular. It is important to conduct studies specifically in these populations because exercise programs not only have to be designed carefully for individuals with obesity,[244] but they also need to be designed and implemented differently for older individuals compared to younger individuals, with an emphasis on personalization to account for the heterogeneity of the older population and the fact that people age differently.

Proposed mechanisms underlying exercise-induced reductions in VAT mass

Although dietary modification and caloric restriction are central to weight loss, the fact that exercise interventions might be superior in terms of inducing VAT mass loss in the absence of weight loss might be particularly relevant to geriatric care and geriatric research. Specifically, diet-induced weight loss in older adults should be carefully and cautiously considered because it may negatively impact muscle mass and bone mineral density unless supplemented by adequate exercise.[260,261] This potentially superior effect of exercise on VAT, which appears to be attained even in absence of weight loss, indicates that there would need to be some mechanisms unique to exercise, and perhaps especially that of higher intensity, that explain its preferential effect on VAT.

During vigorous exercise, there is a high activation of the sympathetic nervous system which promotes the release of catecholamines such as noradrenaline, stimulating lipolysis.[262] In VAT, there is a higher content of β-adrenergic receptors as compared to in subcutaneous adipose tissue.[87] Thus, one pathway through which vigorous exercise could decrease VAT mass is through its influence on lipolysis in VAT, which is partly driven by release of interleukin-6 from skeletal muscle.[263] As a result, free fatty acids are released into the bloodstream where they are absorbed by skeletal muscle and used for energy. In this regard, vigorous exercise has indeed shown to be particularly effective for improving fat oxidation.[264] These mechanistic data may help to partly explain a causal effect of

VPA and exercise on VAT which was recently observed in a mendelian randomization study.[265] Further, exercise also increases post-exercise energy consumption, and intense exercise such as interval training may also be more appetite suppressing compared with continuous training.[266] Collectively, there is some evidence to suggest that vigorous exercise may favor a decrease in VAT through sympathetic nervous system activation and increased lipolysis due to increasing circulating catecholamines and other lipolytic hormones, together promoting the release of free fatty acids to the bloodstream during exercise and a subsequent higher fat oxidation after exercise is completed.

Rationale

During the next two and a half decades, the number of older adults is projected to at least double. Among older adults, CVD is a leading cause of disability, morbidity, and mortality, and most of the burden is attributed to stroke and myocardial infarction. Even though the incidence and mortality has decreased during the last decades, negative trends in modifiable risk factors along with population aging indicate that an increasing number of people may be at risk of experiencing a stroke or myocardial infarction. Besides individual complications for the person affected and their family, this could lead to spillover effects on the healthcare sector and society at large. Prevention of these major cardiovascular events in older people through intervening on modifiable risk factors should therefore be of interest to stakeholders, policymakers, and authorities. However, the implementation of large-scale interventions targeting such factors should be underpinned by a strong body of evidence confirming their effectiveness, in order to be justifiable. It is well known that older adults are underrepresented in research, and the field of physical activity is no exception. In addition, most of the evidence on physical activity in relation to CVD and mortality is based on self-reported data, which may suffer from different forms of biases, hence the WHO has requested that additional studies using device-measured data are needed. Furthermore, although visceral obesity is more strongly associated with CVD and mortality in adults than overall obesity, evidence in older adults is lacking. This would be important given that crude measures of overall obesity may be inappropriate and of limited use in old age. Consequently, interventions targeting VAT in this population need to be evaluated, and despite that exercise can be effective in healthy and young adults, this requires further delineation in high-risk populations such as older adults with visceral obesity. It is also paramount to determine whether causal conclusions can confidently be drawn from estimates based on observational studies and trials with surrogate outcomes. Therefore, to guide future research and clinical practice, it would be relevant to explore and understand how well observational evidence on the link between physical activity, CVD, and mortality aligns with findings from RCTs.

Purpose and aims

The overall purpose of this thesis was to create a deeper understanding of the links between physical activity, VAT, and CVD in older adults, by studying it from both an observational and an interventional perspective. The specific, primary aims of the four papers included in this thesis are specified below. Secondary exposures, outcomes, analyses, or results that were reported in the published articles, but which are not described from hereon, are considered outside the scope of this thesis.

Paper I
Investigate the associations of accelerometer-measured physical activity of different intensities and sedentary time with the risk of stroke, myocardial infarction, and all-cause mortality in 70-year-old individuals.

Paper II
Investigate the association of VAT mass with the risk of stroke, myocardial infarction, and all-cause mortality in 70-year-old individuals.

Paper III
Investigate the effects of vigorous-intensity exercise on VAT mass in 70-year-old individuals with visceral obesity.

Paper IV
Review the effects of exercise on CVD and all-cause mortality in general older adults and in people with chronic conditions based on evidence from RCTs.

Materials and Methods

Overview

Throughout this thesis, the four papers will be referred to by their Roman numerals (I-IV). An overview of the design of each paper is presented in Table 1. The description of materials and methods in this thesis is divided into four sections.

1. The first section describes the Healthy Ageing Initiative, a population-based study which Papers I-III are based upon.

2. The second section describes aspects related to study designs, participants, and procedures for the papers. The section is split into three parts. The first one covers Papers I and II, both of which are cohort studies. The second one covers Paper III which is the RCT. The final one covers Paper IV which is the review.

3. The third section describes statistical analyses.

4. The fourth section describes ethical considerations.

Table 1. Overview of Papers I-IV.

	Paper I	Paper II	Paper III	Paper IV
Study design	Cohort, prospective	Cohort, prospective	RCT	Narrative review of RCTs
Years of data collection	2012-2017	2012-2018	2018	2021
Population	70-year-old individuals	70-year-old individuals	70-year-old individuals with visceral obesity	Older adults and individuals with chronic conditions
Sample size	3,343	3,294	77	19,162 and 37,443
Main exposure(s) /intervention	Baseline LPA, MPA, MVPA, and ST	Baseline VAT mass	Vigorous-intensity exercise	Exercise interventions
Primary outcome(s)	Composite endpoint of stroke, MI, or all-cause mortality	1) Composite endpoint of stroke or MI. 2) All-cause mortality	Mean change in VAT mass	CVD and all-cause mortality
Follow-up time/duration	Mean 2.7 years	Mean 3.6 years	10 weeks	Mean 0.5-10 years
Statistical analysis	Cox regression	Cox regression	Linear regression	-
Covariates	Accelerometer wear time, sex, smoking, SES, previous CVD, medications, and CVD risk factors	Sex, smoking, alcohol consumption, SES, MVPA, previous CVD, medications, and CVD risk factors	VAT mass at baseline	-
My contributions	Conception and design, data analysis, drafting the manuscript	Conception and design, creating the merged data file under supervision, data analysis, drafting the manuscript	Randomization, intervention design and implementation, partial data analysis under supervision, drafting the manuscript	Conception and design, identification and review of included papers, drafting the manuscript

Abbreviations: CVD = cardiovascular disease, LPA = light-intensity physical activity, MI = myocardial infarction, MPA = moderate-intensity physical activity, MVPA = moderate-to-vigorous physical activity, RCT = randomized controlled trial, SES = socioeconomic status, VAT = visceral adipose tissue.

Healthy Ageing Initiative

Papers I-III were based on the cohort study Healthy Ageing Initiative (HAI). The aim of HAI is to identify well-known and novel risk factors for age-related injuries and diseases such as falls, fractures, and CVD in 70-year-olds, and to promote healthy lifestyle habits, in terms of adequate physical activity, good nutrition, smoking cessation, and limited alcohol consumption, in this population. The study is conducted in the town of Umeå in northern Sweden, which had 132,235 residents on 31 December 2022. All 70-year-olds living in Umeå are eligible to participate, and there are no exclusion criteria.

The study was initiated in spring 2012, and at the time of printing this thesis, around 7,000 individuals have participated. The public population register is used to obtain a list of eligible individuals, who are contacted and invited upon turning 70 years of age. An analysis of the participation rate between 2012 and 2019 showed that 68.4% of all 70-year-olds in Umeå had participated.[267] Of those who could be contacted by telephone, the participation rate was 83.5%.[267] Those who wish to participate are asked to provide written informed consent, after which they are offered a comprehensive health examination.

The procedure follows a standardized approach. Each participant arrives to the clinic in a fasting state (at least four hours), where they are greeted by a research nurse who is responsible for leading the participant through the entire health examination. The examination usually begins with measurement of height and weight, after which a series of assessments are performed, including anthropometrics, body composition, gait and balance, physical function, blood lipids and glucose, blood pressure, cognition, respiratory function, and others. The participants also fill in questionnaires about their perceived quality-of-life, dietary habits, physical activity, smoking status, alcohol consumption, history of falls, history of CVD, and current medications. The examination takes about three hours in total and ends with the participant being equipped with an accelerometer for one week to measure their physical activity and sedentary behavior.

The participant returns to the clinic after one week for a follow-up meeting with the research nurse who presents and discusses the results from the examination together with the participant. Based on the results of the assessments, the research nurse uses motivational interviewing to promote healthy lifestyle behaviors, with an emphasis on physical activity, dietary habits, weight loss and smoking cessation, according to individual applicability. Participants who have elevated levels of blood lipids, blood glucose or blood pressure are recommended to contact their general practitioner for further counseling.

Paper I and Paper II

Design and participants

Papers I and II were prospective cohort studies. Paper I was based on all participants in HAI from May 2012 until October 2017 with complete accelerometry-data. The main exposures in this study were LPA, MPA, MVPA, and sedentary time. The primary outcome was a composite endpoint of stroke, myocardial infarction, and all-cause mortality during follow-up. Additionally, these outcomes were analyzed separately. Paper II was based on all participants in HAI from May 2012 until January 2018 with complete body composition data. The main exposure was VAT mass. Co-primary outcomes included a composite endpoint of stroke or myocardial infarction, and all-cause mortality during follow-up.

Assessment of physical activity

For the assessment of physical activity and sedentary time, all participants were equipped with an Actigraph GT3X+ accelerometer (Actigraph, Pensacola, FL, USA) which was attached to an elastic band and positioned over the participant's non-dominant hip. The participants were instructed to wear the device for one week and to remain normally active during this period. They were instructed to always wear the accelerometer except for when showering, bathing, and sleeping.

The Actigraph GT3X+ is a small device which measures accelerations in three movement planes (vertical, medio-lateral, antero-posterior) in a dynamic range of ± six units of gravity. Using micro-electromechanical technology, the mechanical movements are converted to electrical signals and the data is stored directly into a non-volatile flash drive. The raw data were collected using the default frequency of 30 Hz, and subsequently processed using Actilife software version 6.11.3, where the accelerations were transformed into counts that were used to determine time spent in different intensities of physical activity and sedentary time. The data were filtered using the standard proprietary Actigraph filter algorithm to minimize noise and eliminate accelerations unlikely to be the result of voluntary human movements, and the data were then summarized across 60 second intervals, known as epoch lengths.

Next, wear time validation was implemented. For the data to be considered valid and eligible for subsequent analysis, the criteria as proposed by Troiano et al. were applied.[268] Specifically, participants were required to have sufficient wear time defined as at least 10 hours per day for at least four days, as determined by subtracting non-wear time from wear time.[268] Thus, non-wear time was defined as intervals of at least 60 minutes of consecutive zero-counts, with an allowance

for 1 to 2 minutes of <100 counts per minute.[268] Next, thresholds to determine specific intensities of physical activity as well as sedentary behavior were applied. The predetermined cut-points used in HAI and in this thesis were those proposed by Freedson et al., which are based on vertical-axis counts.[269] These cut-points were determined from motorized treadmill protocols using direct measurements of oxygen consumption.[269] Specifically, sedentary time was defined as <100 counts per minute, while LPA, MPA and VPA were defined as 100-1,951, 1,952-5,724, and ≥5,725 counts per minute, respectively, and thus, MVPA was defined as ≥1,952 counts per minute.[269] Daily averages were computed by dividing the total number of minutes in each intensity throughout the week of registration by the number of wear days for each participant.

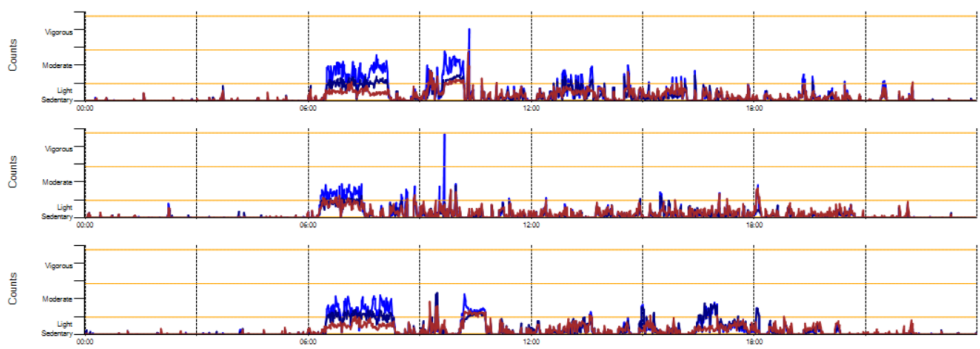

Figure 1. *Example output of data during three days of physical activity measurements for a 70-year-old woman using the Actigraph GT3X+. The light blue line, dark blue line, and red line shows accelerations in the vertical, medio-lateral, and anterior-posterior axes, respectively. The y-axis shows the corresponding intensity of physical activity based on the Freedson cut-points.*

Assessment of visceral adipose tissue

To measure VAT mass, participants underwent a full-body DXA scan using a Lunar iDXA device (Figure 2) with the incorporated CoreScan software (GE Healthcare Lunar, Madison, WI, USA). Prior to the scan, participants were instructed to remove any loose metal objects. Next, they were placed on the device in a supine position with their legs extended and feet secured using Velcro straps. The arms were placed parallel to the body, but ensuring no touching, and with the forearms pronated. Each scan took around 10 to 20 minutes.

Figure 2. *A research nurse preparing a participant for a scan using the Lunar iDXA.*

Unlike the standard DXA scan, which only provides measures of total- and android fat mass, CoreScan uses an algorithm to quantify VAT in the android region. The android region-of-interest is automatically defined and stretches from the top of the iliac crest to an equivalent of 20% of the distance from the iliac crest to the base of the skull (Figure 3). To provide an estimate of VAT, the algorithm subtracts android subcutaneous adipose tissue from the total amount of fat mass.[106]

In validation studies, the coefficient of determination for DXA-measured VAT is high compared to both computed tomography (r^2=0.96 for women and r^2=0.95 for men) and magnetic resonance imaging (r^2=0.82 for women and r^2=0.85 for men).[106,270] The validity of DXA for measuring VAT has been confirmed also in older adults specifically.[271] Regarding reliability, test-retest precision errors in absolute terms (root mean square standard deviation) for DXA-measured VAT using CoreScan have been estimated to 41.4 g and 65.0 g in individuals with overweight and obesity, respectively.[272] In relative terms, expressed as percent coefficient of variation ([standard deviation/mean]*100), the numbers have been estimated to 13.0% and 6.4%, respectively.[272] The precision error has been estimated to be higher in men than in women, mainly due to the differences in absolute VAT mass between the sexes.[272] From the same DXA scan, measures of total fat mass and total lean body mass were also obtained. Absolute and relative precision errors for total fat mass has been estimated to 369 g and 1.8% (in overweight) and 523 g and 1.2% (in obesity). For total lean body mass, the numbers have been estimated to 410 g and 0.8% (in overweight), and 506 g and 0.9% (in obesity).[272]

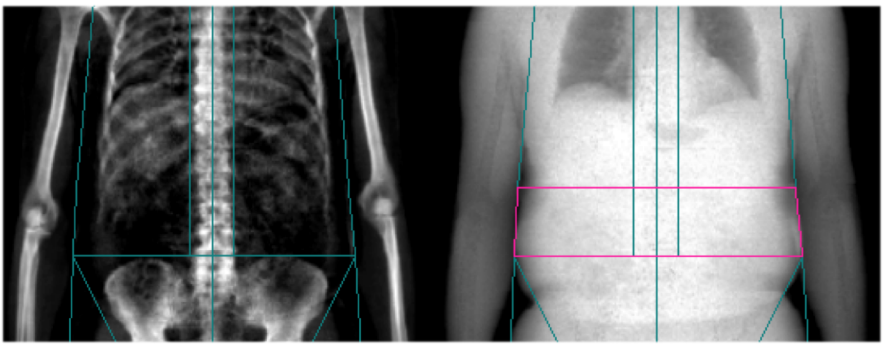

Figure 3. *Images from a full body scan using the Lunar iDXA and CoreScan. The green lines represent the automatically defined regions-of-interest, and the pink lines highlight the android region.*

Ascertainment of cardiovascular disease and all-cause mortality

Data on all-cause mortality was collected from the National Cause of Death Register, which includes data on all deaths in Sweden since 1952.[273] Cases of stroke and myocardial infarction were collected from the National Patient Register, using the International Classification of Diseases, 10th revision, codes I61-I64 for stroke and I21 for myocardial infarction. The National Patient Register includes data on all diagnoses made in inpatient care since 1987 and all diagnoses in secondary outpatient care since 2001, and all Swedish healthcare providers are obliged to report to the register. The positive predictive value is generally high, with a value >90% for most diagnoses. Specifically, the positive predictive value is high also for stroke (69% to 99%) and myocardial infarction (86% to 100%).[274-276] Although sensitivity is generally lower, it has been shown to be about 90% for stroke and myocardial infarction.[274] Both the National Cause of Death Register and the National Patient Register are administered by the National Board of Health and Welfare.

Covariates and additional measurements

The participants reported their current smoking status and alcohol consumption in a questionnaire. Body weight was measured using a digital scale (HL 120; Avery Berkel) and height was measured using a stadiometer (Holtain Limited; Crymych), after which the BMI was calculated as weight divided by height squared. Systolic and diastolic blood pressure was measured in the upper arm after at least 15 minutes rest using the validated digital automatic device Omron M6 Comfort HEM-7221-E (Omron Healthcare, Kyoto, Japan).[277] Capillary blood glucose was measured using the HemoCue 201 RT system (Radiometer Medical ApS, Brønshøj, Denmark). Daily quality control was conducted by the research nurses, with a 2.3% coefficient of variation. Blood lipids were measured by venipuncture and analyzed at the accredited laboratory at the Department of

Clinical Chemistry, University Hospital of Umeå, where the coefficient of variation for these measurements is 3.0%. Total fat mass was measured using the iDXA device, as described previously. Mid-calf skeletal muscle density, a proxy of intramuscular adipose tissue,[278,279] was estimated using peripheral quantitative computed tomography technique and a Stratec XCT-2000 device (Stratec Medizintechnik, Pforzheim, Germany).

Data on previous CVD, defined as a previous diagnosis of myocardial infarction (I21), stroke (I61-I64), or angina pectoris (I20), were retrieved from the National Patient Register. Data on prescription medications were obtained from the National Prescribed Drug Register, which covers data on all prescribed medications that are collected at Swedish pharmacies since July 2005.[280] The type of medication is described using Anatomic Therapeutic Chemical codes. For this thesis, the medications selected were antithrombotic agents (B01A), antihypertensive agents (C03, C08, C09), and lipid-lowering agents (C10A).

Socioeconomic data were obtained from registers held by Statistics Sweden, which is the agency of government statistics. Specifically, data on annual household disposable income and highest level of education were obtained from the Longitudinal Integration Database for Health Insurance and Labour Market Studies,[281] which covers the Swedish population aged $\geq$16 years since 1990 ($\geq$15 years since 2010). Data on marital status were obtained from the Total Population Register.[282] In Paper I, data on income was obtained from the year participants turned 60, whereas data on education and marital status was obtained from the year prior to participation in HAI. In Paper II, all socioeconomic data were obtained from the year participants turned 65.

Data linkage

The HAI data were linked with the registry data through the following procedure. First, the raw file with HAI data was sent to Statistics Sweden who attached socioeconomic data and replaced the Personal Identification Number with a unique pseudonymized identifier. Next, Statistics Sweden sent the raw data file and the code list to the National Board of Health and Welfare, who attached data from the National Patient Register, the National Cause of Death Register, and the National Prescribed Drug Register. Finally, each of the respective files were returned to us, after which we merged the files to form a combined file to be used for data analysis. The code list is deleted by Statistics Sweden after three months.

Paper III

Design

Paper III was a parallel, two-armed, single-blinded RCT conducted in Umeå at the same clinic as HAI. The primary aim was to investigate the effect of supervised, vigorous-intensity exercise as compared with no exercise, on VAT mass in 70-year-old individuals with visceral obesity. Participants were randomly allocated in a 1:1 ratio to either an intervention group or to a control group. The intervention group was offered a 10-week long exercise intervention, while the control group were told to keep on living as usual. After 10 weeks, all participants returned for follow-up assessments.

Participants and eligibility criteria

Individuals considered for inclusion were participants in HAI within the previous year. The inclusion and exclusion criteria are presented in Table 2. In addition to these criteria, all participants were required to pass a resting electrocardiogram before proceeding with randomization and study entrance. The chief physicians and research nurses in charge of baseline assessments resolved any situations regarding individuals who had contraindications for participation or deviating electrocardiogram readings.

Table 2. Eligibility criteria for participation, Paper III.

Inclusion criterion	Exclusion criteria
· Visceral obesity defined as: ≥1,000g VAT for women[a] ≥2,000g VAT for men[a]	· Physical disability impeding the ability to exercise · Stroke or myocardial infarction within one year prior to the study · Heart failure · Severe degenerative conditions such as malignant cancer or multiple sclerosis · CVD that could worsen with aerobic exercise such as angina pectoris · Systolic blood pressure ≥175 mmHg or diastolic blood pressure ≥100 mmHg

[a]Based on earlier observations in HAI, these values were found to correspond roughly to visceral obesity defined by waist circumference. Abbreviations: CVD = cardiovascular disease, VAT = visceral adipose tissue

All participants were recruited between January and February 2018. Using G*Power version 3.0.10,[283] a power calculation showed that a sample of 33 men and 45 women would be needed in order to detect a 20% reduction in VAT with 80% power, with a number within that range needed for mixed groups.

Assessments and randomization

All assessments were performed by the HAI research nurses who remained blinded to group allocation. The assessments were conducted on weekdays between 08:00 and 17:00, with efforts made to standardize and match the time of day as closely as possible. All participants were instructed to not perform vigorous exercise and to not consume alcohol on the day preceding assessments. They were also instructed to have fasted for a minimum of four hours. After baseline assessment, participants were randomized to either the intervention group or to the control group, using 80 prepared, opaque, sealed envelopes (40 denoting "Training" and 40 denoting "Control"). Prior to randomization of each participant, all envelopes were shuffled. Post-intervention assessments were performed within 10 days of the final training session.

Outcomes

The primary outcome was mean change in VAT mass measured using the Lunar iDXA, as described earlier. Secondary outcomes were BMI, total fat mass, and total lean body mass obtained from the iDXA device as described previously. Changes in the outcomes were expressed and analyzed in absolute terms (e.g., grams) and in relative terms (percentage).

Intervention

Piloting

Prior to the start of the trial, a draft version of the exercise program was piloted to ensure its potential feasibility and acceptability. Ten participants from the ongoing HAI study were invited to partake in an exercise session. After the session, the participants provided individual written feedback, and a group discussion was held among all participants together with the supervisors. The feedback from the participants was then discussed internally within the research group and taken into consideration upon finalizing the exercise intervention ahead of the study start.

Exercise program design

The intervention consisted of supervised, vigorous-intensity exercise sessions performed three times per week for a total of 10 weeks. This dosage (intensity, frequency, duration) aligns with the criteria used in previous meta-analyses of exercise and VAT.[249-251,255] All sessions were performed in groups of 8 to 10 participants under the supervision of me and a colleague in the research group. Each session started with a general dynamic warm-up for 10 minutes, after which the main part of the session started. The training modality was circuit-based

interval training using dynamic, body weight exercises which were performed at a 40:20 second work/rest ratio. The exercises were a mix of aerobic and functional strength exercises targeting large muscle groups (Figure 4). All exercises were carefully designed to allow personalization and challenge according to individual capacity and preference, while using minimal equipment. There was a weekly progression in exercise dosage, through gradually increasing the number of sets of the intervals, thereby increasing the total duration of the interval training. During the first week, each session comprised approximately 18 minutes of training, which was gradually increased throughout the intervention, reaching about 36 minutes per session by the tenth week. The training was followed by a cool down for about five minutes. Thus, combining the duration of the warm-up, interval training, and cool down, the total length of the exercise sessions ranged from 33 minutes per session during the first week, ending at about 51 minutes per session by the tenth week.

Figure 4. *The exercises included in the exercise intervention. One additional exercise not shown in the figure was "Sprint" (running back-and-forth).*

During the intervals, all participants were encouraged to aim for a vigorous exertion. This was facilitated by using a modified version of the Borg CR10 scale,[284] which is a category-ratio scale ranging from 1 to 10 (Figure 5). The Borg CR10 is a general intensity scale that can be used to measure both exertion and pain.[284] To promote usability and user experience, the scale was color-coded, and the values of the scale were divided into the following subcategories: 1) extremely light exertion, 2-3) light exertion, 4-5) moderate exertion, 6-7) vigorous exertion, 8-9) very vigorous exertion, 10) maximal exertion. Each level of exertion was accompanied by a brief description of the characteristics of that specific level. The participants were instructed to aim for 6-7 on this scale.

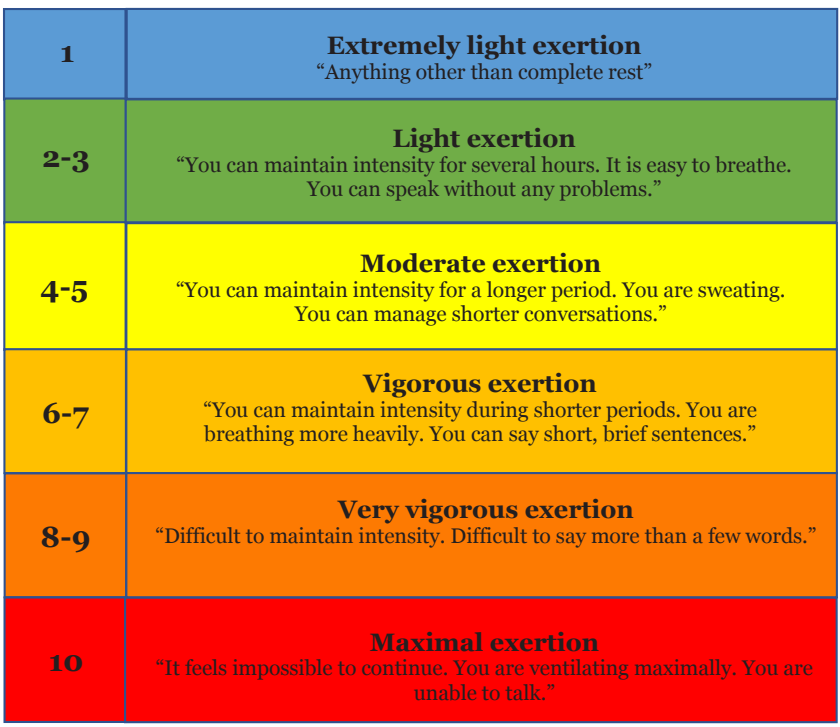

Figure 5. *The modified Borg CR10 scale translated into English.*

Paper IV

Paper IV was a narrative literature review of evidence from RCTs. The aim was to scrutinize the evidence for the effect of exercise on CVD and all-cause mortality in older adults and in people with chronic conditions. While the published article covered other outcomes, such as fracture and type 2 diabetes, only the findings related to CVD and all-cause mortality are within the scope of this thesis.

No systematic literature search was conducted, although PubMed and Cochrane databases were searched, using terms such as "physical activity", "exercise", "cardiovascular", and "death". In addition, reference lists of included studies were scanned. Studies considered were RCTs that prescribed exercise as a single intervention or as one of the main components of a combined intervention, and who reported on the outcome of CVD or all-cause mortality in general older adults or in individuals with chronic conditions. Meta-analyses of such RCTs were also considered. From the included studies, information was extracted related to the description of study design, population age and characteristics, intervention duration and characteristics, as well as risks of the outcomes.

Statistical analyses

Paper I

Outcome occurrence in terms of incidence rates was calculated by dividing the number of outcomes by the sum of person-years of follow-up. To account for the fact that participants had varying follow-up time, Cox regression models were used to estimate hazard ratios (HRs) for the outcomes in relation to the amount of physical activity and sedentary time at baseline (modelled as continuous exposures). Participants were censored upon date of first outcome event or end of follow-up (31 December 2017), whichever came first. Assessment of the proportional hazards assumption using covariate-by-time interaction terms did not suggest that the assumption was violated. The models were run separately for each exposure, with adjustment for covariates as follows: Model 1 included sex and accelerometer wear time. Model 2 added smoking status and socioeconomic factors. Model 3 added previous CVD and medications. Model 4 added CVD risk factors. To test for potential nonlinearity, quadratic exposure terms were created and added to the fully-adjusted Cox model.

A sensitivity analysis was performed to investigate potential reverse causation, where the models were repeated after excluding everyone with previous CVD and everyone with $\leq$6 months of follow-up. In an exploratory analysis, potential effect modification by physical activity on the association between sedentary time and the composite endpoint was tested by adding a product term between MPA and

sedentary time to the fully-adjusted Cox model, after which the association between sedentary time and the composite endpoint was investigated across strata of MPA.

Paper II

As in Paper I, Cox regression was used to estimate HRs for the outcomes in relation to the amount of VAT mass at baseline (continuous exposure). Participants were censored upon date of first outcome event or end of follow-up (31 December 2018), whichever came first. Assessment of the proportional hazards assumption using covariate-by-time interaction terms did not suggest that the assumption was violated. The models were adjusted for covariates as follows: Model 1 was unadjusted. Model 2 added sex, smoking status, alcohol consumption, and socioeconomic factors. Model 3 added CVD risk factors, previous CVD, medications, and MVPA. Model 4 added muscle density. In exploratory analyses, effect modification by sex and MVPA was tested by adding product terms to the fully-adjusted Cox model. In the event of a statistically significant product term, stratified analyses were conducted.

Two sensitivity analyses were conducted. In the first, to investigate potential reverse causation, the Cox models were repeated after excluding everyone with previous CVD and everyone with $\leq$12 months of follow-up. In the second, to test for nonlinearity, a quadratic exposure term was added to the fully-adjusted Cox models. In the event of a statistically significant quadratic exposure term, the association was investigated further with VAT modelled as a categorical variable (tertiles).

Paper III

All participants who completed baseline and follow-up assessments were included in the analyses regardless of amount of study participation. Paired samples t-tests were performed for within-group comparisons of the outcome measures at baseline and at the 10-week follow-up. Between-group comparisons in the outcome measures were performed using linear regression models, adjusted for baseline values. Additionally, for the writing of this thesis, SMDs in terms of Cohen's *d* were also calculated to facilitate comparisons with results from previous meta-analyses. The following cut-points determined the magnitude of effect: 0.2 (small), 0.5 (medium), 0.8 (large).[285]

In exploratory analyses, potential effect modification by sex was tested by adding a product term between sex and group assignment to the linear regression model, after which subgroup analyses stratified by sex were performed.

General

All analyses were conducted using SPSS v25.0 and v26.0 (IBM, Corp. Armonk, NY, USA). Baseline characteristics were presented as means with standard deviations or as frequencies with percentages, with between-group comparisons tested using independent samples t-test and chi-square tests as applicable. The covariates included in the multivariable-adjusted models were selected based on clinical expertise in the research group and in line with previous studies. Statistical significance was determined as P values <0.05 or as HRs with 95% confidence intervals (CIs) not crossing 1.0.

Ethics

All studies were conducted in accordance with the World Medical Association's Declaration of Helsinki, followed the appropriate reporting guidelines,[286,287] and were approved by the Regional Ethical Review Board in Umeå, Sweden (number 07-031M with extensions and number 2017-521-31). All participants gave their verbal and written informed consent to participate and were informed of their rights, including the possibility to terminate their participation at any time without needing to state a reason. The risks pertaining to the studies in this thesis were deemed small. For example, DXA is a noninvasive method with radiation doses that are very small compared with computed tomography and similar to daily background radiation.[105] This makes DXA particularly useful for repeated measurements. Regarding the intervention, exercise can acutely result in falls, fall-related injuries, shortness of breath, and discomfort. Initially, it can also cause muscle soreness especially in those not regularly exercising. Adequate measures were taken to minimize these risks. Individuals with conditions that contraindicated exercise were ineligible, and those eligible had to pass an electrocardiogram reading, where individuals with deviating readings were excluded and referred to their general practitioner. The intervention was piloted to ensure an adequate level of difficulty and appropriateness of the chosen movements and the overall structure of the training program. This was done also to promote adherence and to maximize safety and minimize risks. All participants were encouraged to use available suspension bands for support of balance when necessary. They were also instructed to employ individual progressions in their training according to personal preference, which is of importance to high-risk populations such as those with obesity,[244] and to regress when necessary. During the intervention, the participants were instructed to pause and consult with the instructors should they experience discomfort, chest pain, or light-headedness. In addition, healthcare personnel were located nearby in the building.

Results

Paper I and Paper II

Participant characteristics

Papers I and II included 3,343 and 3,294 participants respectively after excluding individuals with missing/invalid data for the main exposures (Figure 6). Baseline characteristics are presented in Table 3 and Table 4. There was a similar proportion of men and women, few participants were smokers, and few had a history of CVD. Previous prescription of antihypertensive, lipid-lowering, and antithrombotic agents were common. Mean time spent sedentary was about 9 hours per day, mean LPA was about 264 minutes per day, and mean MPA was about 33 minutes per day (with a similar value for MVPA given the negligible amount of time spent as VPA). Mean VAT mass was about 1.5 kg (2.3 kg in men and 0.9 kg in women).

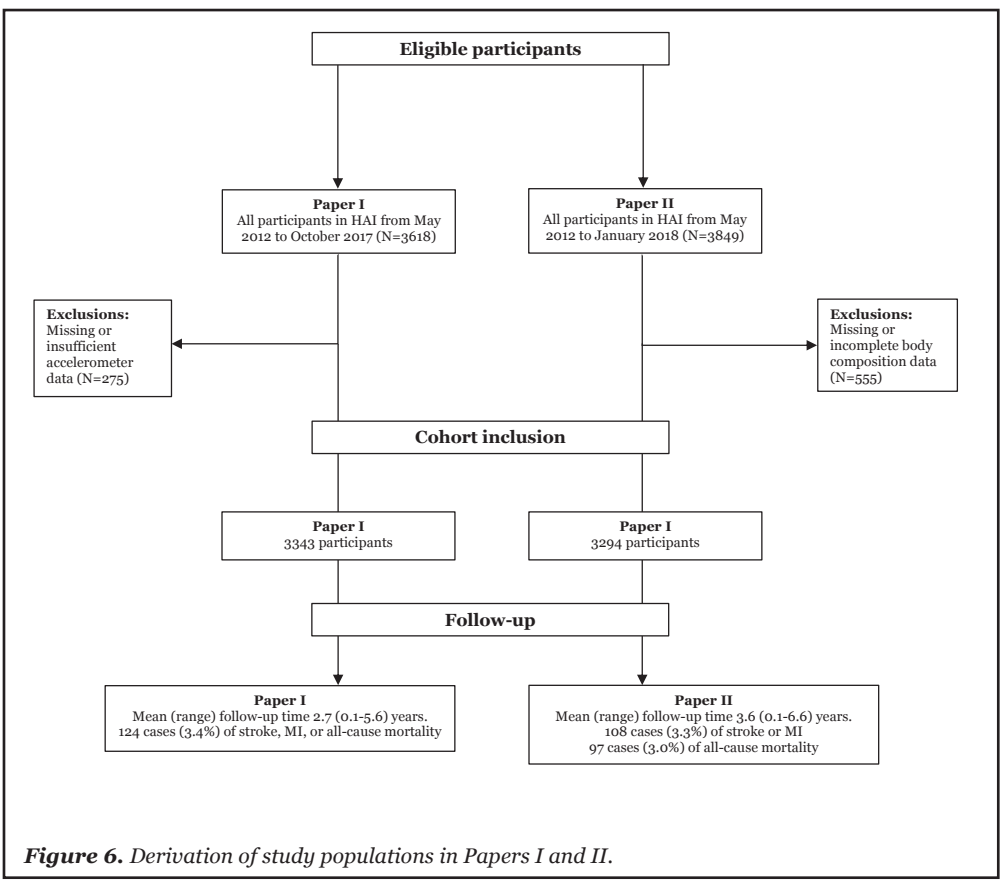

Figure 6. *Derivation of study populations in Papers I and II.*

Table 3. Participant characteristics at baseline for the 3,343 participants in Paper I. Shortened and adapted version for this thesis.

Age, years	70.5 (0.1)
Female sex, N (%)	1,693 (50.6)
Current smoker, N (%)	199 (6.0)
Cardiovascular risk factors	
VAT, g	1,495 (972)
Systolic blood pressure, mmHg	139 (17)
Fasting blood glucose, mmol/l	5.7 (1.2)
Low-density lipoprotein cholesterol, mmol/l	3.3 (1.1)
Accelerometer measurements	
ST, hours/day	8.9 (1.4)
LPA, minutes/day	263.6 (71.6)
MPA, minutes/day	32.5 (24.9)
VPA, minutes/day	0.9 (4.1)
MVPA, minutes/day	33.4 (25.7)
[a]Adherence to physical activity recommendations, N (%)	1,604 (48.0)
Wear time, hours/day	13.8 (1.34)
Wear days	6.6 (1.0)
Socioeconomic data	
Disposable income at 60 years of age, 1000 Swedish Krona	245 (175)
Education, N (%)	
Primary	578 (17.3)
Secondary	1,356 (40.6)
Post-secondary	1,445 (42.1)
Missing data	4 (0.1)
Marital status, N (%)	
Married	2,219 (66.4)
Never married	287 (8.6)
Widowed	260 (7.8)
Divorced	577 (17.3)
Missing data	0
Previous cardiovascular disease, N (%)	
Stroke	112 (3.4)
Myocardial infarction	143 (4.3)
Angina pectoris	252 (7.5)
Prescription medications, N (%)	
Antihypertensive agents	1,912 (57.2)
Lipid-lowering agents	1,410 (42.2)
Antithrombotic agents	1,276 (38.2)

Data are presented as means (standard deviation) unless stated otherwise.
[a]Calculated based on daily averages. Participants with at least 30 min/day of MVPA were considered to meet the recommendations.
Abbreviations: LPA = light-intensity physical activity, MPA = moderate-intensity physical activity, MVPA = moderate-to-vigorous physical activity, ST = sedentary time, VAT = visceral adipose tissue, VPA = vigorous-intensity physical activity.

Table 4. Participant characteristics at baseline for the 3,294 participants in Paper II. Shortened and adapted version for this thesis.

Age, years	70.4 (0.1)
Female sex, N (%)	1,633 (49.6)
Body composition	
Total fat mass, kg	27.1 (8.5)
VAT, g	1,491 (959)
Skeletal muscle density, mg/cm^3	71.7 (4.2)
Current smoker, N (%)	189 (5.7)
Alcohol consumption, N (%)	
Never	359 (10.9)
Once/month or less	756 (23.0)
2-4 times/month	1,258 (38.2)
2-3 times/week	727 (22.1)
≥4 times/week	137 (4.2)
MVPA, minutes/day	33.1 (25.7)
Missing data due to insufficient wear time, N	136
Cardiovascular risk factors	
Systolic blood pressure, mmHg	139.2 (16.7)
Diastolic blood pressure, mmHg	81.5 (8.8)
Fasting blood glucose, mmol/l	5.7 (1.1)
Low-density lipoprotein cholesterol, mmol/l	3.26 (1.07)
Socioeconomic data	
Disposable income, 1000 Swedish Krona	250 (174)
Education, N (%)	
Primary	550 (16.7)
Secondary	1,336 (40.6)
Post-secondary	1,401 (42.6)
Missing data	7
Marital status, N (%)	
Married	2,239 (68.1)
Never married	290 (8.8)
Widowed	185 (5.6)
Divorced	574 (17.5)
Missing data	6
Previous cardiovascular disease, N (%)	
Stroke	110 (3.3)
Myocardial infarction	145 (4.4)
Angina pectoris	271 (8.2)
Prescription medications, N (%)	
Antihypertensive agents	1,876 (57.0)
Lipid-lowering agents	1,409 (42.8)
Antithrombotic agents	1,273 (38.6)

Data are presented as means (standard deviation) unless stated otherwise.
Abbreviations: MVPA = moderate-to-vigorous physical activity, VAT = visceral adipose tissue.

Physical activity, cardiovascular disease, and all-cause mortality
During a mean (range) follow-up time of 2.7 (0.1 to 5.6) years, there were 124 events of the composite endpoint stroke, myocardial infarction, or all-cause mortality (incidence rate = 14.2 per 1,000 person-years).

Table 5 shows the results of the Cox models. In the fully-adjusted model, every 30 minutes per day of LPA was associated with 11% lower risk of the composite endpoint, while the same amount of MPA and MVPA was associated with 36% lower risk. In contrast, every 1 hour per day of sedentary time was associated with 33% higher risk. The results were similar after excluding participants with previous CVD and short follow-up, and the associations did not appear nonlinear ($P_{nonlinearity} > 0.5$ for all associations).

Exploratory interaction analyses suggested that the risks associated with sedentary time appeared to be attenuated by greater amounts of MPA ($P_{interaction} = 0.034$). Thus, every 1 hour per day of sedentary time was associated with higher risk of the composite endpoint in those with <15 minutes per day of MPA (HR = 1.29; 95% CI, 1.01 to 1.65), but not in those with 16 to 29 minutes (HR = 1.20; 95% CI, 0.86 to 1.6) or ≥30 minutes per day of MPA (HR = 1.11; 95% CI, 0.82 to 1.50).

Table 5. Risk of stroke, myocardial infarction, and all-cause mortality in relation to physical activity and sedentary time, Paper I. Adapted version for this thesis.

		Hazard ratio (95% CI)			
Outcome	**Participants (outcomes)**	**Per 30-min increment of LPA/day**	**Per 30-min increment of MPA/day**	**Per 30-min increment of MVPA/day**	**Per 1-hour increment of ST/day**
Stroke, MI or all-cause mortality					
Model 1	3,343 (124)	0.87 (0.80-0.95)	0.56 (0.43-0.73)	0.56 (0.43-0.74)	1.43 (1.22-1.68)
Model 2	3,334 (124)	0.88 (0.81-0.96)	0.62 (0.47-0.80)	0.61 (0.47-0.80)	1.38 (1.18-1.61)
Model 3	3,334 (124)	0.89 (0.82-0.96)	0.65 (0.50-0.85)	0.65 (0.50-0.84)	1.34 (1.15-1.56)
Model 4	3,280 (121)	0.89 (0.82-0.97)	0.64 (0.48-0.84)	0.64 (0.49-0.83)	1.33 (1.14-1.56)
Sensitivity analysis[a]	2,779 (97)	0.88 (0.80-0.98)	0.70 (0.52-0.96)	-	1.32 (1.10-1.59)
Stroke or MI					
Model 1	3,343 (74)	0.88 (0.78-0.98)	0.50 (0.35-0.73)	0.51 (0.35-0.73)	1.45 (1.18-1.78)
Model 2	3,333 (74)	0.88 (0.78-0.98)	0.55 (0.38-0.79)	0.55 (0.38-0.79)	1.41 (1.15-1.73)
Model 3	3,333 (74)	0.89 (0.79-0.99)	0.59 (0.41-0.84)	0.58 (0.41-0.83)	1.37 (1.12-1.68)
Model 4	3,279 (71)	0.88 (0.78-0.99)	0.59 (0.40-0.87)	0.59 (0.41-0.86)	1.38 (1.12-1.72)
All-cause mortality					
Model 1	2,961 (57)	0.83 (0.74-0.94)	0.57 (0.39-0.85)	0.57 (0.39-0.84)	1.50 (1.21-1.86)
Model 2	2,953 (57)	0.85 (0.75-0.95)	0.62 (0.42-0.92)	0.62 (0.43-0.91)	1.43 (1.16-1.76)
Model 3	2,953 (57)	0.85 (0.76-0.95)	0.68 (0.47-0.97)	0.68 (0.47-0.96)	1.39 (1.13-1.70)
Model 4	2,901 (56)	0.87 (0.78-0.97)	0.61 (0.41-0.89)	0.60 (0.42-0.98)	1.36 (1.11-1.65)

Model 1: adjusted for sex and accelerometer wear time.
Model 2: added smoking status, marital status, education, income.
Model 3: added previous CVD, antihypertensive agents, antithrombotic agents, lipid-lowering agents.
Model 4: added systolic blood pressure, visceral adipose tissue, fasting blood glucose, low-density lipoprotein cholesterol.
[a]Excluding participants with previous CVD and with ≤6 months follow-up. The analysis was adjusted as per Model 4.
Abbreviations: CI = confidence interval, CVD = cardiovascular disease, LPA = light-intensity physical activity, MI = myocardial infarction, MPA = moderate-intensity physical activity, MVPA = moderate-to-vigorous physical activity, ST = sedentary time.

Visceral adipose tissue, cardiovascular disease, and all-cause mortality

During a mean (range) follow-up time of 3.6 (0.1 to 6.6) years, there were 108 events of stroke or myocardial infarction (incidence rate = 9.4 per 1,000 person-years) and 97 deaths (incidence rate = 8.3 per 1,000 person-years).

Table 6 shows the results of the Cox models. In the fully-adjusted model, greater VAT mass (per standard deviation) was associated with 56% higher risk of stroke or myocardial infarction. Greater VAT mass was associated with higher risk of all-cause mortality before, but not after, adjustment for covariates. In the first sensitivity analysis excluding those with previous CVD and short follow-up, the association with stroke or myocardial infarction was confirmed. The association with all-cause mortality was slightly strengthened, but not statistically significant.

Exploratory interaction analyses did not suggest that MVPA modified the association between VAT and all-cause mortality ($P_{interaction}$ = 0.3), or stroke or myocardial infarction ($P_{interaction}$ = 0.9). Sex did not seem to modify the association between VAT and all-cause mortality ($P_{interaction}$=0.3), but seemed to modify the association with stroke or myocardial infarction ($P_{interaction}$ = 0.038), where greater VAT mass was significantly associated with higher risk of stroke or myocardial infarction in men (HR = 1.86; 95% CI, 1.19 to 2.91), but not in women (HR = 0.60; 95% CI, 0.25 to 1.42).

Table 6. Risk of stroke, myocardial infarction, and all-cause mortality in relation to VAT, Paper II. Shortened and adapted version for this thesis.

	Participants (outcomes)	Hazard ratio (95% CI) per SD greater VAT[a]
Stroke or MI		
Model 1	3,294 (108)	1.40 (1.19-1.64)
Model 2	3,227 (107)	1.29 (1.07-1.55)
Model 3	3,064 (102)	1.57 (1.10-2.24)
Model 4	3,064 (102)	1.56 (1.09-2.22)
Sensitivity analysis[b]	2,547 (65)	1.68 (1.08-2.61)
All-cause mortality		
Model 1	3,294 (97)	1.22 (1.02-1.46)
Model 2	3,228 (95)	1.07 (0.87-1.32)
Model 3	3,065 (89)	0.97 (0.66-1.42)
Model 4	3,065 (89)	0.95 (0.65-1.41)
Sensitivity analysis[b]	2,592 (60)	1.42 (0.88-2.27)

[a]1 SD = 959 g. [b] Excluding participants with previous CVD and ≤12 months follow-up. Adjusted as per Model 4.
Model 1: unadjusted.
Model 2: added sex, smoking status, alcohol consumption, marital status, education, income.
Model 3: added previous CVD, antihypertensive agents, antithrombotic agents, lipid-lowering agents, systolic blood pressure, fasting blood glucose, low-density lipoprotein cholesterol, total fat mass, MVPA.
Model 4: added skeletal muscle density.
Abbreviations: CI = confidence interval, CVD = cardiovascular disease, MI = myocardial infarction, MVPA = moderate-to-vigorous physical activity, SD = standard deviation, VAT = visceral adipose tissue.

The second sensitivity analysis did not suggest that the association of VAT with stroke or myocardial infarction was nonlinear ($P_{nonlinearity} = 0.4$), but there was an indication of nonlinearity for the association with all-cause mortality ($P_{nonlinearity} = 0.004$). Thus, the association was further examined across tertiles of VAT mass. Compared to participants with the least amount of VAT, there was a trend towards higher risk of all-cause mortality in participants with the greatest amount of VAT (Table 7), but this was not statistically significant.

Table 7. All-cause mortality by tertiles of VAT, Paper II.

	VAT, median (min-max)	**Participants (deaths)**	**Unadjusted hazard ratio (95% CI)**
VAT, g			
Tertile 1	576 (5-925)	1,098 (30)	1.0 (Referent)
Tertile 2	1,318 (976-1,762)	1,098 (23)	0.80 (0.47-1.35)
Tertile 3	2,362 (1,764-7,033)	1,098 (42)	1.36 (0.85-2.18)
P for trend			0.09

Abbreviations: CI = confidence interval, VAT = visceral adipose tissue.

Paper III

Participant characteristics

Participant flow from time of enrollment through allocation, follow-up, and analysis, is presented in Figure 7. Out of 427 eligible participants, 90 accepted the invitation and 77 completed the baseline assessment and were randomized to the intervention group (N=38) and to the control group (N=39). During the study, two participants in the intervention group and three participants in the control group voluntarily withdrew from the study. Thus, 72 participants (36 in each group) completed the study and were included in the analysis. Baseline characteristics are shown in Table 8.

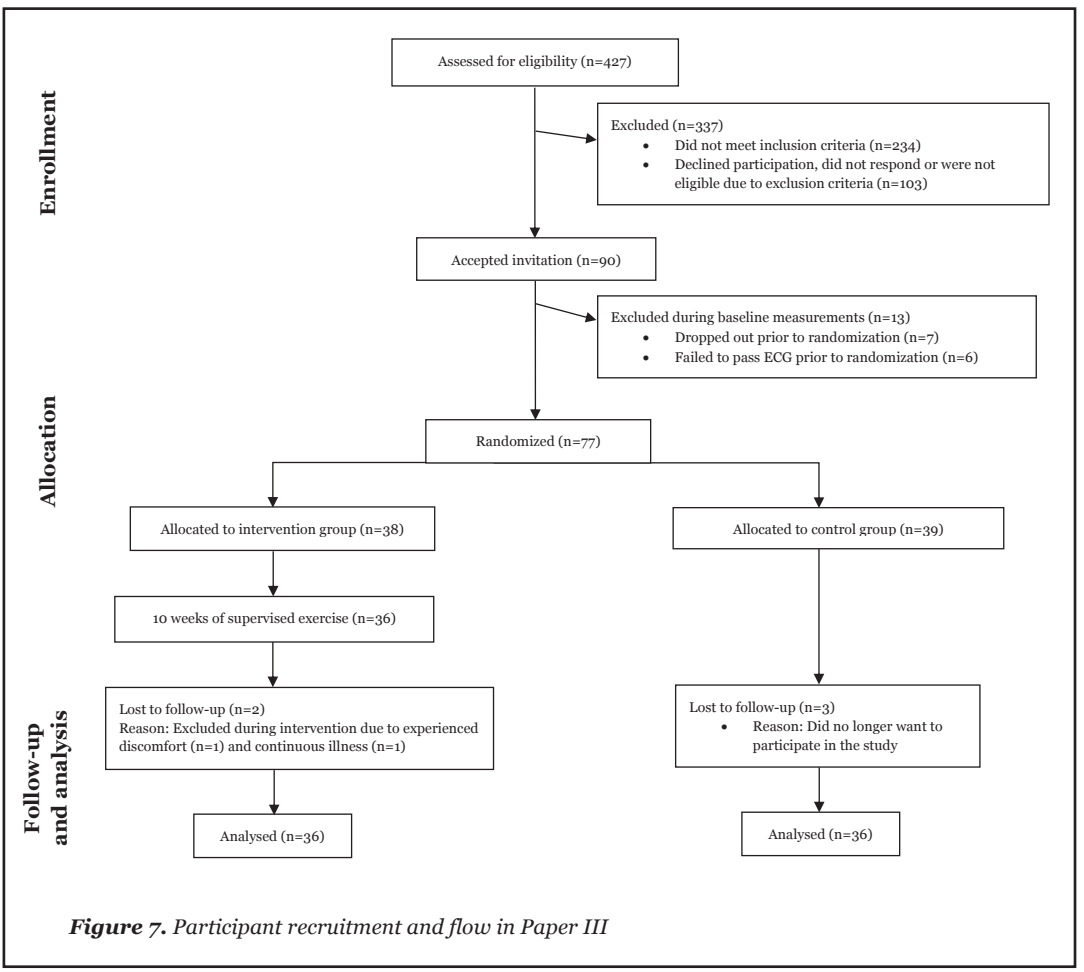

Figure 7. *Participant recruitment and flow in Paper III*

Table 8. Participant characteristics at baseline for the 77 participants in Paper III. Shortened and adapted version for this thesis.

Variables	Total sample N=77	Intervention group N=38	Control group N=39	P
Age, years	70.7 (0.24)	70.7 (0.25)	70.7 (0.24)	0.9
Female sex, N (%)	40 (52)	18 (47)	22 (56)	0.6
Current smoker, N (%)	2 (3)	2 (6)	0	0.2
BMI, kg/m²	29.2 (3.3)	29.7 (3.1)	28.7 (3.5)	0.3
Systolic blood pressure, mmHg	140 (15)	143 (15)	137 (15)	0.06
Diastolic blood pressure, mmHg	84 (7)	84 (7)	83 (7)	0.7
Body composition				
VAT, kg	2.23 (0.92)	2.30 (0.82)	2.16 (1.01)	0.6
FM, kg	33.23 (5.89)	33.36 (5.82)	33.10 (6.04)	1.0
LBM, kg	48.18 (9.07)	48.56 (8.73)	47.81 (9.48)	1.0
Self-reported diagnoses and medications, N (%)				
Stroke	2 (3)	1 (3)	1 (3)	0.9
Myocardial infarction	6 (8)	2 (5)	4 (10)	0.5
Type 2 diabetes	10 (13)	4 (11)	6 (15)	0.5
Lipid-lowering agents	32 (42)	13 (34)	19 (49)	0.3
Antihypertensive agents	47 (61)	23 (61)	24 (62)	0.7

Data are presented as means (standard deviation) unless stated otherwise. Abbreviations: BMI = body mass index, FM = total fat mass, LBM = total lean body mass, VAT = visceral adipose tissue.

Effect of exercise on visceral adipose tissue

The median (interquartile range) attendance rate to the exercise sessions was 89% (80-96), with no significant difference (P = 0.5) between men (96%, [82-100]) and women (89%, [73-95]). Table 9 and Figure 8 shows the changes in the outcomes. For the primary outcome VAT, both the intervention group and the control group experienced statistically significant reductions, with mean decreases of 6.4% and 3.5%, respectively. However, the between-group difference in VAT reduction was not statistically significant (mean difference = -77 g; [95% CI, -171 to 16], Cohen's *d* = -0.41; [95% CI, -0.88 to 0.06]). For the secondary outcomes, the intervention group lost significantly more total fat mass (mean difference = -716 g; [95% CI, -1274 to -159], Cohen's *d* = -0.61; [95% CI, -1.08 to -0.13]) and gained more total lean body mass (mean difference = 508 g, [95% CI, 64 to 951], Cohen's *d* = 0.53; [95% CI, 0.06 to 1.00]).

Five participants in the intervention group reported minor adverse events in terms of lateral epicondylitis, swelling in the metacarpophalangeal joint, muscle strains, knee bursitis, and Achilles tendinitis (N=1 each). In addition, three participants reported adverse events unrelated to the exercise intervention, in terms of lumbago, muscle strain, and wrist fracture (N=1 each). However, none of these conditions lasted longer than the 10-week intervention period and did not affect the participants' capabilities to complete the follow-up assessment.

Table 9. Changes in visceral adipose tissue and secondary outcomes, Paper III. Shortened and adapted version for this thesis.

	Changes within groups						Between-group comparison		
	Intervention (exercise) N=36			Control (no exercise) N=36			Intervention (exercise) N=36	Control (no exercise) N=36	
Outcome	**Baseline**	**10 Weeks**	**P[a]**	**Baseline**	**10 Weeks**	**P[a]**	**Change**	**Change**	**P[b]**
VAT, g	2,339 (809)	2,176 (758)	<0.001	2,226 (1019)	2,147 (998)	0.028	−163 (204)	−78 (205)	0.10
FM, g	33,424 (5940)	32,353 (6004)	<0.001	33,475 (6047)	33,120 (6109)	0.054	−1071 (1281)	−355 (1067)	0.013
LBM, g	48,621 (8837)	48,900 (8918)	0.08	48,699 (9293)	48,472 (9607)	0.17	280 (929)	−227 (969)	0.026
BMI, kg/m²	29.8 (3.1)	29.4 (3.1)	<0.001	29.0 (3.5)	28.7 (3.6)	0.006	−0.4 (0.5)	−0.3 (0.5)	0.5

Data are presented as means (standard deviation).
[a]Derived from paired samples t-tests.
[b]Derived from linear regression models adjusted for baseline values.
Abbreviations: BMI = body mass index, FM = total fat mass, LBM = total lean body mass, VAT, visceral adipose tissue.

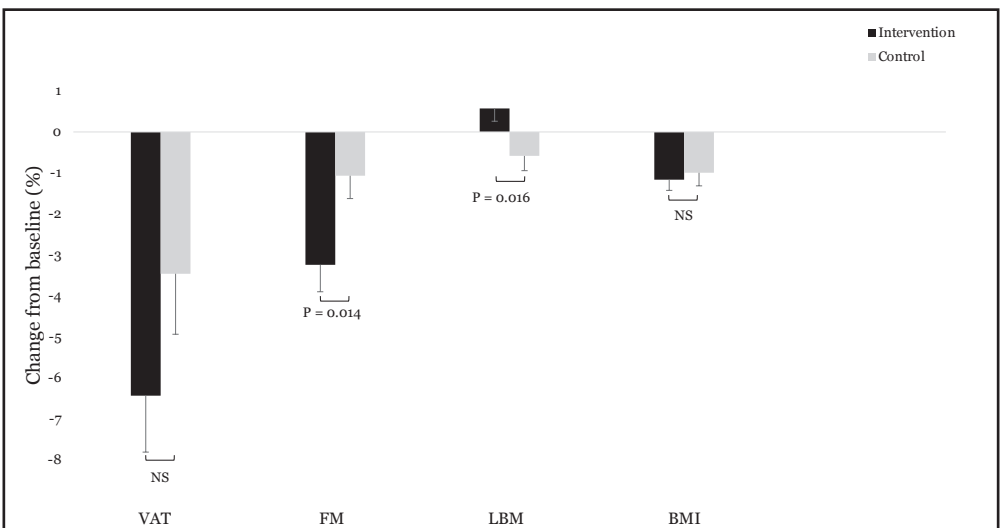

Figure 8. *Mean percentage changes in visceral adipose tissue and secondary outcomes in the study groups, Paper III. Shortened and adapted version for this thesis. Error bars show standard error of the mean. Abbreviations: BMI = body mass index, FM = total fat mass, LBM = total lean body mass, NS = not statistically significant, VAT = visceral adipose tissue.*

Exploratory analyses suggested that the effect of the intervention on VAT and FM appeared to be modified by sex ($P_{interaction} < 0.05$ for both), with significant effects in men but not in women (Figure 9). For example, in men, VAT mass decreased by a mean of 8.6% in the intervention group and by 2.2% in the control group, corresponding to a mean difference of -175 g (95% CI, 3 to 347). In contrast, in women, VAT mass decreased by a mean of 4.0% in the intervention group and by 4.6% in the control group.

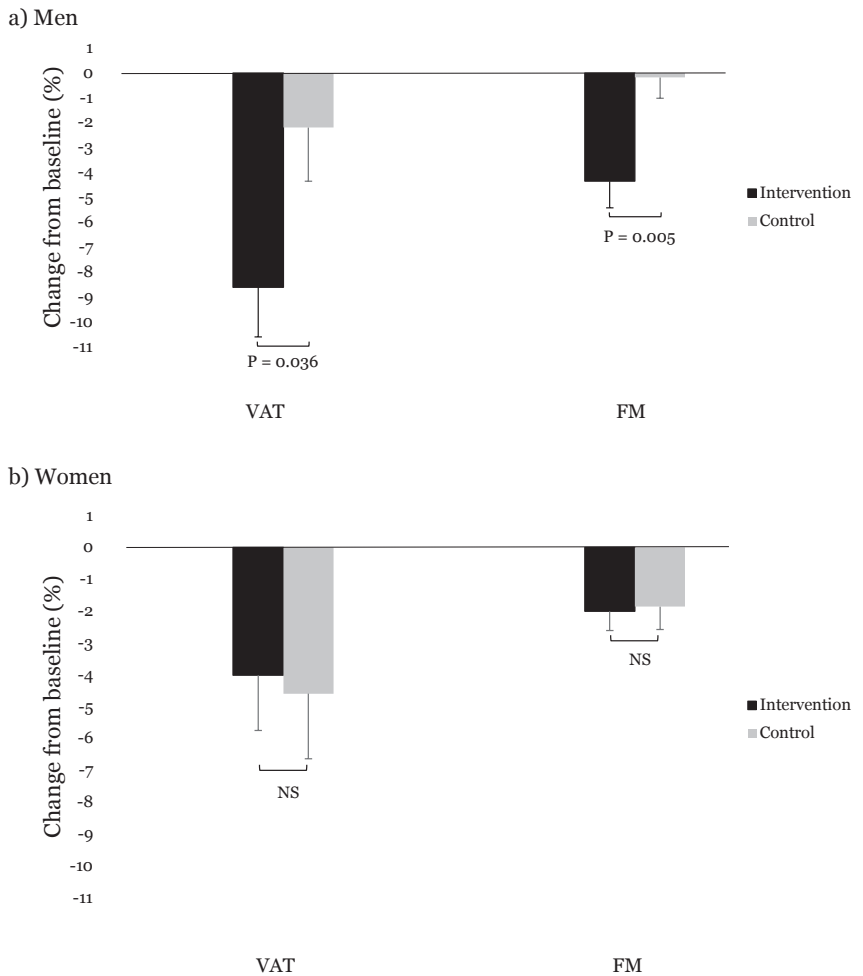

Figure 9. *Mean percentage changes in visceral adipose tissue and total fat mass in the study groups in men (a) and women (b) separately, Paper III. Adapted version for this thesis. Error bars represent standard error of the mean. Abbreviations: FM = total fat mass, NS = not statistically significant, VAT = visceral adipose tissue.*

Paper IV

Effect of exercise on cardiovascular disease and all-cause mortality

Figure 10 shows the results of RCTs and meta-analyses of RCTs on the effect of exercise, as a single intervention or as one of the main components of a combined intervention, on CVD and all-cause mortality in general older adults and in people with chronic conditions.[288-299] For the outcome of CVD, five individual RCTs and one meta-analysis of 36 RCTs, together comprising 19,162 participants and about 2,400 events, were reviewed. For the outcome of all-cause mortality, five RCTs and five meta-analyses of 108 RCTs, altogether comprising 37,443 participants and about 3,600 deaths, were reviewed. Mean age ranged from 49 to 78 years and mean intervention duration ranged from around 0.5 to 10 years.

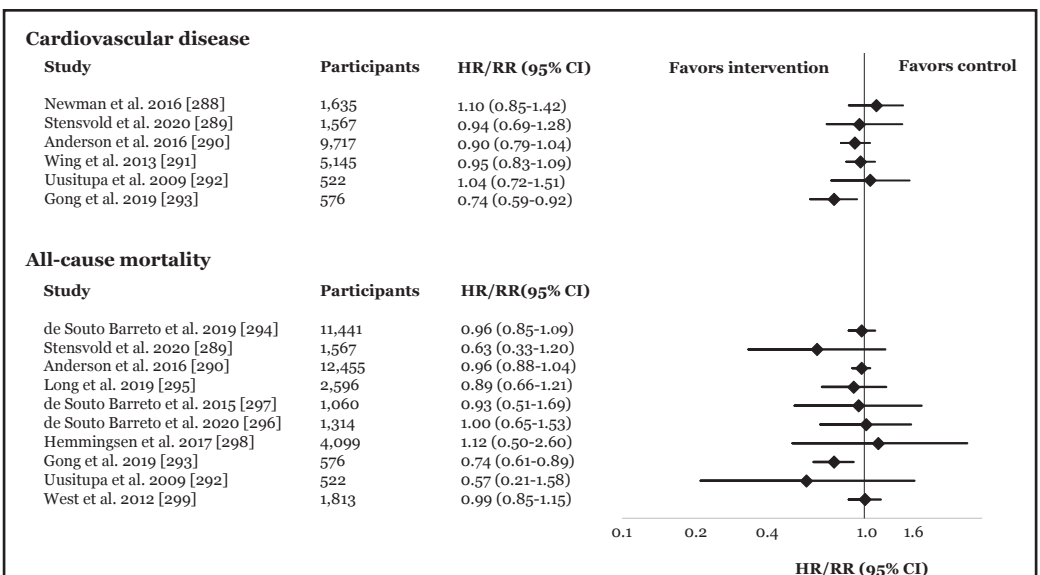

Figure 10. *Effect of exercise on cardiovascular disease and all-cause mortality in older adults and in individuals with chronic conditions. Adapted version for this thesis. CI = confidence interval, HR = hazard ratio, RR = relative risk.*

Effects in general older adults

Across the studies conducted in general older adults, exercise was not shown to reduce incident CVD or all-cause mortality. In a meta-analysis of 29 RCTs including 11,441 participants, de Souto Barreto et al. studied the effect of exercise interventions on all-cause mortality in older adults. All exercise interventions lasted at least one year, were of at least moderate intensity, and were performed on average three times per week for 50 minutes per session, with an average

compliance rate of 65%. The results showed that the exercise interventions did not reduce all-cause mortality as compared with mostly active controls.[294]

In the LIFE Study, Newman et al. randomized (1:1) 1,635 older men and women aged 70 to 89 years to either an exercise intervention or to a control group during a median of 2.6 years.[288] To be included, participants were required to be sedentary, defined as reporting less than 20 minutes per week of regular exercise and less than 125 minutes per week of MPA. Participants in the intervention group received two supervised exercise sessions per week, each of which comprised 40 minutes of moderate-intensity walking, 10 minutes of strength exercises, and 10 minutes of balance exercises. In addition, three to four sessions per week were performed at home. The control group received health education workshops.

The compliance towards the intervention was 63%. The results showed that the exercise intervention did not reduce the risk of a composite endpoint of nonfatal or fatal CVD.[288] Proposed explanations to the lack of observed effect included lack of statistical power, limited follow-up time, and insufficient exercise duration or intensity. Another proposed explanation was that the control group was not sedentary enough, as they reported an increased amount of physical activity at follow-up. Yet, accelerometer-based measurements showed that the intervention group had 40 more minutes per week of MPA during the study compared with the control group.[300]

In the Generation 100 Study, Stensvold et al. randomized 1,567 men and women aged 70 to 77 years (2:1:1) to either general recommendations on physical activity (control group), MICT (intervention), or HIIT (intervention) for five years.[289] The control group were recommended to follow the national guidelines for physical activity (i.e. 30 minutes per day of MPA). The MICT and HIIT group were given the same recommendations but with the difference that they were asked to replace two of the weekly 30-minute sessions with two sessions of MICT or HIIT, respectively. Each MICT session included 50 minutes of continuous, moderate-intensity exercise, and each HIIT session included 4x4 minute intervals at a high intensity.

At the 5-year follow-up, the compliance was 69% (control group), 51% (MICT), and 47% (HIIT). In the primary analysis, mortality was compared between the control group and the combination of the MICT and HIIT groups. The results showed that all-cause mortality was not significantly lower in the combined intervention groups than in the control group.[289] Similar results were seen for the outcome of incident CVD, for which the number of outcomes was greater.[289] In exploratory analyses, a nonsignificant trend favoring HIIT for reducing all-cause mortality was seen when it was compared with MICT, but this was not evident for

CVD.[289] A limitation of the study was that very few participants reported low physical activity at baseline and most were in good health, possibly leading to a ceiling effect regarding the possibility to reduce mortality through increased exercise. Also, the authors noted that the participants in the control group were rather active throughout the study, and more so than they were intended to be, which may have negatively affected the possibility to detect an effect of the intervention.

Effects in people with chronic conditions

A lack of effect of exercise was also reported in nearly all the remaining studies that were conducted in older adults with dementia or in middle-aged individuals with various chronic conditions such as prediabetes, type 2 diabetes, overweight, obesity, and preexisting CVD (Figure 10).

The largest of these studies was a 2016 Cochrane systematic review and meta-analysis of the effect of exercise-based cardiac rehabilitation in people with coronary heart disease. The study was based on up to 47 trials including up to 12,455 participants.[290] On average, the interventions lasted for six months with sessions occurring between 1 and 7 times per week, each lasting 20 to 90 minutes and featuring exercise of moderate to vigorous intensity. The primary analyses showed that exercise-based cardiac rehabilitation had no effect on recurrent myocardial infarction or all-cause mortality, and the authors also identified signs of publication bias.[290]

A lack of effect was also reported in the Look AHEAD Study where the intervention duration was much longer. Here, the effect of a combined diet and exercise intervention on CVD incidence was evaluated in 5,145 middle-aged individuals with prediabetes and overweight/obesity during a median of nearly 10 years.[291] The intervention aimed to achieve >7% weight loss through reduced caloric intake and >175 minutes per week of MPA, and was prescribed through individual and group-based counseling sessions which occurred on a weekly basis during the first six months, and less frequent thereafter. Participants in the control group received diabetes support and education delivered in group-based sessions three times per year during the first four years of the study, and once per year during the rest of the study. The results showed that the intervention did not reduce the risk of CVD.[291]

The only study that found a statistically significant effect was the Da Qing Study, a small study including 576 middle-aged individuals with prediabetes, where a 6-year lifestyle intervention targeting diet and exercise reduced the risk of incident CVD and all-cause mortality during 30 years of extended follow-up.[293]

Discussion

Principal findings

This thesis, which examined associations and effects regarding physical activity, VAT, and CVD in older adults, led to the following principal findings:

1. Greater amounts of physical activity of any intensity were associated with lower risk of future stroke, myocardial infarction, and all-cause mortality.

2. Physical activity of at least moderate intensity was associated with greater risk reduction per unit of time than that of light intensity, and it seemed to attenuate part of the increased risk of the outcomes associated with greater sedentary time.

3. Greater VAT mass was associated with higher risk of future stroke and myocardial infarction.

4. Short-term vigorous-intensity exercise seemed to decrease VAT mass slightly, but the effect was not statistically significant.

5. Current RCTs have not shown that exercise is effective for reducing the risk of CVD or all-cause mortality.

Association of physical activity with cardiovascular disease and all-cause mortality

Most of the daily physical activity that older adults perform is typically of light intensity. Therefore, if cardiovascular benefits can be attained from increasing LPA this would offer an attractive target for intervention. In Paper I, we found that a 30-min/day increment in LPA was associated with 11% lower risk of the composite endpoint of stroke, myocardial infarction, and all-cause mortality, with similar associations when assessing the outcomes separately. This corroborates and extends the growing body of evidence from meta-analyses of cohort studies, supporting a beneficial association between accelerometer-measured LPA and all-cause mortality.[206,208,211] Our findings also add new knowledge with respect to the outcome of CVD which has been less studied. In a cohort study of older women, LaCroix et al. found that a 1-hour/day increment in LPA was associated with 8% lower risk of a composite CVD outcome.[213] Similarly,

in a cohort study of middle-aged and older men and women, Hooker et al. found that 1-hour/day increment in LPA was associated with 14% lower risk of stroke.[301] In contrast, Jefferis et al. found no beneficial association between LPA and a composite CVD endpoint in a cohort study of older men.[217] Our study showed that LPA was associated with lower risk of CVD and all-cause mortality in a cohort comprising both older women and men. The different results in these studies may relate to factors such as differences in the population characteristics, length of follow-up, definitions and ascertainment of outcomes, adjustment for covariates, and accelerometry-data processing.

From a clinical standpoint, an association between LPA and lower risk of CVD, assuming it is causal, would seem to have implications especially to older adults who accumulate a lot of sedentary time and for whom performing MVPA is not feasible. This part of the population would, based on the results of Paper I, benefit from even modest increments in LPA, as also suggested by recent studies estimating mortality benefits from increasing LPA at the expense of sedentary time, using more novel analytical approaches.[302,303]. Even so, due to the relatively limited body of evidence on LPA in relation to health outcomes, especially with respect to CVD, the WHO has called for more evidence.[153] As more data emerges, this will subsequently open up for the possibility of data pooling and harmonization, which could inform future physical activity guidelines.

In Paper I we also found that a 30-min/day increment in MVPA was associated with greater risk reduction compared with a similar dose of LPA, supporting the WHO guidelines which recommends a gradual increase in the amount and intensity of physical activity in older adults when feasible.[153] The possible superiority of higher intensity have some support from previous cohort studies[207,219,220] and RCTs using surrogate outcomes,[254] as well as a meta-analysis of cohort studies which showed that considerably less time needed to be spent as MVPA compared to LPA to reach the same associated risk reduction of all-cause mortality.[206] Interestingly, our exploratory analysis also suggested further benefits from MVPA in the sense that the harmful association between sedentary time and the outcomes was attenuated by greater amounts of MVPA. Although emerging evidence indicates an association of sedentary time with CVD and mortality,[202,204-206,223] which we also observed in our main analysis, the question is to what extent sedentary behavior poses an independent risk or whether its impact is modified by physical activity.[304] For example, meta-analyses based on self-reported data have estimated that 60 to 75 minutes per day of MVPA eliminates the association of sitting time with all-cause and cardiovascular mortality,[203,305] although one large individual study found a lower threshold corresponding to about 21 to 43 minutes per day.[224] Similarly, a meta-analysis based on accelerometry data found that about 30 to 40 minutes per day of MVPA eliminated the association between sedentary time and all-cause mortality.[175] The

findings from our study extend this previous evidence, indicating that this phenomenon might apply also to CVD, and that the threshold may be at the lower range of the proposed estimates. The exploratory nature of our analysis, including a small sample size and few cases, calls for further studies in larger and more diverse cohorts of older adults. Should this association be confirmed and proven causal, it would have clinical relevance for older adults who often spend a lot of time in sedentary behaviors, in the sense that long periods of sedentary behavior would not be a cause for concern if they perform a sufficient amount of MVPA throughout the rest of their day.

Association of visceral adipose tissue with cardiovascular disease and all-cause mortality

In Paper II we found that excess VAT constituted a strong risk factor for CVD, where a standard deviation increase in VAT mass was associated with about 60% increased risk of stroke or myocardial infarction. This is of interest given the known age-related increase in VAT mass that may occur even in absence of BMI change,[77] as well as the fact that even individuals with a normal BMI may have excess VAT.[306]

Prior to this study, few studies had been conducted in similar populations and with conflicting results. Nicklas et al. found that greater VAT mass (per standard deviation increase) was associated with 24% increased risk of myocardial infarction in older adults.[124] However, when the analyses were stratified by sex, an association appeared to be present only in women. In contrast, Mongraw-Chaffin et al. found that middle-aged and older individuals in the upper tertile of VAT mass had 73% higher risk of CVD compared with those in the bottom tertile, with no sex differences.[116] Similarly, in a smaller study of older men, Fujimoto et al. found that greater VAT mass (per standard deviation increase) was associated with 60% increased risk of CVD.[307] In contrast, the study by Schousboe et al. found no association between greater VAT mass and CVD in older men.[125] One reason for the lack of association among men in the studies by Nicklas et al. and Schousboe et al. could be the higher baseline age of their participants and the longer follow-up, which may introduce selection bias. In other words, it is possible that only older men predisposed to live up to a very old age were included, while those who had already suffered consequences from excess VAT and died were ineligible. The likelihood of this bias might increase due to the fact that these studies were conducted in the US where life expectancy at birth and after the age of 65 is lower than in Sweden.[308,309] In our study, the lack of observed association in women, as suggested by the interaction and sex-stratified analyses, is similar to findings from the Framingham Heart Study, where VAT was not associated with CVD in the female subcohort.[115] These findings are difficult to explain and should be interpreted with caution given the small sample size and

few cases. As the influence of sex and old age on the association of VAT with CVD remains incompletely understood, further investigation is needed.

Our primary analysis did not show a significant association between greater VAT mass and increased risk of all-cause mortality. There have been relatively few previous studies to investigate this relationship in an older population. In a study of Korean older adults, greater VAT mass (per standard deviation increase) was actually associated with lower risk of all-cause mortality.[130] In a larger study of Icelandic older individuals, greater VAT mass (per standard deviation increase) was associated with 13% increased risk of all-cause mortality in women, but not in men.[131] In a smaller study of Brazilian older individuals, greater VAT mass (per 100 cm^3) was associated with twofold higher odds of all-cause mortality in men, but there was no association in women.[132] Finally, a longitudinal analysis in the Health ABC Study showed that changes in VAT were not associated with mortality in older individuals.[133]

Some of these studies were limited by lack of adjustment for covariates such as socioeconomic status and medical history[130] or participant loss to follow-up,[132] and none of the studies addressed the potential influence of reverse causation.[130-133] In addition to these limitations, the conflicting findings may be influenced by variations in sample size, participant characteristics, and follow-up time. Most studies were conducted in populations of older age than ours already at baseline, in addition to a long follow-up with a high mortality rate in several studies. As outlined previously, this may introduce selection bias. Based on the results of our sensitivity analyses, we cannot rule out that the association between VAT and all-cause mortality in our primary analysis was underestimated partly due to selection bias and reverse causation, but also due to the association appearing to be nonlinear. Yet, these results were obtained in a smaller subsample with fewer cases and lower statistical power, and they were not statistically significant. Therefore, they still remain rather exploratory and limit the possibility to make firm inferences based on these data.

Is there an obesity paradox in older adults?

Reaching a robust understanding of the role of excess adiposity for health in older populations is critical from a public health perspective. Incorrectly initiating a shift in obesity policy based on a potentially biased epidemiological finding, such as the "obesity paradox", could have severe consequences. To begin with, it is important to recognize the heterogeneity in aging. It would be bold to assume that estimations of the associations between measures of adiposity and health outcomes would not vary between or within populations of older people depending on factors such as age, health status, biases and confounders, varying follow-up, and analytical approaches. For example, adjusting for smoking status

in the statistical models may still leave residual confounding, and confounding may also be present if participants with certain comorbidities are included in the analysis, or if such comorbidities are not adjusted for in the statistical models. Therefore, future studies would benefit from a sufficiently large, deeply phenotyped sample with granular data on participant characteristics. This includes, but is not limited to, data on various chronic diseases that are associated with unintentional weight loss, such as cancer, dementia, and mental health problems. Future studies would also be strengthened by having sufficient follow-up in order to assess potential reverse causation. In an English study of almost one million older adults, a comprehensive approach to address reverse causation was used. The results showed that obesity was associated with higher risk of mortality even up to 84 years of age.[310]

Altogether, our results do not the support an "obesity paradox" in 70-year-old individuals, as such findings might be explained by failure to account for body fat distribution as well as various biases and confounding factors, all of which may lead to spurious associations. In further support, mendelian randomization studies have shown that genetically predicted VAT is strongly associated with stroke, myocardial infarction, and premature death.[120-123] Interestingly, based on our interaction analysis, physical activity did not seem to have the ability to compensate for excess VAT, in line with findings from a recent large case-control study.[311] By implication, although Paper I showed that physical activity was associated with lower risk of CVD after controlling for VAT, Paper II suggest both factors may be important to target.

Effect of exercise on visceral adipose tissue

In Paper III, VAT mass decreased by on average 6.4% among participants performing vigorous exercise in terms of interval training over a period of 10 weeks. This corresponded to a small effect size as compared with the control group. However, the effect did not meet the designated threshold for statistical significance. This can probably be attributed to a combination of factors such as slightly reduced statistical power following exclusions of participants during baseline assessment and dropouts during the intervention, the significant decrease in VAT mass in the control group which made it more difficult to detect a difference between the groups, and the precision error for DXA-estimated VAT mass.[272] This should however not depreciate the relevance of our study given that preexisting evidence is predominantly based on studies in young and healthy individuals. Our findings therefore add knowledge regarding the potential ability of exercise to induce VAT loss in an understudied, high-risk population such as older adults with visceral obesity. Although our effect estimate was smaller compared to some individual studies of exercise and VAT in older adults,[312-315] it was similar to or larger than in other studies.[316-318] It is difficult to directly

compare results between individual studies, as different results may be influenced by many factors such as differences in aspects of the exercise intervention design and in study population characteristics, as well as that some interventions prescribed caloric restriction to induce weight loss in addition to exercise. Still, our effect estimate was very similar to that reported in several meta-analyses.[249-251,255,256,319,320]

Other relevant findings from Paper III include the effect on lean body mass. Whereas the previous studies in older adults which reported the largest effects on VAT also reported a decrease in lean body mass,[312,313] our intervention managed to slightly increase lean body mass. This would be a strength given the importance of maintaining muscle mass during aging.[321] Another interesting, albeit exploratory finding was that the effect of the intervention on VAT appeared greater in men than in women, even after adjustment for baseline VAT, similar to a previous meta-analysis.[251] It is difficult to firmly explain these findings. For instance, there was no difference between men and women in terms of attendance rate. Yet, differences in exertion during the training sessions were not tracked, hence we could not determine whether such a difference, if one existed, had an impact. Moreover, the postmenopausal estrogen decline has been associated with decreased fat oxidation during both rest and exercise,[322] which might be another contributing explanation. Regardless, this finding of ours should be viewed as preliminary due to the small sample size and because the study was not powered to determine sex differences.

Finally, as far as determining the effective exercise dosage for decreasing VAT goes, our results were recently included in a network meta-analysis.[320] Both HIIT (SMD = -0.38) and continuous exercise (SMD = -0.29) was shown to decrease VAT compared with control groups.[320] Regarding intensities, light-intensity exercise was ineffective whereas moderate and vigorous-intensity exercise had similar effects. Neither the weekly frequency of sessions nor the duration of the interventions seemed to modify the effect. The authors concluded that an effective dosage to decrease VAT is a continuous exercise intervention or HIIT intervention lasting 12 to 16 weeks, with three sessions weekly lasting 30 to 60 minutes (or <30 minutes for HIIT). Taken together, based on the findings from Papers I-III, one might argue that physical activity would effectively reduce the risk of CVD if tested in a randomized setting. Specifically, an effect from increased physical activity alone might be expected, regardless of other risk factors, and perhaps especially if also leading to decreased VAT. Thus, with Paper IV we decided to explore whether such an assumption is supported by evidence from current RCTs that have tested the effect of physical activity on CVD.

Effect of exercise on cardiovascular disease and all-cause mortality

Evidence from RCTs showing that regular physical activity can improve an abundance of cardiovascular risk factors,[323] [253] [251,255,320,324] coupled with an extensive body of observational studies estimating large risk reductions even independent of such risk factors, probably makes most people claim that it is already well established that exercise effectively prevents CVD. Although this evidence is indeed highly suggestive of an effect on clinical outcomes, one might very well argue that this evidence is insufficient, especially with respect to the magnitude of effect.

Interestingly, we found that exercise has not been shown to effectively reduce incident CVD or all-cause mortality in the general older population or in other high-risk populations based on current RCTs. Regarding general older adults, the trials have been quite small and lacked statistical power, or been rather short, or not designed to specifically investigate the effect of long-term exercise on CVD or all-cause mortality as a primary outcome. For example, de Souto Barreto et al. found no effect of moderate-intensity exercise interventions lasting at least one year on all-cause mortality in their meta-analysis.[294] Interestingly, individual RCTs that lasted longer also failed to show an effect. The LIFE Study showed no effect of moderate-intensity exercise for a median of two and a half years on CVD in sedentary older women.[288] Similarly, the Generation 100 Study showed that as compared with providing general recommendations on physical activity, neither five years of MICT nor HIIT had an effect on incident CVD or all-cause mortality in general older adults.[289,325] Although a trend favoring HIIT was seen when it was compared with MICT, the effect was not statistically significant and the analysis was considered exploratory.

Based on the totality of the results from the aforementioned studies, it cannot be ruled out that the dosage of exercise could be more important than is often presumed. Possibly, exercise has to be sustained for a long time and at a high intensity in order to lead to a clinically relevant effect. However, in the Look AHEAD Study, an intensive lifestyle intervention that lasted almost 10 years and targeted both weight loss and physical activity had no effect on CVD in individuals with overweight/obesity and type 2 diabetes.[291] Since the publication of Paper IV, a lack of effect in Look AHEAD was reported also for the outcome all-cause mortality during extended follow-up.[326] Null findings were also reported in a long-term follow-up of the Diabetes Prevention Program trial, where an intensive lifestyle intervention for three years targeting weight loss and increased physical activity had no effect on CVD in people with prediabetes during 21 years of follow-up.[327] Moreover, there was another recent meta-analysis of RCTs conducted in various clinical populations, although primarily patients with CVD, which found

a small positive effect of exercise on all-cause mortality (13% relative risk reduction).[328] Yet, all of the included trials were deemed to be at high risk of bias. Furthermore, the 2016 Cochrane meta-analysis of RCTs in patients with coronary heart disease was recently updated, again confirming a lack of effect on all-cause mortality, in studies wherein the overall risk of bias was low or unclear.[329] Although the same meta-analysis found that exercise had a positive effect on recurrent myocardial infarction (18% relative risk reduction), there was evidence of publication bias for this outcome.[329]

Altogether, these findings indicate that there is a lack of solid RCT evidence showing that exercise effectively reduces the risk of CVD and all-cause mortality. As this is stands in sharp contrast to the results of observational studies, a natural question to ask is what might explain the conflicting findings.

Observational studies and randomized trials – why do the findings conflict?

The reasons for the conflicting findings between observational studies and RCTs are probably complex and multifactorial. A lack of statistical power could partly explain why no effects have been detected in RCTs conducted in the general population of older adults, but it is unlikely to explain the null findings in RCTs conducted in clinical populations, as some of these trials, including meta-analyses of trials, have been large.

It could also be argued that insufficient quantity, duration, and adherence to exercise programs may have contributed, although this explanation is not as straightforward as it seems. This is exemplified by considering findings from pharmacological trials. Specifically, despite well-known problems with nonadherence to medications,[330] as well as the limited duration (<5 years) of most trials, medications such as those targeting hypertension, dyslipidemia, and type 2 diabetes have been shown to reduce CVD,[331-333] also in older adults.[334-336]

Another potential explanation could be that the exercise trials enrolled older adults and patients with chronic conditions, who are more likely to be taking such medications. This means that in order to detect an exercise-specific effect, exercise would have to result in an additional effect on top of that from medication. In this way, part of the effect of exercise may have been masked.

Furthermore, and as highlighted earlier, the healthy exerciser bias is a dilemma in exercise trials, whereby the study sample comprises disproportionally healthy and physically active individuals. Consequently, this introduces a risk of a ceiling effect, where it becomes more difficult to detect an effect of exercise.

On the other hand, the strong associations estimated in conventional observational studies may be overestimated. First of all, it is relevant to note that these studies typically adjust for an abundance of other common risk factors for CVD, and when the (typically strong) association with physical activity remains it is often concluded to be "independent" of the other factors adjusted for. In other words, physical activity is expected to exert a large and meaningful effect on CVD risk that is not explained by other common risk factors, and by implication, the conclusion is often that increasing physical activity alone is paramount in CVD prevention.

Yet, despite extensive regression adjustment, conventional observational studies are still susceptible to sources of bias and confounding that are left incompletely accounted for. For example, the issue of reverse causation has been demonstrated in studies showing that the beneficial associations weaken as minimum follow-up time between baseline (physical activity assessment) and incident outcome is increasingly restricted.[337,338] Furthermore, selection bias may also be present in observational studies, where a lower risk of CVD or mortality in physically active older adults as compared with their inactive peers might not be the result of a causal effect of physical activity. Rather, higher physical activity in these individuals may serve as an indicator of good overall health, where the absence of chronic disease and frailty makes it easier for these people to be physically active, hence they could experience a lower risk of the outcomes regardless of their level of physical activity.

There have also been results from animal models,[339] twin studies,[340-342] and polygenic risk score analyses,[343] pointing in the direction that unmeasured confounding due to genetic pleiotropy (where the same genes affecting physical activity also independently affect the risk of the outcome) might partly explain the strong associations in conventional observational studies. Indeed, genetic correlations between physical activity and sedentary behavior on the one hand, and CVD and longevity on the other hand, was identified in a recent meta-analysis.[344] Altogether, these lines of evidence indicate that these traits have a partly shared genetic architecture. Similarly, results from current mendelian randomization studies have been conflicting in terms of whether physical activity has a causal effect on incident CVD,[345-348] and the most recent meta-analysis of mendelian randomization studies suggested that the effect may be confounded by BMI.[344] Thus, while evidence from conventional observational studies and short-term RCTs using surrogate outcomes suggest that physical activity as a single intervention has a profound effect on CVD and mortality, triangulating evidence from studies using various designs to strengthen causal inference suggests that the effect is probably overestimated.

Methodological considerations

This thesis has strengths and limitations that should be considered. The primary strengths include the inclusion of a large population-based sample with a high participation rate, use of objective measures to assess physical activity and VAT, collection of outcomes using nationwide registers with high precision and virtually zero loss to follow-up, and adjustment for several potential confounders obtained from clinical examinations and nationwide registers, which are good for the internal and external validity of the findings in Papers I and II. Additionally, the randomized design with blinded assessors is the most important strength in Paper III, where we investigated the effect of exercise on VAT. In terms of limitations, the primary ones, as outlined previously, include the possibility of residual and unmeasured confounding, relatively short follow-up time and small number of outcomes, and potential lack of statistical power in the RCT. There are also other methodological considerations, of which some are discussed thoroughly below.

Selection bias

In the cohort analyses, selection bias may have influenced the associations if HAI participants differed from Umeå residents who chose not to participate. Although there is a high participation rate in HAI, a previous study suggested that HAI participants were generally healthier than nonparticipants, with for example a slightly lower prevalence of CVD and diabetes.[349] Regardless, even under ideal circumstances with a 100% participation rate, the issue regarding potential confounding due to genetic pleiotropy, as described earlier, would remain.

Moreover, the issue of selection bias should be discussed also with respect to the RCT (and to the RCTs in the review). Individuals who choose to participate in exercise trials are not only more motivated than nonparticipants, but they also tend to have better health status.[350] This problem is very difficult to avoid in exercise trials and inevitably hampers the generalizability. On the one hand, higher motivation among participants than nonparticipants would mean that the effectiveness of the intervention would probably be smaller if prescribed under real-life circumstances in a population-wide setting. On the other hand, if participants were more healthy and physically active than nonparticipants, the effect could be underestimated due to a ceiling effect, as previously discussed.

The HAI prevention program

In HAI, the participants were offered a health examination as well as a follow-up session where a research nurse used motivational interviewing to promote healthy lifestyle behaviors, such as physical activity and good nutrition. Given

that an earlier cohort study found that HAI participants had a lower risk of CVD during follow-up compared with matched controls from the general population,[349] the prevention program may potentially have influenced the results in the cohort analyses. Specifically, if participants with low levels of physical activity increased their physical activity as a result of the prevention program, the association between greater amounts of physical activity at baseline and lower risk of CVD and all-cause mortality during follow-up would become attenuated. A similar scenario could be the case for VAT, if participants increased their physical activity and improved their diet due to the prevention program, thereby experiencing loss of VAT mass.

However, it is probably unrealistic to expect that providing individual advice regarding physical activity and diet at a single occasion would have a pronounced, long-lasting effect on a population level. It should also be noted that the strength of the associations in our analyses were similar to, or greater than, in previous comparable studies. A more plausible explanation for the reduced risk of CVD in HAI participants might be improved medication, as indicated by an increase in prescription of antihypertensives and lipid-lowering agents during follow-up among HAI participants who had elevated levels of blood pressure or blood lipids.[349] Alternatively, confounding could explain the results.

Reverse causation

In cohort studies, factors that may introduce reverse causation include for example short follow-up time, outcomes occurring shortly after baseline, and the presence of preexisting disease in some participants. As outlined earlier, this could result in distorted associations. In this thesis, the mean length of follow-up was 2.7 and 3.6 years in Papers I and II respectively, and the primary analyses were not restricted to participants free from all CVDs. In sensitivity analyses where we excluded participants with a previous diagnosis of stroke, myocardial infarction, or angina pectoris, and participants with short follow-up time ($\leq$6 months in Paper I and $\leq$12 months in Paper II), the associations were generally the same. Yet, in the field of physical activity and health epidemiology, a cut-off of 6 months might have been insufficient as some studies have suggested that a cut-off of 5 to 10 years may be necessary to minimize the risk of reverse causation.[338,351] A 5-year cut-off has been used also in obesity epidemiology.[62] At the same time, critics could point out that restricting the minimum follow-up time might introduce other problems, such as immortal time bias. Finally, although we excluded participants with a previous diagnosis of certain CVDs in the sensitivity analyses, we did not exclude participants with other chronic diseases (including other subtypes of CVD), as this would probably have reduced the number of outcomes available for the analysis beyond what would be reasonable. Altogether, despite that our sensitivity analyses confirmed our

primary analyses, we cannot rule out, and it is in fact very likely, that there was confounding remaining.

Assessment and analysis of physical activity

Because people tend to overestimate their physical activity and underestimate their sedentary time,[147,352,353] our use of accelerometers is a strength. However, device-measured physical activity and health is a relatively young and rapidly evolving field of research with known challenges. There are several types of accelerometers available which can be worn at various places on the body, and the data can be processed using different criteria and analyzed through numerous analytical approaches.[354] In this thesis, the cut-points used to classify the intensity of physical activity are based on the relationship between vertical-axis counts and measures of absolute intensity which were determined in younger adults.[269] The use of only vertical-axis counts based on ambulatory activities likely means that there was residual physical activity remaining that was not captured.[355] Regarding these cut-points, their application in certain older people, especially those who are frail, could result in misclassification of physical activity intensities as they do not account for the relative fitness level.[356,357] Although calibration studies for older people have been conducted in some samples,[356,357] it is unclear whether these are applicable to large and diverse cohorts of older people, especially given the heterogeneity of aging. Until consensus is reached on standard intensity thresholds, the common cut-points used in this thesis facilitate interstudy comparisons, assuming the study sample is relatively healthy. This seemed to be the case in this thesis where mean MVPA was higher than in other cohorts of a similar age.[358,359]

Another thing to consider is the extent to which a 7-day assessment of physical activity and sedentary behavior is stable over time. A study in older women found that 7-day assessments of physical activity and sedentary time measured by Actigraph GT3X+ correlated strongly with measures obtained two to three years later,[360] corresponding to the average follow-up in this thesis. However, within-person variability is still present,[361] which may potentially bias the point estimates with health outcomes towards the null.

Finally, we analyzed time-use of physical activity spent in different intensities in relation to the outcomes using a traditional approach. Some have proposed novel approaches such as compositional data analysis, where the codependency of physical behaviors is considered, or utilizing isotemporal substitution models to examine the theoretical effects of substituting one behavior for another.[354] We chose the conventional approach because it facilitates interstudy comparisons and because I did not have the skills to conduct compositional data analysis. Regardless, there is currently no jointly agreed gold standard method, and each

approach has both strengths and limitations.[354] Reaching consensus and agreeing on best practice will be key as the field moves forward.

Exercise intervention design

The exercise intervention in Paper III has both limitations and strengths. A limitation is that we were unable to confirm the extent to which participants reached a vigorous intensity, for example using objective measures such as heart rate monitors. Self-reported rate of perceived exertion is however a viable alternative and recommended for prescribing exercise intensity in older adults.[362]

A strength is the level of compliance which was high compared to what was reported in a systematic review.[363] Many factors can influence compliance to exercise interventions in older adults,[364,365] of which some can be found in our study. These relate to individualization, supervision, exploration of participant's characteristics, facilitators, and barriers, participant education and knowledge about risks and benefits, promoting exercise enjoyment, social support and relatedness, self-efficacy and competence, and communication and feedback.[364,365] Specifically, the pilot exercise session held in a group of potential participants preceding the start of the trial explored the plausibility of the exercises, considering participants' needs and interest. The final exercise program was therefore influenced by participants characteristics, barriers, and facilitators, and allowed for individualized progression during the intervention. Moreover, two supervisors were present during all sessions, and the participants were briefed on the expected benefits and potential risks of the intervention. Another factor is that the participants were included based on having visceral obesity. This may have promoted social support and feelings of relatedness, as the participants could more easily identify with each other knowing that they were there for the same reason. Further, participants received communication and feedback continuously throughout the study. The gradual progression during the intervention likely promoted self-efficacy and feelings of competence, as participants were encouraged to familiarize with the exercises and select an appropriate level based on their own capacity, and to progress when feasible or regress if necessary. Finally, the intervention had pragmatic benefits in terms of the minimal use of expensive equipment, which is of importance given that cost is a barrier to exercise adherence in older adults.[364,365]

Non-systematic review

Because Paper IV did not include a systematic search strategy we cannot rule out that some relevant papers might have gone unnoticed. However, it is unlikely that we missed any major studies on the topic, at least with respect to studies conducted specifically in general older adults, given that such trials have

remained extremely rare. For example, the Generation 100 Study, published in a high-impact journal in late 2020, was the first to test the effect of long-term exercise on all-cause mortality as a primary outcome in general older adults. Regardless, it would also not have been practically feasible to perform a systematic review for this paper given the width of the original paper which covered two additional outcomes outside the scope of this thesis. Thus, performing all steps of a systematic review on the effect of exercise on four different outcomes in a variety of populations for a single paper would have been a near overwhelming task.

Clinical implications

As the aging population is expected to grow further in the near future, CVD will remain a significant burden on society and the healthcare sector. Research and implementation of strategies that have been shown to effectively prevent or delay CVD is therefore of importance. Assuming causality, the findings from Papers I-III would suggest that promoting an increase in physical activity, regardless of the amount or intensity, as well as decreasing VAT, would aid in reducing CVD incidence in older adults. We then studied whether vigorous exercise could be a plausible strategy for decreasing VAT mass, indicating that it might have a small positive effect, but this could not be statistically confirmed. Taken together, these findings would support increased routine surveillance of physical activity and VAT among older adults to help identify individuals at increased risk of CVD who would benefit from subsequent interventions targeting these factors (i.e. exercise), with the underlying assumption that it would prevent incident CVD.

However, a conclusion such as the one outlined above does not factor in the findings from Paper IV. As shown, current evidence from RCTs does not confirm that physical activity as a single intervention has a strong protective effect against CVD or premature all-cause mortality in older adults or in other high-risk populations. As discussed, there could be a myriad of reasons for why the findings between RCTs and conventional observational studies conflict. From a clinical perspective, this indicates that caution is warranted regarding overly optimistic expectations and claims about the role of physical activity alone in CVD prevention. To avoid relying on assumptions based on conventional observational studies that carry the risk of yielding inflated estimates, more robust lines of evidence supporting causality are needed.

While the overall body of evidence indicates that it is rather unlikely that physical activity is completely ineffective, the reality might well be that the effect is not as large as suggested by some conventional observational analyses (>50% when comparing the most active to the least active individuals). Thus, in order to obtain a clinically relevant effect of physical activity on CVD or mortality one might need

to ensure that physical activity is adhered to for a duration and with an intensity that is greater than often presumed. This would be an important message as it portrays quite a different landscape than the one typically communicated to the public, for instance through physical activity guidelines which suggest substantial health benefits from even small amounts of physical activity.

Overall, these findings suggest that researchers, clinicians, relevant stakeholders, and public health authorities ought to carefully consider how they communicate the evidence on physical activity in relation to CVD and mortality to the general public. This is prudent both for reducing the risk of imposing individuals with unwarranted feelings of guilt and self-blame, and to not undermine the need for future high-quality research within the field. Those working with older adults and physical activity promotion also need to be aware of the sizeable influence that heritability has on variations in physical activity levels, exercise adaptation, and susceptibility to disease and longevity. Therefore, it is fair to request more caution and nuance when communicating to general individuals that increasing one's level of physical activity alone will extend lifespan and protect against future CVD.

As far as communication and promotion of physical activity goes, one might also raise the question of whether other motives for physical activity should be more emphasized, at least on the individual level. In older adults, some of the primary ones include enjoyment, being physically fit, and psychological well-being.[366] Could we perhaps achieve better compliance if the motives for physical activity are better considered in the design and implementation stages of physical activity interventions?

Furthermore, if the effect of physical activity alone is smaller than is commonly presumed, relying on it disproportionately as a means of preventing CVD could lead to the prescription of ineffective interventions. This would result in a waste of resources from both a clinical and a research perspective. However, it could be hypothesized that if physical activity is implemented alongside other components in a multimodal intervention it might be more effective. Perhaps it is even a necessity? This mindset has been adopted by prevention research on other age-related outcomes such as dementia, where multimodal lifestyle interventions are highlighted by the WHO as the way forward.[367] One example comes from the FINGER trial, where older adults with elevated dementia risk were randomized to regular health advice or to a 2-year intensive lifestyle intervention. The intervention consisted of five domains, including exercise, diet, cognitive training, social activities, and management of cardiovascular risk factors. In secondary analyses the intervention was effective for reducing the risk of new chronic diseases[368] and for both primary and secondary prevention of cerebrovascular disease and total CVD.[369] Evidence also shows that pharmacotherapy plus lifestyle interventions lead to greater loss of body weight

and VAT mass compared with lifestyle interventions alone.[370-372] Even so, most Swedish patients with obesity only receive lifestyle interventions, with only 1% receiving pharmacotherapy.[373] As such, this thesis, supported by the evidence above, suggests that physical activity alone may not be as powerful a tool for CVD prevention as typically expected, and that it may be more effective when part of a multimodal intervention including other lifestyle changes and/or medication, to target different risk factors and act through different mechanisms.

Research implications

The paradigm of the role of physical activity in CVD and longevity has grown extremely strong since the landmark studies in the 1950s. Despite this, the findings from this thesis question the common belief, held by both experts and laypeople, that physical activity alone leads to substantial reductions in CVD risk. While conventional observational studies show strong associations, there is a lack of evidence from RCTs to confirm a causal relationship of such a magnitude as is commonly presumed. Our findings underscore the need for additional scientific progress to expand our understanding of the physical activity-health paradigm.

Trials

First of all, further large, sufficiently powered, high-quality trials are warranted. This has also been highlighted by others, such as the US Preventive Services Task Force.[374] It is of course important to be humble before the fact that such trials are very challenging to conduct, not only due to the large number of participants required and the fact that they need to adhere to lifestyle changes for many years, but also due to infrastructural demands, including human and economic resources.

Nevertheless, reality shows that such trials can be performed. The Generation 100 was the first RCT to test the effect of long-term exercise as a single intervention on all-cause mortality as a primary outcome and CVD as a secondary outcome in older adults, showing no convincing effect. Currently, WHISH is an ongoing pragmatic RCT testing the effectiveness of a 9-year physical activity intervention on incident CVD in 50,000 older women.[375] This study has the possibility to provide robust evidence regarding the role of physical activity in CVD prevention under real-world circumstances.

Observational studies

Nevertheless, it is probably unrealistic to expect an abundance of high-quality trials to suddenly be performed. At the same time, in the strive towards deepening our knowledge on the causal effect of physical activity on CVD, simply repeating

the same type of conventional observational analyses over and over is unlikely to lead to remarkable progress. One option could therefore be that trials are complemented by triangulation of evidence that is obtained using a variety of epidemiological study designs which aim to address different sources of bias and confounding, thereby strengthening causal inference.[376,377] Below follows some concrete examples of what type of study designs that could be considered.

1) Sibling comparison is a method known for its ability to reduce unmeasured confounding. This is achieved by comparing the risk of an outcome between siblings who are discordant for the exposure. By doing so, all shared factors, including unobserved genetic and environmental factors, are inherently controlled for.[378]

Current studies conducted in twins suggest some extent of confounding due to shared familial factors with respect to the relationship between physical activity, CVD, and mortality.[340-342] For instance, my colleagues and I conducted a study to examine the association between adolescent cardiorespiratory fitness and later risk of CVD and all-cause mortality. Our findings showed that adjustment for shared familial factors through a co-twin model weakened the association between higher fitness and a lower risk of the outcomes.[340] However, because there have been few reports similar to ours, and because twin studies are typically limited in statistical power, additional studies were deemed needed. To address this gap, we conducted another study to investigate the association between various adolescent cardiovascular risk factors, including cardiorespiratory fitness, and CVD, but this time we broadened our analysis to full sibling comparisons instead of restricting it to twins. Our new study had a much larger sample size, with over 460,000 full siblings and over 18,000 outcomes, compared to less than 500 outcomes in our previous twin study. At the time of printing this thesis, the study is undergoing external peer-review, but preliminary results indicate that the association between high cardiorespiratory fitness and reduced risk of CVD is significantly attenuated when accounting for shared familial factors.

2) Negative control outcomes can be used to detect whether bias and confounding are present. A negative control outcome is one that is not a cause of the exposure being studied, but shares the same sources of bias and confounding.[379] For example, if physical activity is found to be associated both with CVD and with a negative control outcome like traffic accidents, it may suggest the presence of confounding.

Negative control outcomes have not been widely implemented in observational studies on physical activity and health outcomes, but one study did utilize accidental death as a negative control outcome in its examination of the

association between physical activity and cardiovascular mortality.[380] The results indicated that physical activity was associated with a lower risk of both cardiovascular mortality and accidental death, although the latter to a lesser extent. This suggests some degree of confounding and that the beneficial association between physical activity and cardiovascular mortality may be of smaller magnitude than commonly observed.

3) Instrumental variable analysis is another method to reduce bias and confounding. Here, one utilizes a variable that is associated with the exposure but not with the confounders of the exposure or outcome, and the only way that this instrumental variable is associated with the outcome is through its association with the exposure.[381] For example, in a study of the risk of parental CVD, offspring physical activity could serve as an instrumental variable for parental physical activity. To my knowledge, no study has leveraged this design in physical activity epidemiology yet, but it has been used in obesity epidemiology.[382,383]

4) Finally, the use of genetically informed designs is an interesting and emerging area of research also in the field of physical activity. One such design is mendelian randomization. This is a type of instrumental variable analysis where genetic variants (in this case for physical activity) are used as instrumental variables to reduce bias and confounding.[384]

A recent systematic review of six genome-wide association studies identified 10 single-nucleotide polymorphisms (SNPs) associated with self-reported or device-measured physical activity and sedentary behavior,[385] and mendelian randomization analyses based on these SNPs have so far yielded mixed findings with respect to whether physical activity has a causal effect on CVD.[345-348] Moreover, in a large meta-analysis, where 99 SNPs associated with self-reported MVPA or sedentary behaviors were identified, mendelian randomization analyses found that the beneficial effects of physical activity on CVD and longevity were mediated or confounded by BMI.[344] Further studies were deemed necessary given that the instruments for MVPA were judged to be rather weak.

Theoretically, scientific advancements on genetics and physical activity may, in addition to supporting mendelian randomization analyses, be applied in trials. For instance, polygenic risk scores could be used to evaluate who may benefit more or less from an intervention based on genetics, which eventually might be used for informing tailored and personalized interventions. However, it is critical to note that the genetic variants that have been identified so far only explain a very small proportion of the variance in physical activity.[386] Therefore, in order for an approach such as the one proposed above (polygenic risk scores) to have a high probability of success and yield clinically important results, much more evidence on genetic variants related to physical activity is needed.

In sum, from an epidemiological perspective, the field of physical activity and health would benefit from more observational studies using designs that seek to strengthen causal inference. Given the scarcity of such studies as of today, I believe that this kind of broadening of the epidemiological arsenal will be paramount to getting a better sense of the causal nature of the relationship between physical activity, CVD, and longevity.

Conclusions

The findings of this thesis indicate that the protective effect of physical activity as a single intervention against CVD and all-cause mortality in older adults is probably not as substantial as is commonly presumed. This implies that individuals who start engaging in physical activity in old age may not achieve the large benefits to their risk of CVD and all-cause mortality that are typically expected and frequently communicated. Therefore, I believe it is important to speak in a more cautious and nuanced manner when discussing the role of physical activity in CVD prevention, both in the scientific sphere and when communicating with the general public. Importantly, this thesis highlights the need for further research to advance the field and uncover the true role of physical activity in CVD prevention. This includes both high-quality trials and innovative observational studies that seek to strengthen causal inference by addressing sources of bias and confounding that are often incompletely accounted for in conventional observational studies. As the aging population continues to grow, it becomes increasingly important to take these scientific steps in order to provide a more definitive answer to the question of how much physical activity alone can reduce the risk of CVD.

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