PHYSICAL ACTIVITY, SLEEP AND CARDIOVASCULAR DISEASES

PERSON-ORIENTED AND LONGITUDINAL PERSPECTIVES

Heini Wennman

ABSTRACT

Physical activity (PA) is a well established behavioral risk factor for cardiovascular diseases (CVD), a leading cause of death globally. Also poor sleep and sedentary behaviors associate with higher CVD risk. Despite decreased CVD mortality in Finland, many people do not get enough PA, sleep-related problems are common in the working aged population and sedentary behaviors take up large parts of the time spent awake. Health behaviors tend to cluster and epidemiological literature suggest that also PA and sleep are interrelated. However, actual clustering has seldom been modeled in large-scale population data. Associations between PA and sleep can be modified by qualitative factors, such as domain of PA, sleep-related problems and timing of sleep, as well as sociodemographic characteristics. There is little existing literature on interactions between PA and sleep with CVD and it warrants further research.

The aim of this thesis was to study the interrelationship between PA and sleep and their joint association with CVD risk and mortality. The focus was on modelling inter-individual variation in the behaviors and on studying cardiometabolic risk factors and total CVD risk based on the clustering of the behaviors. Furthermore, the interrelationships between a history of sports, PA, sleep and all-cause and CVD mortality was studied in a population of former elite athletes.

This study comprises data from the National FINRISK 2012 Study (n=6424, men=3041; women=3383) and the Finnish former elite athlete cohort (n=2141, all men). In the FINRISK 2012 Study, a sample of the Finnish general population aged 25 to 74-years underwent a health examination and filled in health questionnaires. The former athletes (n=1364) and non-athletic referents (n=777) of the Finnish former elite athlete cohort provided information about health behaviors on a questionnaire in 1985 and were then followed-up for mortality until 31 December 2011 from national registers.

Main statistical methods in this thesis included latent class analysis, weighted logistic regression, analysis of variance, and Cox proportional hazards model. The latent class analysis is a person-oriented latent variable model where underlying groups of persons are identified based on similarities in their behavioral patterns or profiles, characterized by conditional likelihoods in the measured behavioral variables.

This study showed that differences in clustering of PA and sleep behaviors characterized underlying groups of men and women among the initially CVD-free, Finnish general population. Low PA, high screen time sitting, short and insufficient self-reported sleep made up a Profile, in which membership among women associated with unfavorable levels in several cardiometabolic risk factors and a higher total CVD risk. In men,

membership in the ”*Physically inactive, poor sleepers*” Profile showed only one statistically significant association (out of 10) with unfavorable levels in cardiometabolic risk factors, but was associated with a high estimated 10-year CVD risk. Different chronotypes in the population were strongly characterized by evening preference, but also by morning tiredness. Both "*evening types*" and "*tired, more evening types*" had low leisure time PA (LTPA) compared to morning types and "*evening types*" also had high sitting. There was a significant joint association of insufficient LTPA level and short sleep with a higher mortality, especially CVD mortality, in a cohort of former elite athletes and non-athletic referents.

To conclude, this study supports the importance of PA and sleep as health behaviors related to CVD risk, and provide evidence particularly for a joint association with CVD risk. Not only the duration of sleep, but also the quality and self-estimated sufficiency of sleep, as well as a person's chronotype all contribute to the clustering of PA and sleep and consequent CVD risk. The results of this study are generalizable to the general adult population in Finland, apart from the mortality results that apply to a more selected male population.

TIIVISTELMÄ

Sydän- ja verisuonitaudit ovat johtava kuolinsyy maailmassa, ja vähäinen liikunta on yksi tunnettu riskitekijä sydän- ja verisuonitautien synnyssä. Myös unella ja paikallaan ololla on osoitettu olevan yhteys sydän- ja verisuonitautien riskiin. Suomessa sydän- ja verisuonitautikuolleisuus on laskenut viimeisten 40 vuoden aikana, mutta moni suomalainen ei liiku riittävästi, unettomuusoireet ovat lisääntyneet työikäisillä ja suuri osa valveillaoloajasta vietetään liikkumattomana. Elintavat ja terveyskäyttäytymiset kasaantuvat ja epidemiologiset tutkimukset ovat osoittaneet kaksisuuntaisia yhteyksiä myös liikunnan ja unen välillä. Isoissa väestöaineistoissa on kuitenkin harvoin mallinnettu todellista käyttäytymisten ryhmittymistä henkilötasolla. Liikunnan ja unen välistä määrällistä yhteyttä monimutkaistavat esimerkiksi liikunnan ja unen laadulliset ominaisuudet sekä ihmisten sosiodemografinen tausta. Liikunnan ja unen suhde sydän- ja verisuonitautien riskiin vaatii lisää tutkimusta, koska olemassa olevaa näyttöä on vähän ja todellista vuorovaikutusta on tutkittu vain harvoin.

Tämän väitöskirjatutkimuksen tavoitteena oli tutkia liikunnan ja unen välisiä yhteyksiä sydän- ja verisuonitautien riskiin. Tavoitteena oli mallintaa liikuntakäyttäytymisen ja unen ryhmittymistä ihmisten välillä sekä tutkia sydän- ja verisuonitautien riskitekijöitä ja kokonaisriskiä näiden ryhmittymien pohjalta. Lisäksi aiemman urheilutaustan, liikunnan ja unen vuorovaikutusta sydäntautikuolleisuuden kanssa tutkittiin entisistä huippu-urheilijamiehistä koostuvassa aineistossa.

Tämän tutkimuksen aineistoina on käytetty Kansallista FINRISKI 2012-tutkimusta (n=6424, miehiä=3041; naisia=3383) ja Ikääntyvien entisten huippu-urheilijoiden terveystutkimusta (n=2414, kaikki miehiä). FINRISKI 2012 -tutkimuksen otos koostuu 25–74-vuotiaista aikuisista, jotka vastasivat terveyskäyttäytymiskyselyyn ja osallistuivat terveystarkastukseen. Entisten huippu-urheilijoiden kohortin urheilijamiehet (n=1364) ja ei-urheilevat verrokit (n=777) täyttivät vuonna 1985 terveyskyselylomakkeen. Kohortin kuolleisuutta seurattiin kansallisista rekistereistä 31. joulukuuta 2011 asti.

Väitöskirjan pääasialliset tilastomenetelmät ovat latentti luokka-analyysi, painotettu logistinen regressioanalyysi, painotettu varianssianalyysi ja Coxin suhteellisen vaaran malli. Latentti luokka-analyysi on henkilökeskeinen, latentti muuttujamalli, jossa piileviä ryhmittymiä tunnistetaan samankaltaisten käyttäytymisprofiilien avulla. Profiileja kuvaavat ehdolliset todennäköisyydet mitatuissa muuttujissa.

Tämä tutkimus osoittaa, että liikuntakäyttäytymisen ja unen ryhmittyminen tai Profiili erottelee lähtökohtaisesti sydänterveessä väestössä neljä piilevää ryhmää niin miehissä kuin naisissa. Naisilla vähäinen liikunnan määrä, runsas istuminen ja lyhyt ja riittämättömäksi koettu uni

kuvaavat Profiilia, jonka jäsenillä oli havaittavissa myös korkeita sydän- ja verisuonitautien aineenvaihdunnallisia riskitekijäarvoja. Miehillä jäsenyys tähän vähäisen liikunnan ja huonon unen Profiiliin oli tilastollisesti yhteydessä vain yhteen yksittäiseen riskitekijään (kymmenestä), mutta miehillä oli tässä Profiilissa muita Profiileja korkeampi ennustettu 10 vuoden tautiriski. Tutkimuksessa havaittiin myös, että väestössä erottuu vahvasti kronotyyppejä iltatyyppisyyden ja aamuväsyneisyyden mukaan. Iltatyypit ja aamuväsyneet, jotka olivat enemmän ilta- kuin aamutyyppejä, harrastivat vähän liikuntaa vapaa-ajalla verrattuna aamutyyppeihin, ja iltatyypit myös istuivat paljon. Niin entisillä huippu-urheilijamiehillä kuin ei-urheilleilla verrokeilla havaittiin riittämättömän vapaa-ajan liikunnan ja lyhyen unen välillä merkitsevä yhdysvaikutus kuolleisuuteen, etenkin sydäntautikuolleisuuteen.

Tämä tutkimus vahvistaa sen, että liikunta ja uni ovat tärkeitä elintapoja sydän- ja verisuoniterveydelle. Tutkimuksen tulokset osoittavat ennen kaikkea, että liikunta ja uni vaikuttavat yhdessä sydäntautiriskin syntyyn. Unen pituuden lisäksi myös unen laatu ja unen itsearvioitu riittävyys sekä henkilön kronotyyppi vaikuttavat liikunnan ja unen suhteeseen. Tämän tutkimuksen tulokset ovat yleistettävissä suomalaiseen aikuisväestöön, lukuun ottamatta kuolleisuustuloksia, jotka koskevat valikoituneempaa miesväestöä.

Avainsanat: liikunta, uni, kronotyyppi, sydän- ja verisuonitaudit, sydäntautikuolleisuus

SAMMANFATTNING

Fysisk aktivitet är bland de mest etablerade hälsobeteenden som har ett samband med risken för hjärt- och kärlsjukdomar, en ledande dödsorsak världen över. Dålig sömn och mycket stillasittande har också visats vara anknytna till högre risk för hjärt- och kärlsjukdomar. I Finland har dödligheten i hjärt- och kärlsjukdomar minskat stadigt under de senaste 40 åren. Många vuxna i Finland uppnår ändå inte tillräckligt med fysisk aktivitet, sömnproblem förekommer ofta bland befolkningen i arbetsför ålder och stora delar av dagen spenderas stillasittande. Våra hälsobeteenden tenderar att hopa sig och epidemiologiska studier har också funnit ömsesidiga samband mellan fysisk aktivitet och sömnvanor. Epidemiologiska studier har ändå sällan studerat hur beteenden hopar sig på individnivå. Sambanden mellan fysisk aktivitet och sömn kan kompliceras av kvalitativa faktorer relaterade till fysisk aktivitet och sömn, samt sociodemografiska faktorer. Samverkan mellan fysisk aktivitet och sömn för risken för hjärt- och kärlsjukdomar kräver mer forskning eftersom det fortfarande i nuläget finns endast lite kunskap i ämnet och verklig samverkan studerats sällan.

Målet med denna doktorsavhandling var att studera sambanden mellan fysisk aktivitet och sömn och deras samverkan för risken för hjärt- och kärlsjukdomar. Målet var att forska hur likheter i fysisk aktivitet och sömnvanor grupperar människor och att studera både särskilda riskfaktorer för hjärt- och kärlsjudomar och den totala risken bland dessa grupperingar. Dessutom studerades sambanden mellan en idrottslig bakgrund, fysisk aktivitet, sömn och dödlighet från hjärt- och kärlsjukdomar bland före detta toppidrottsmän.

I denna avhandling används tvärsnittsdata från den nationella hälsoundersökningen FINRISKI 2012 (n=6424, män=3041 ; kvinnor=3383) och prospektivt data från the Finnish former elite athlete cohort (n=2141, alla män). FINRISKI 2012 urvalet består av män och kvinnor i åldern 25-74 år, vilka besvarade en hälsoenkät och deltog i en hälsoundersökning. The Finnish former elite athlete cohort är ett urval av före detta toppidrottarmän (n=1364) och ej-idrottande män (n=777) som år 1985 besvarade en hälsoenkät och som följts upp i nationella register för dödlighet fram till 31 december 2011.

De huvudsakliga statistiska analysmetoderna i denna avhandling innefattar Latent Class Analysis (LCA), regressionsanalys (logistisk, multinomial, Cox proportional hazards model), och variansanalys. LCA är en person-orienterad latent analysmetod, som försöker kartlägga underliggande grupperingar i datat på basen av information om mätta variabler. Konditionella sannolikheter för inkluderade variabler beskriver Profilerna som i sin tur särskiljer de underliggande grupperingarna.

Denna studie visar att fyra olika Profiler som beskrivs av fysisk aktivitet och sömn, identifierar grupperingar av män och kvinnor i urvalet. Låg fysisk aktivitet, långvarigt stillasittande, kort sömntid och sömn som upplevs otillräcklig beskriver kvinnor hos vilka också flera samband med enskilda riskfaktorer och en högre total risk för hjärt- och kärlsjukdomar förekom. Bland män fanns endast ett statistiskt samband (utav 10) mellan Profilen av låg fysisk aktivitet och otillräcklig sömn och de enskilda riskfaktorerna, men män i denna Profil hade en hög total hjärt- och kärlsjukdoms risk. Det visade sig också att förutom en sen dygnsrytm särskiljer också morgontrötthet starkt mellan olika kronotyper i befolkningen. Inte bara de absolut kvällsorienterade men också de mer kvällsinriktade men morgontrötta hade låg fysisk aktivitet på fritiden och de kvällsinriktade hade också mer stillasittande i vardagen. Bland män, såväl med en idrottarbakgrund som utan idrottslig bakgrund fanns en betydande samverkan mellan låg fysisk aktivitet och kort sömntid för en större dödlighetsrisk från hjärt- och kärlsjukdomar.

Denna avhandling stärker befattningen om fysisk aktivitet och sömn som viktiga hälsobeteenden. Resultaten visar framför allt på en samverkan mellan fysisk aktivitet och sömn för risken för hjärt- och kärlsjukdomar. I tillägg till sömntid är också sömnens kvalitet och vår kronotyp viktiga faktorer i sambanden mellan fysisk aktivitet och sömn och vidare för risken för hjärt- och kärlsjukdomar. Resultaten kan till största delen generaliseras till den finländska vuxna befolkningen, förutom resultaten angående dödlighet, vilka gäller ett mer selektivt urval av den manliga befolkningen.

Nyckelord: fysisk aktivitet, sömn, kronotyp, hjärt- och kärlsjukdomar, dödlighet i hjärtsjukdom

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I   Wennman H, Kronholm E, Partonen T, Tolvanen A, Peltonen M, Vasankari T, and Borodulin K. Physical activity and sleep profiles in Finnish men and women (2014). BMC Public Health, 14:82.

II   Wennman H, Kronholm E, Partonen T, Peltonen M, Vasankari T, and Borodulin K. Evening typology and morning tiredness associates with low leisure time physical activity and high sitting. (2015). Chronobiology International, Aug 28:1-11.

III   Wennman H, Kronholm E, Partonen T, Tolvanen A, Peltonen M, Vasankari T, and Borodulin K. Interrelationships of Physical Activity and Sleep with Cardiovascular Risk Factors: a Person-Oriented Approach. (2015). International Journal of Behavioral Medicine, 22, (6):735-747

IV   Wennman H, Kronholm E, Heinonen O. J., Kujala U, Kaprio J, Partonen T, Bäckmand H, Sarna S, and Borodulin K. Low physical activity and short sleep predict mortality in former elite athlete men and their referents. (submitted 2016).

The publications are referred to in the text by their roman numerals. Original publications are reprinted with kind permission of the copyright holders.

ABBREVIATIONS

ANOVA   Analysis of variance
BMI   Body mass index
cm   Centimeter
CI   Confidence intervals
CPA   Commuting physical activity
CRP   C-reactive protein
CVD   Cardiovascular diseases
dl   Decilitres
$HbA1_c$ Glycated hemoglobin
HDL   High density lipoprotein
HR   Hazard ratio
ICD   International classification codes of disease
kcal   Kilocalories
kg   Kilogram
L   Litre
LCA   Latent class analysis
LDL   Low density lipoprotein
LTPA   Leisure time physical activity
M   Meters
MET   Metabolic equivalent
MEQ   Horne and Östberg morningness-eveningness questionnaire
mg   milligram
mmHg   millimeter of mercury
ml   milliliter
mmol   millimole
OPA   Occupational physical activity
OR   Odds ratio
PA   Physical activity
RERI   Relative Excess Risk due to Interaction
SD   Standard deviation
THL   The National Institute for Health and Welfare
TV   Television
vs   versus

1 INTRODUCTION

Sleep is a fundamental behavior for the restoration and construction of body functions and eventually even survival (Jackson et al., 2015; Luyster et al., 2012). Physical activity (PA) has been a requirement of survival in generations before us, beginning with the hunting and gathering of food and later the manual demands of work and daily life (Archer and Blair, 2011; Myers et al., 2015). Today, in industrialized societies people spend considerable time of the day sedentary, while PA is mainly a leisure time activity (Archer and Blair, 2011; Matthews et al., 2008). In a 24-hour society, social and economic demands, the use of technology, and the availability of artificial light, also comes with a cost to sleep (Jackson et al., 2015; Rajaratnam and Arendt, 2001).

Modern epidemiological research about the associations between PA and the risk of mortality began with the studies of Jeremy Morris in the 1950's (Morris et al., 1953; Myers et al., 2015), whereas sleep epidemiology has its roots some years later (Ohayon et al., 2010). The disappearing physical exertion of daily life, the high amounts of time spent sedentary and the high prevalence of physical inactivity are important factors for the epidemic of non-communicable diseases, importantly cardiovascular diseases (CVD) (Archer and Blair, 2011; Lee et al., 2012). Cardiometabolic consequences and increased risk of mortality have also been related to occurrence of sleep problems and short or long sleep duration (Cappuccio et al., 2010; Knutson, 2010; Luyster et al., 2012).

CVD are a leading cause of death worldwide and the burden of disease is high (World Health Organization, 2014; World Health Organization, 2015). In Finland, CVD are a major cause of death among the working aged population (Suomen virallinen tilasto, 2014), even if CVD mortality and incidence in general has decreased since the 1970's (Jousilahti et al., 2016; Koski et al., 2015). Progression of the disease happens over time (Dzau et al., 2006) with an important influence of our behaviors (World Health Organization, 2015).

The clustering of health behaviors and the consequences thereof for cardiovascular health is acknowledged (Eguchi et al., 2012; Odegaard et al., 2011). Often, however, health behavior clustering is only studied in terms of co-occurrence by for example indexing-methods that do not model actual clustering (McAloney et al., 2013). There are also not many who have included both PA and sleep among the studied clustering health behaviors (Noble et al., 2015). In epidemiological studies it is common to use methods that assume population homogeneity in respect to the variables under study and result in statements actually reflecting associations between the variables (Bergman and Trost, 2006; McAloney et al., 2013). Furthermore, most often when studying the health outcomes related with PA and sleep, the

other is only adjusted for and interaction between the two has more seldom been investigated (Pepin et al., 2014).

The relationship between PA and sleep is likely bidirectional, but not necessarily straightforward. Even if studies have shown physically active persons to report better sleep more often than physically inactive persons (Kredlow et al., 2015; Pepin et al., 2014), very high levels of PA or occupational physical activity (OPA) can be inversely associated with sleep (Lastella et al., 2015; Soltani et al., 2012). Where poor sleep seems to predict low future PA, the reverse has not been observed (Chennaoui et al., 2015; Haario et al., 2012). Several physiological mechanisms relate PA and sleep with each other, including metabolism, thermoregulation and endocrine functions (Atkinson and Davenne, 2007; Chennaoui et al., 2015; Driver and Taylor, 2000). On an energy expenditure scale, sleep, sedentary behaviors and PA can be thought to proceed each other (Tremblay et al., 2010), while from a time-use perspective, PA, sedentary time and sleep make up the division of time during the 24-hours (Buman et al., 2014b; Tudor-Locke et al., 2011).

The interaction of PA and sleep with cardiovascular health, all-cause and cardiovascular mortality has so far had little attention and the existing results are not compelling (Pepin et al., 2014). Taken into account the fundamental role of both behaviors for the functioning and health of the body, and furthermore, the suggested but likely complex interrelationship between these behaviors, the interaction between PA and sleep for risk of CVD and mortality warrant studying.

2 REVIEW OF THE LITERATURE

2.1 CARDIOVASCULAR DISEASES

Cardiovascular diseases (CVD) consist of a group of disorders of the heart and blood vessels including coronary heart disease, cerebrovascular disease, elevated blood pressure, peripheral artery disease, rheumatic heart disease, congenital heart disease, and heart failure (World Health Organization, 2015). Approximately 30% of all deaths worldwide are caused by CVD that is among the biggest non-communicable diseases (GBD 2013 Mortality and Causes of Death Collaborators, 2015; World Health Organization, 2015). In Finland, mortality from CVD in the working aged population has constantly been decreasing since the 1970's (Jousilahti et al., 2016; Koski et al., 2015), but CVD is still one of the main causes of death among working aged persons (Suomen virallinen tilasto, 2014). The prevalence of CVD has also steadily been decreasing, but as the population is aging, it is estimated that at least the prevalence of stroke can increase unless preventive actions are successful (Koski et al., 2015).

The progression of atherosclerotic CVD happens over time. Continuous exposure to risk factors results in atherosclerotic changes that lead to formation of unstable atherosclerotic plaques causing narrowing of blood vessels and with a risk of rupturing. In the case of a plaque rupture or erosion, inflammation occurs that further initiates the forming of clots. The clots can cause obstruction of blood flow to the target tissue i.e. heart or the brain, ultimately with detrimental consequences (Dzau et al., 2006; World Health Organization, 2007).

2.1.1 RISK FACTORS FOR CARDIOVASCULAR DISEASES

Modifiable risk factors for CVD can be grouped as cardiometabolic factors and behavioral factors, with most established risk factors being elevated blood pressure, high total cholesterol, hyperglycemia, smoking, and obesity (Dzau et al., 2006; Goff et al., 2014; World Health Organization, 2015). There are also risk factors that cannot be modified such as older age, male gender, heredity, and ethnicity (World Health Organization, 2007). In Finland, a substantial change on population level in several of the most established risk factors has been observed over the past 40 years, explaining for the most part the lowered CVD mortality (Borodulin et al., 2014b; Jousilahti et al., 2016).

Total risk of CVD depends on the combination of risk factors that usually coexist and act multiplicatively. Total CVD risk may be higher having several moderately raised risk factors than high levels on only one risk factor (Lloyd-Jones, 2014; World Health Organization, 2007). The causal chain between CVD risk factors and disease is not always straightforward. While some risk

factors act relatively direct as cause of the disease (eg. high blood pressure), there is considerably much interaction between many risk factors and some have an indirect, mediated effect upon disease (Dzau et al., 2006; World Health Organization, 2009).

Many different risk calculators have been developed for physicians and health practitioners to assess total CVD risk (Simmonds and Wald, 2012; World Health Organization, 2007). One of the first risk estimation indexes was based on data from the Framingham Heart Study to describe the estimated 10-year risk of coronary heart disease (D'Agostino et al., 2008; Goff et al., 2014; World Health Organization, 2007). Later the index has been modified and a formula for calculating a gender-specific total CVD risk score, estimating the percentage risk of total CVD within the next 10 years was specified (D'Agostino et al., 2008). The Framingham Risk Score includes information on age, total cholesterol, high density lipoprotein (HDL) cholesterol, systolic blood pressure, blood pressure medication, diabetes, and smoking.

The FINRISK calculator was developed by the National Institute for Health and Welfare (THL) as a tool for health practitionaires and private persons to assess total CVD risk (Vartiainen et al., 2007). The calculator is based upon information about gender, age, total cholesterol level, HDL cholesterol level, systolic blood pressure, smoking status, diabetes status and parental history of acute myocardial infarction. It results in an estimation of a person's 10-year risk of total CVD.

The ideal cardiovascular health concept was launched by the American Heart Association in 2010 (Lloyd-Jones et al., 2010). The definition of an ideal cardiovascular health for adults consists of ideal levels in 7 established risk factors (Table 1). Since 2010 it has been reported that in adult populations over the world, mostly in high income countries, the prevalence of an ideal cardiovascular health is very low (Lloyd-Jones, 2014). In Americans, the prevalence of ideal cardiovascular health or meeting at least five of the seven ideal levels in different risk factors was reported to be around 12% (Folsom et al., 2011). For Finnish men and women the same was true in 3% and 8%, respectively (Peltonen et al., 2014).

Table 1   *Examples of ideal levels for the seven risk factors included in the definition for an ideal cardiovascular health as suggested by the American Heart Association. Adapted from Lloyd-Jones et al. (2010).*

Risk factor	Definition for ideal level
Smoking	Never or former smoker since at least 12 months
Body mass index	<25 kg/m^2
Physical activity	≥150 minutes at least moderate physical activity weekly OR ≥75 minutes of vigorous physical activity weekly
Diet	Including, but not limited to 4-5 of the following: eating fruits or vegetables daily AND eating fish at least two times a week AND consuming fiber-rich whole grains daily AND consuming less than 1500mg sodium per day AND consuming ≤450 kcal from sugar-sweetened beverages per week
Total cholesterol	<200 mg/dl (<5.18 mmol/L), without medication
Blood pressure	<120/<80 mmHg, without medication
Fasting serum glucose	<100 mg/dl (<5.6 mmol/L), without medication

Note: kg= kilogram; m=meters; mg=milligrams; kcal=kilocalories; dl=deciliters; mmol=millimole; L=liter; mmHg=millimeter of mercury

Cardiometabolic risk factors

Cardiometabolic risk factors refer to the biomarkers and anthropometric measures that are related with an increased risk of CVD. The most important cardiometabolic risk factors include high blood pressure (hypertension), elevated total cholesterol, elevated blood glucose (hyperglycemia) and obesity, all of which are among the top 6 leading risk factors for death worldwide (World Health Organization, 2009). Other important biomarkers that have been studied in relation to CVD risk include C-reactive protein (CRP), apolipoproteins A and B and fibrinogen (Emerging Risk Factors Collaboration et al., 2012; Ridker and Silvertown, 2008; Ridker, 2009).

A high blood pressure or hypertension is defined as a systolic blood pressure of 140 mmHg or higher and a diastolic blood pressure of 90 mmHg or higher, assessed as the average of at least two measurements (Working group appointed by the Finnish Medical Society Duodecim and the Finnish Hypertension Society, 2014). In year 2014 the global prevalence of high blood pressure was about 22% (World Health Organization, 2014). In Finland, almost 50% of men and 40% of women aged 30 years or older, have high blood pressure or use antihypertensive medication (Working group appointed by the Finnish Medical Society Duodecim and the Finnish Hypertension Society, 2014). According to national health examination study in Finland, population levels of systolic blood pressure have been decreasing since the 1970's, but a levelling off and even a small increase in the mean

diastolic blood pressure is observed between 2002 and 2012 (Borodulin et al., 2014b).

Cholesterol is an essential component in the body, transported in the blood by lipoproteins, HDL and low density lipoprotein (LDL) (Nelson, 2013). A high total cholesterol level (>5 mmol/L) is an established risk factor for CVD, but lipoprotein specific cholesterol levels are important as well (Nam et al., 2006; Nelson, 2013; Steinberg, 2005). Elevated LDL cholesterol levels (>3 mmol/L) and low HDL cholesterol levels (<1.0 mmol/L in men and <1.2 mmol/L in women) indicate an increased CVD risk. Serum triglycerides are acknowledged as a biomarker of CVD (Goldberg et al., 2011; Jacobson et al., 2007), with levels of >1.7 mmol/L interpreted as high (Working group set up by the Finnish Medical Society Duodecim and Finnish Society of Internal Medicine, 2013). However; the role of triglycerides in CVD is perhaps more likely as a marker of disease than an independent risk factor (Emerging Risk Factors Collaboration et al., 2009; Goldberg et al., 2011). In 2012 among Finnish adults aged 25 to 74 years, the mean serum total cholesterol was 5.3 mmol/L and 60% of adults had high total cholesterol above 5 mmol/L (Borodulin et al., 2014b). Also, men more often than women had elevated LDL cholesterol levels (12% vs. 10%), low HDL cholesterol levels (28% vs. 13%) and elevated triglyceride levels (7% vs. 3%).

An impaired glucose metabolism increases the risk of CVD (Schottker et al., 2016; World Health Organization, 2015). Glycated hemoglobin (HbA1$_c$) is a biomarker of long term glucose regulation, reflecting the glucose metabolism over the past 6 to 8 weeks (Goldstein et al., 2003; Working group appointed by the Finnish Medical Society Duodecim, the Finnish Society of Internal Medicine and the Medical Advisory Board of the Finnish Diabetes Society, 2016). A HbA1$_c$ level of ≥48 mmol/L or >6.5% is used as a definition of diabetes (Authors/Task Force Members et al., 2013; Working group appointed by the Finnish Medical Society Duodecim, the Finnish Society of Internal Medicine and the Medical Advisory Board of the Finnish Diabetes Society, 2016). Persons with an elevated HbA1$_c$ level can be referred to as pre-diabetic and it has been observed that there is an increased risk of CVD among these subjects (Schottker et al., 2016). However, studies that have measured either fasting glucose or glucose tolerance have found only a modest, almost non-significant association between an impaired glucose metabolism and CVD (Ford et al., 2010).

Obesity can be defined based on the Body mass index (BMI) that is calculated as the ratio of body weight in kilograms (kg) and height in squared meters (m) (kg/m²) (World Health Organization, 2000). A BMI between 18 and 24.9 kg/m² describes normal weight whereas a BMI lower than 18 kg/m² represents underweight and between 25 and 29.9 kg/m² represents overweight, respectively. A BMI ≥30 kg/m² is the definition for obesity (Working group appointed by the Finnish Medical Society Duodecim and the Finnish Association for the Study of Obesity, 2013). The prevalence of overweight and obesity is increasing worldwide, and overweight and obesity

are a leading cause of disease and death in high income countries (World Health Organization, 2009). According to recent population data, the mean BMI in Finland was 27.4 kg/m² with over half of the population being overweight or obese (Borodulin et al., 2014b). In both women and men the prevalence of obesity has been increasing during the past 40 years, even though a small levelling off in the trend for BMI has been detected between 2007 and 2012.

Even though many risk factors are common for all CVDs, there are evidence of a differential pattern of risk factors for stroke and ischemic heart disease (Hamer et al., 2011). The role of more novel risk factors such as C-reactive protein (CRP) (Hamer et al., 2011), apolipoprotein A and B (Simons et al., 2009), and fibrinogen in different CVDs is debated. Inflammation is an important step in the progression of atherosclerosis and CVD and therefore CRP as a marker of inflammation is held as a risk factor (Libby, 2006). The impact of different cardiometabolic risk factors on CVD risk may also differ across different populations and cultures (Liu et al., 2014).

Behavioral risk factors

The most established behaviors that influence the progression of CVD include smoking, diet, alcohol consumption and PA (World Health Organization, 2015). These are all listed among the top 10 leading causes of death in high-income countries (World Health Organization, 2009). In addition, increasing amount of evidence from the literature also suggest that sleep disturbances and sedentary time both are distinct risk factors for CVD (Dempsey et al., 2014; Dunstan et al., 2012a; Redline and Foody, 2011) having important independent associations with cardiovascular health (Borodulin et al., 2014a; Cappuccio et al., 2011; Jackson et al., 2015; Luyster et al., 2012; Tremblay et al., 2010).

Smoking predisposes both a direct and indirect risk of CVD with the risks being proportional to the time and amount of smoking (Burns, 2003; World Health Organization, 2014). The association between alcohol and CVD is more complex since low amounts of usage have been found to be related with a lower risk but high doses and regular consumption relate with an increased risk (Klatsky, 2015; World Health Organization, 2014). High alcohol consumption as well as poor diet including high consumption of saturated fats, salt and low amounts of dietary fibers, increase CVD risk (World Health Organization, 2015). Unfavorable diet and alcohol use negatively impact cardiometabolic risk factor levels such as blood cholesterol and blood pressure (World Health Organization, 2009)

People with several healthy behaviors are at lower risk of CVD mortality than people with no or only a few healthy behaviors (Eguchi et al., 2012; Odegaard et al., 2011). Health-related behaviors tend to cluster and there are increasing evidence that certain demographic characteristics such as male gender and lower socioeconomic status associate with the clustering of health

behaviors (Berrigan et al., 2003; Ding et al., 2014; Poortinga, 2007; Silva et al., 2013). A low socioeconomic status may also predict a worse cardiovascular risk profile over years to come (Kestilä et al., 2012). The population prevalence of patterns of clustered behaviors is higher than the product for estimated prevalence of independent behaviors (Berrigan et al., 2003; Ding et al., 2014; Silva et al., 2013).

In the following chapters are PA and sleep and their relationships with CVD risk discussed in more detail. Sedentary behaviors are in this study considered in the context of PA.

2.2 PHYSICAL ACTIVITY

PA is defined as any bodily movement caused by muscle actions with a concomitant increase in energy expenditure (Caspersen et al., 1985). Planned, repetitive PA in order to improve one's physical fitness is defined as exercise (Caspersen et al., 1985). Dimensions of PA include its type (e.g. walking, running, gardening), duration (how long PA takes place), frequency (how often PA is undertaken), and intensity (the effort needed for PA) (Strath et al., 2013). A measure for the intensity of PA relative to rest, is the metabolic equivalent (MET), a multiple of the resting metabolic rate. One MET equals a resting oxygen consumption of 3.5 ml/kg/minute (Ainsworth et al., 2011; Strath et al., 2013). Low intensity PA is defined as a MET <3.0, moderate intensity as MET between 3.0 and 5.9 and when MET ≥6.0 PA is considered as vigorous (Strath et al., 2013). Physical inactivity can be defined as no PA beyond light-intensity activity required for daily living (The U.S. Department of Health and Human Services, 2008).

The human body is evolved to meet the requirements of travelling long distances by feet in order to survive as hunters and gatherers (Bramble and Lieberman, 2004). The PA related with work and daily living has been sufficient to stress the cardiovascular and metabolic systems of the body and further been protective against related diseases (Archer and Blair, 2011). However, the modern society offers people more and more opportunities to remain sedentary and PA is no longer a requirement for survival, but rather a leisure time hobby (Archer and Blair, 2011). Leisure time PA (LTPA) directly relates with socioeconomic status, particularly in high-income countries (Bauman et al., 2012; Mäkinen et al., 2012). Other important correlates of PA in adults are male gender, younger age, better reported health and self-efficacy, as well as previous adulthood PA (Bauman et al., 2012).

2.2.1 SEDENTARY BEHAVIORS

Sedentary behaviors are classified as any waking behaviors of less than 1.5 METs, including activities both sitting and lying down (Pate et al., 2008; Sedentary Behaviour Research, 2012). Sedentary behaviors have been

suggested to be a risk factor for CVD independent of PA (Same et al., 2016). Television (TV) viewing and other screen time behaviors are common leisure time and domestic sedentary behaviors, while sedentary behaviors in occupational settings are often job-related screen-based sitting, and transportational sedentary behaviors include sitting in motorized vehicles (Owen et al., 2011).

There is increasing information available about sedentary behavior epidemiology and it seems that adult persons spend on average two thirds of their time awake as sedentary (Diaz et al., 2016; Matthews et al., 2008). Among Europeans, 18.5% report sitting more than 7.5 hours daily, with a median sitting time of 5 hours across Europe (Loyen et al., 2016). In 2002, the mean daily sitting time in Finland, as assessed by self-report was 6.4 hours (Borodulin et al., 2014a). Objectively assessed daily sedentary time was on average 9 hours for adults in Finland in 2011 (Husu et al., 2014). High education and currently being in working life with a non-manual occupation are associated with higher sedentary time (Borodulin et al., 2014a; Harrington et al., 2014; Loyen et al., 2016).

2.2.2   ASSESSMENT OF PHYSICAL ACTIVITY IN POPULATION STUDIES

There are mainly four domains where PA commonly can take place: occupation, household, transportation and leisure time (Strath et al., 2013). Domains of PA are important for the understanding of the context associated with PA (Kohl and Murray, 2012b). In large-scale studies it has so far been more convenient to assess PA by self-report methods, including interviews, questionnaires, and diaries (Ainsworth et al., 2015; Kohl and Murray, 2012b; Strath et al., 2013). Questionnaires and other self-report instruments usually assess the respondent's PA within one or several domains over a defined period (from one week to over a year), or on a global level (Ainsworth et al., 2015; Shephard, 2003). Self-report methods are generally accepted by the research and medical communities, they are of low burden to the respondent and easy and cost-effective to use in large-scale population studies (Ainsworth et al., 2015). The main concern related to self-report instruments is recall bias that can lead to inaccurate or selective reporting of activities, or over- and underestimation of behaviors (Ainsworth et al., 2015; Kohl and Murray, 2012b). There is also limited ability to assess the intensity of PA from questionnaires (Shephard, 2003).

Tools for objective PA assessment include devices such as pedometers, heart rate monitors, and accelerometers (Strath et al., 2013). There is, however, no golden standard device among tools to objectively assess free-living PA (Ainsworth et al., 2015). The technological development of the devices has enabled and increased their use in large population-based studies. Objective measures are less prone to reporting bias and can provide more precise measures of physiological and mechanical components that

relate to PA (Ainsworth et al., 2015). However, weaknesses with objective measurement include the inability to separate between different types of PA, the possibility of false or interfered sampling and issues related to data reduction and processing. The transformation steps are essential for the conversion of raw data into PA outcomes (Strath et al., 2013).

2.2.3 ASSESSMENT OF SEDENTARY BEHAVIORS IN POPULATION STUDIES

Many large population studies have relied on self-report methods to assess sedentary behaviors (Borodulin et al., 2014a; Chau et al., 2014; Staiano et al., 2014). Self-report measures of sedentary behaviors include questionnaires, recalls and behavioral logs, with some assessing sitting while some only define the context of sedentary behavior such as viewing TV (Healy et al., 2011; Same et al., 2016). TV viewing time is the most commonly measured non-occupational sedentary behavior in adults (Clark et al., 2009). The correlates of sedentary behavior vary significantly by the type of sedentary behavior that is measured (Rhodes et al., 2012). Therefore when assessing sedentary behaviors, it is important to keep in mind that sedentary behavior is not a single construct and also domain-specific sedentary behaviors should be assessed (Healy et al., 2011; Rhodes et al., 2012). Having both self-report and objective measures is the optimal means of assessment in population studies (Gibbs et al., 2015; Healy et al., 2011).

Objective assessment of sedentary behavior in population studies is becoming more common and results of objectively measured sedentary time are being reported in many populations (Diaz et al., 2016; Husu et al., 2014; Stamatakis et al., 2012) Accelerometry can provide a more accurate measurement of time spent sedentary as compared to self-report methods (Healy et al., 2011). Objective measurements can also provide more exact information on the patterning of sedentary time (Gibbs et al., 2015). However, there are several measurement issues such as data cleaning, wear-time and cut-off values that are important to consider when sedentary behaviors are assessed objectively (Healy et al., 2011).

2.2.4 CURRENT RECOMMENDATIONS FOR PHYSICAL ACTIVITY

The current guidelines for all adults are to have at least 150 minutes of at least moderate intensity aerobic PA or alternatively at least 75 minutes of vigorous intensity aerobic PA every week (Haskell et al., 2007; World Health Organization, 2010). Daily life activities of moderate or vigorous intensity, such as gardening or brisk walking for errands, performed in bouts of at least 10 minutes can be counted towards the recommendation. It is advisable to also include at least moderate intensity muscle-strengthening activity at least two times a week (Haskell et al., 2007; World Health Organization, 2010). The Finnish recommendations follow closely the international guidelines

(Working group appointed by the Finnish Medical Society Duodecim and the Executive Board of Current Care, 2016). There are special guidelines for children and youth and for older adults as well as people with disabilities (The U.S. Department of Health and Human Services, 2008; Working group appointed by the Finnish Medical Society Duodecim and the Executive Board of Current Care, 2016).

Insufficient PA can be defined as not meeting the guidelines for aerobic PA (Lee et al., 2012; World Health Organization, 2010). Globally the prevalence of insufficient PA among adults (18 years or older) in 2010 was 27% for women and 20% for men, respectively (World Health Organization, 2014). In Finnish working-aged adults the prevalence of LTPA has increased, while the prevalences of both OPA and commuting PA (CPA) have decreased during the past 40 years (Borodulin et al., 2016). In 2012, about one fifth of the adults were physically inactive (Borodulin et al., 2016).

2.2.5   CURRENT RECOMMENDATIONS FOR SEDENTARY BEHAVIOR

There is to date no recommendation for maximum amount of sedentary behaviour to consider for health effects. However, in 2015 the Finnish Ministry of Social Affairs and Health launched the first ever national recommendations to decrease sitting (Working group for health promoting physical activity/Ministry of Social Affairs and Health, 2015). In these recommendations, the children, adults, as well as the elderly, should avoid long continuous time spent sitting or being sedentary, and are encouraged to break up prolonged time spent sitting during the day. There are also some international guidelines for PA which also include recommendations for adults to avoid prolonged time spent sedentary (Australian Government, The Department of Health, 2014; The Canadian Society for Exercise Physiology, 2012).

2.3   SLEEP

Sleep is a fundamental behavior for human survival, ensuring optimal physiological and behavioral conditions for restorative metabolic processes to occur (Borbely et al., 2016; Luyster et al., 2012). For sleep to be restorative a repeated and continuous progress through four different stages of sleep is required. The four stages of sleep are characterized by increasing depth of sleep and different brain and autonomous nervous system activity (Jackson et al., 2015).

According to the two-process model of sleep regulation sleep is thought to happen as an interplay between two processes, the circadian and the homeostatic process (Borbely et al., 2016). The homeostatic drive to sleep, also called the process S, builds up with time awake and is reduced during sleep. The circadian process C refers to the internal clock located in the

suprachiasmatic nucleus in the hypothalamus that control the fluctuation in body rhythms such as temperature and melatonin (Borbely et al., 2016). The circadian clock can be entrained by environmental stimuli, primarily light, but also by activity (Borbely et al., 2016; Luyster et al., 2012; Morris et al., 2012). Energy metabolism is linked with the circadian process and relative to the internal clock it determines the phase of sleep-wake rhythm. The human sleep-wake rhythm is a marker of the interplay between process C and process S and some of the detrimental effects of sleep deprivation are due to disruption in the synergy between the two processes (Borbely et al., 2016).

The needed amount of sleep is individual, but there is evidence that women need more sleep and actually sleep longer than men and also that sleep duration decrease with increasing age (Ferrara and De Gennaro, 2001; Jackson et al., 2015; Kronholm et al., 2006). Further, women more often than men report insufficient sleep, i.e. sleep duration shorter than the self-reported need for sleep (Hublin et al., 2001). The population average sleep duration is 7 to 8 hours and people sleeping far more or less than this average are called long and short sleepers, respectively (Ferrara and De Gennaro, 2001). From a population perspective short sleep is more common than long sleep (Luyster et al., 2012) but despite common belief, there is no scientific support to adults sleeping less nowadays than before (Youngstedt et al., 2016).

Sleep quality and sleep duration are separate even if partly overlapping and correlated characteristics of sleep (Buysse et al., 2010; Grandner and Drummond, 2007; Grandner et al., 2010). Sleep quality issues are often referred to as insomnia symptoms or insomnia-like symptoms that include difficulties initiating or maintaining sleep, non-restorative sleep or global dissatisfaction with sleep (Ohayon, 2002). Depending on the way to operationalize sleep quality the average population prevalence of poor or disturbed sleep vary between 6% and 30% (Ohayon, 2002). In Finland, epidemiological data from 1972 to 2013 indicate a continuing considerable increase in occasional insomnia-like symptoms in the working-aged population (Kronholm et al., 2008; Kronholm et al., 2016). Sleep related problems more often occur in women than in men, and are also more common along with increasing age (Barclay and Gregory, 2013; Kronholm et al., 2006; Ohayon, 2002; Sivertsen et al., 2009).

2.3.1   ASSESSMENT OF SLEEP IN POPULATION STUDIES

In large study settings sleep is most often assessed by self-report with the most common question being: "How many hours do you sleep on an average night?" (Ferrie et al., 2011) , providing either open (Buman et al., 2014a; Kronholm et al., 2011; McClain et al., 2014) or categorized response alternatives (Hublin et al., 2007; Yoon et al., 2015). There are also some questionnaires that are being used in population studies to assess both the duration and quality of sleep, as for example the Pittsburgh Sleep Quality

Index (Buysse et al., 1989; Casas et al., 2012; Soltani et al., 2012). It is also possible to assess times for going to bed and getting up from bed (Kronholm et al., 2006; Stenholm et al., 2011), however the calculated difference between the reported times do not necessarily reflect sleep duration as much as the time spent in bed. Self-reported measures of sleep in population-based research can be held sufficiently valid when compared to polysomnography (Zinkhan et al., 2014) but inconsistency between self-report and accelerometry has been reported (Girschik et al., 2012).

The golden standard method to measure sleep is the polysomnography that simultaneously measures the electrical activity of the brain, heart, and muscles, movements of the eye and respiratory actions while the person is at sleep (Knutson, 2010; Krystal and Edinger, 2008). In large scale studies polysomnography is an inconvenient method due to its practical and economical requirements. Developments in accelerometer technology have enabled the increasing use of accelerometry as a means to assess sleep in large scale settings (Ferrie et al., 2011). The agreement between wrist worn accelerometers with polysomnography has shown to be superior to that of hip placement with polysomnography (Zinkhan et al., 2014). The validity of wrist worn accelerometers in sleep assessment seem to be accepted in the literature relative to polysomnography, at least in terms of total sleep time and sleep efficiency (Girschik et al., 2012; Zinkhan et al., 2014). In middle-aged the day-to-day variation in actigraphy is high, whereas the year-to-year variation is not significant, indicating that one multiple day collection will likely be reflecting a true habitual average for that person (Knutson et al., 2007).

2.3.2 CHRONOTYPE

Chronotype refers to the intrinsic circadian process (process C) that underlie our timing of sleep (Adan et al., 2012; Di Milia et al., 2013; Dobree, 1993). According to differences in the timing of sleep and wake, and differences in preferences for performing physical and mental tasks, different chronotypes can be identified (Adan et al., 2012; Roenneberg et al., 2007). Those with early bed times and morning awakenings and high morning alertness are called morning types and those with peak alertness later in the afternoon with a preference for later bed times are called evening types (Adan et al., 2012; Di Milia et al., 2013; Roenneberg et al., 2007). Approximately 60% of people do not belong to either of these two extreme chronotypes, but rather have an intermediate type (Adan et al., 2012).

The chronotype is affected by individual and environmental factors such as age, gender, daylight and activity (Adan et al., 2012; Gangwisch, 2009). There is some evidence from cross-sectional data that chronotype shifts with age, with young children being morning type and a pronounced tendency to evening type during adolescence where after morning preference again becomes more prevalent with increasing age (Adan et al., 2012; Roenneberg

et al., 2007). Women experience the maximum in eveningness at an earlier age than men, and women also have a shorter intrinsic circadian period than men (Adan et al., 2012). However, a different distribution of morning type and evening type by gender is not altogether supported by the literature (Paine et al., 2006).

In Finland the population prevalence of evening types among men seem to have increased from the 1980's to the 2000's (Broms et al., 2014) while the trend among women has not been reported. In a large sample of mainly central European participants a significant change in the average chronotype to more evening types from 2002 to 2010 was observed (Roenneberg et al., 2012).

Social jetlag describes the discrepancy in social vs. biological time (Roenneberg et al., 2007; Wittmann et al., 2006) and it develops as a result of living against one's own circadian rhythm. The risk for social jetlag is often higher in evening types because they are more often forced to follow an earlier social rhythm compared to their intrinsic circadian phase (Roenneberg et al., 2012; Wittmann et al., 2006).

2.3.3 ASSESSMENT OF CHRONOTYPE IN POPULATION STUDIES

The chronotype is not directly observable, but repeated measurements of the diurnal fluctuation in body temperature or hormones such as cortisol and melatonin provide the closest measure of our circadian typology (Di Milia et al., 2013). Different self-report tools have been created to provide non-invasive, more practical ways to assess chronotypes, particularly in large-scale studies (Di Milia et al., 2013). The morningness-eveningness questionnaire (MEQ) by Horne and Östberg in 1976 (Horne and Östberg, 1976) is the first and most widely used self-report measure of chronotype (Di Milia et al., 2013). Since then several other questionnaires and ways to assess this trait have been developed (Adan et al., 2012; Di Milia et al., 2013; Roenneberg et al., 2007). One discussed limitation with self-report questionnaires of chronotype is the cutoff values that are being used to distinguish between different chronotypes (Di Milia et al., 2013; Natale and Cicogna, 2002; Randler and Vollmer, 2012).

2.4 INTERRELATIONSHIPS BETWEEN PHYSICAL ACTIVITY AND SLEEP

Associations between PA and sleep are likely bidirectional with effects operating through many different physiological and psychological pathways (Chennaoui et al., 2015; Driver and Taylor, 2000). Both short and long sleep duration is often related with low levels of PA (Grandner and Drummond, 2007; Grandner et al., 2010; Xiao et al., 2014) and high PA compared to none or low PA relate with more favorable sleep (Fabsitz et al., 1997; Feng et al.,

2014; Fogelholm et al., 2007; Morgan, 2003). From the energy expenditure point of view, sleep and vigorous PA are situated in different ends of a continuum, with sedentary behaviors and lighter intensity PA in between the two (Tremblay et al., 2010). The close relationship between PA and sleep is also evident when considering daily use of time as the available 24 hours of a person's day are distributed between sleep, sedentary behavior and PA in different proportions (Aadahl et al., 2013; Buman et al., 2014b; Tudor-Locke et al., 2011).

There are several review articles on intervention studies concluding that both acute and regular PA positively associate with better sleep (Kredlow et al., 2015; Kubitz et al., 1996; Yang et al., 2012; Youngstedt et al., 1997). The sleep enhancing effects of PA can be working through changes in body temperature, circulating hormone levels, inflammatory processes and mood (Chennaoui et al., 2015). While the effects of sleep upon PA are thought to act through the same but reciprocal pathways as PA upon sleep, so far only the psychological effects can be concluded on (Chennaoui et al., 2015). Reviews also point out that at least gender, age, fitness level, and PA duration are important moderators of the PA and sleep association (Kredlow et al., 2015; Kubitz et al., 1996; Youngstedt et al., 1997). More evidence is needed regarding the modifying effect of factors such as light exposure, body composition and diet (Chennaoui et al., 2015).

2.4.1 EPIDEMIOLOGICAL FINDINGS

Physically active persons more often report mid-range than short or long sleep, which has been shown in Korean adults (Yoon et al., 2015), Chinese women (Tu et al., 2012), British men and women (Stranges et al., 2008) and U.S. adults (Shankar et al., 2011). Also in Finland, adults with mid-range sleep are more often physically active than short or long sleepers (Kronholm et al., 2006). Furthermore, physically active adults less often report having self-estimated insufficient sleep than physically inactive adults (Hublin et al., 2001). However, in highly active groups such as athletes, the actual sleep duration is often lower than the mid-range defined in a general population (Lastella et al., 2015). Indeed, also in some general adult populations low PA is more prevalent among those with mid-range or long sleep than those with short sleep (Bellavia et al., 2014; Stranges et al., 2008). Recent findings in physically active preindustrialized societies suggest that these people have shorter habitual sleep duration than populations from less physically active, industrialized societies (Yetish et al., 2015).

There are some evidence that the associations between PA and sleep are affected by age and gender. A direct linear relationship between PA and longer sleep was observed for young U.S. men (20-39 year olds), while in women the same trend occurred only among the middle-aged (aged 40-59) (McClain et al., 2014). Kronholm et al. (2006) observed a significant

interaction between age and LTPA on sleep duration deviation of Finnish adults.

In many cross-sectional epidemiological studies have associations between physical inactivity and more sleep complaints or poorer sleep quality been reported (Kim et al., 2000; Laugsand et al., 2011; Ohida et al., 2001; Soltani et al., 2012). Particularly in older persons, sleep quality is often reported being not so good among the physically inactive than the physically active persons (Brassington and Hicks, 1995; Foley et al., 2004; Soltani et al., 2012). In contrast to LTPA, manual and physically demanding work relates with poor sleep and sleep disturbances (Akerstedt et al., 2002; Green et al., 2012; Soltani et al., 2012), demonstrating to a part of the complex interplay between PA and sleep.

A few reports can be found that conclude that evening chronotype associates with lower PA levels (Haraszti et al., 2014; Schaal et al., 2010) or more time in sedentary behaviors (Kauderer and Randler, 2013; Urban et al., 2011) than earlier chronotype. Interestingly, young evening type persons report themselves to have less confidence in PA and less often to engage in PA as a means to cope with sleepiness than do earlier chronotypes (Digdon and Rhodes, 2009). In the general population, PA is among the most typically self-reported non-pharmacologic management of poor sleep (Aritake-Okada et al., 2009; Vuori et al., 1988).

Studies attempting to reveal a bidirectional association between PA and sleep have not found any significant predictive value of PA for sleep whereas poor sleep quality does seem to predict lower future PA (Haario et al., 2012; Holfeld and Ruthig, 2014). Similarly has an extended time in bed found to be related with a future poor physical functioning in a sample of older (≥65 years) adults (Stenholm et al., 2011). Results from the Aerobics Centre Longitudinal Study cohort suggested that a decline in cardiorespiratory fitness between the ages of 51 and 56 that is thought to mimic reductions in PA levels associate with higher incidence of poor sleep (Dishman et al., 2015).

Lang et al. (2016) reviewed studies that focused on the relationship between PA and sleep in adolescents and young adults. According to their review, it is evident that higher PA levels are related with better sleep in this age group, but there are many methodological shortcomings in the reviewed studies, mainly regarding measurement of PA and sleep. The studies that assessed both PA and sleep with either objective or subjective methods generally reported larger effect than studies combining the approaches (Lang et al., 2016).

Where the association between PA and sleep has received increasing attention, the associations between sleep and sedentary behavior have been studied less and findings are mixed. In the study of McClain et al. (2014) no significant differences in sedentary time were observed between people with different sleep durations. Somewhat contrary, data from the American Time Use Survey indicate that persons with short or long sleep reported more time

spent watching TV (Basner et al., 2007). A recent study including a multinational sample of European adults, show that even if long sleepers spend 3.2% more time being sedentary while awake than the mid-range sleepers do, a significant association was only observed between short sleep and more screen time (Lakerveld et al., 2016).

2.4.2 INTERVENTION STUDIES

Findings from intervention studies suggest that PA can improve sleep, while all possible pathways are not fully clarified (Chennaoui et al., 2015). Kredlow et al. (2015) examined in their meta-analysis 66 experimental studies about the effect of acute and regular PA on sleep. They concluded that the acute effects of PA on sleep are beneficial, though small. Effects of regular PA on sleep on the other hand were stronger and of moderate size with respect to overall sleep quality (Kredlow et al., 2015; Yang et al., 2012). Long PA training programs often yield beneficial changes in physical fitness level that eventually can be one cause of improved sleep at least in persons with low baseline fitness (Lira et al., 2011; Littman et al., 2007).

The benefits of PA on sleep quality can be observed particularly in older persons when PA consists of at least moderate intensity aerobic activities (Kukkonen-Harjula, 2015). There is some support from intervention studies that exercise is an as effective treatment for poor sleep or sleep disturbances as hypnotic drugs in middle-aged and older persons with chronic sleep disturbances (Passos et al., 2012). The adherence to PA programs is an important factor resulting in more beneficial effects of PA on sleep quality (Kredlow et al., 2015).

The timing of PA relative to sleep is also an important factor to consider, and generally it is thought that the most beneficial effects of PA on sleep quality are achieved when PA is performed 3 to 4 hours before bedtime (Kukkonen-Harjula, 2015). However, there are also findings that PA performed near bedtime in the evening does not relate with worsened sleep (Buman et al., 2014a; Myllymaki et al., 2012), but rather can it even have a positive effect on sleep quality (Benloucif et al., 2004; Buman et al., 2014a; Flausino et al., 2012; Vuori et al., 1988). Thus, among initially healthy individuals with no reported sleep problems there is few support to restrict evening PA as long as it does not come with a cost on sleep duration (Chennaoui et al., 2015).

Experimental studies performed in laboratory settings have shown that restricting sleep results in lower subsequent PA levels (Bromley et al., 2012; Schmid et al., 2009), and restricting PA in habitually active individuals worsen subsequent sleep, respectively (Hague et al., 2003). Previous sleep habits seem to impact the magnitude of the effect (Chennaoui et al., 2015). Also, a discordant timing of sleep relative to one's intrinsic circadian rhythm associates with lower PA (Rutters et al., 2014).

2.5 PHYSICAL ACTIVITY, SLEEP AND CARDIOVASCULAR DISEASES

2.5.1 ASSOCIATIONS OF PHYSICAL ACTIVITY WITH CARDIOVASCULAR DISEASES

Aerobic PA and exercise causes favorable adaptations in the vasculature and energy metabolism (Lavie et al., 2015), with effects over long term upon blood pressure, glucose and fat metabolism, autonomic nervous system balance and finally health and disease (Kohl and Murray, 2012a; Powell et al., 2011). The importance of PA in the prevention of CVD is evident already at a young age (Pahkala et al., 2011). The positive relationship between a physically active, even highly active lifestyle at a younger age and the lower risk of CVD does not necessarily sustain throughout life (Paffenbarger and Lee, 1998). Low levels of PA in mid-life strongly associate with the risk of CVD incidence, as the disease often become prevalent later in life (Conroy et al., 2005; Paffenbarger and Lee, 1998).

Findings from cross-sectional, longitudinal as well as intervention studies most consistently show that regular PA is favorably associated with good HDL cholesterol, triglycerides and apolipoprotein B levels (Ahmed et al., 2012) and great deal of evidence support the benefits of PA on insulin sensitivity which has an important role in the control of blood glucose levels (Roberts et al., 2013). There is also evidence from both cross-sectional and longitudinal studies that PA associates with less systemic low grade inflammation (Ahmed et al., 2012; Roberts et al., 2013), lower BMI and waist circumference (Glazer et al., 2013; Waller et al., 2008). Despite the fact that PA only has modest effects for the reduction of body weight as compared to diet, the effects of PA on distribution of body fat are highly important for cardiovascular health (Myers et al., 2015).

One potential pathway for the effect of PA upon lower CVD risk is through an improved cardiorespiratory fitness (Archer and Blair, 2011; Myers et al., 2015). Low levels of cardiorespiratory fitness increase the risk of CVD and premature mortality (Archer and Blair, 2011), particularly in persons with other co-occurring risk factors (Berry et al., 2011) and poor metabolic control (Roberts et al., 2013). The role of cardiorespiratory fitness for CVD thus partly overlaps with the one of PA (DeFina et al., 2015; Myers et al., 2015).

Volume and intensity of PA show a dose-response relationship with total mortality (Lee and Paffenbarger, 2000; Lee and Skerrett, 2001; Oja, 2001; Samitz et al., 2011) and CVD mortality (Myers et al., 2015; Sattelmair et al., 2011). Reductions in all-cause mortality risk are most rapid at lowest volumes of PA, indicating that some PA is better for health than none (Powell et al., 2011). The relationship between PA and CVD mortality was first studied and observed in terms of OPA (Morris et al., 1953), and later the relationship has been confirmed also for LTPA (Archer and Blair, 2011). According to a meta-analysis conducted in 2012, LTPA associates with a

reduced CVD risk in a clear dose-response manner, with moderate levels of LTPA decreasing CVD risk between 10% and 20% and high levels of LTPA between 20% and 30%, respectively (Li and Siegrist, 2012). Similarly moderate OPA levels reduce the CVD mortality risk by 10 to 20%, but higher levels do not consistently associate with a lower CVD risk (Holtermann et al., 2012; Li and Siegrist, 2012). The findings are inconsistent on CPA and CVD risk, (Autenrieth et al., 2011; Hamer and Chida, 2008), as they are on household or domestic PA and CVD (Autenrieth et al., 2011; Sisson et al., 2009; Stamatakis et al., 2007).

There are some gender differences in the associations between PA and CVD outcomes. According to a meta-analysis of 33 epidemiological studies the association between PA and risk of coronary heart disease was clearly stronger in women than in men (Sattelmair et al., 2011). Women with high LTPA level showed a 33% lower risk compared to 22% observed in men, respectively. Furthermore, among women compared to men, a more evident dose-response association between PA and risk of CVD was observed (Sattelmair et al., 2011). CPA often show a more strong association with lower CVD risk in women than in men (Hamer and Chida, 2008). In Finnish adults, CPA associated with lower occurrence of coronary heart disease and risk of CVD mortality in women only, whereas other domains of PA (leisure and occupation) associated with lower occurrence and risk in both genders (Barengo et al., 2004; Hu et al., 2007). Different findings regarding OPA were observed in Danish employees, where higher OPA was related with higher all-cause mortality and myocardial infarction risk in men with low and moderate levels of LTPA, but no associations were observed in women (Holtermann et al., 2012).

2.5.2   ASSOCIATIONS OF SEDENTARY BEHAVIOR WITH CARDIOVASCULAR DISEASES

High levels of sedentary behavior have been concluded to increase CVD mortality risk (Ford and Caspersen, 2012; Same et al., 2016; Wilmot et al., 2012), CVD incidence (Borodulin et al., 2014a; Same et al., 2016) and to negatively influence several cardiometabolic risk factors (Chau et al., 2012; Staiano et al., 2014; Tremblay et al., 2010). The increasing literature in the field suggest that sedentary behaviors associate with cardiovascular health independently of PA (Dunstan et al., 2012a; Healy and Owen, 2010; Katzmarzyk et al., 2009). Sedentary behaviors do not necessarily have the directly inverse responses on cardiometabolic health compared to PA, but by affecting same biological processes they can influence the physiological responses and adjustments to PA (Tremblay et al., 2010). Sedentary behaviors can cause alterations in lipid and glucose uptake and some evidence also exist of vascular changes as a consequence of sedentary behavior (Dempsey et al., 2014; Tremblay et al., 2010).

So far the literature mainly supports associations between longer time spent sitting and unfavorable cardiometabolic risk factors such as waist circumference, glucose metabolism, cholesterol and CRP (Howard et al., 2015; Staiano et al., 2014; Stamatakis et al., 2012). Especially leisure time sitting by TV has gathered evidence of a detrimental relationship with health outcomes (Chau et al., 2014; Gardiner et al., 2011; Hsueh et al., 2016). However, this relationship is partly mediated by eating behaviors (Heinonen et al., 2013). Results for occupational sedentary behavior seems to suggest less definite associations at least with CVD mortality (Stamatakis et al., 2013).

PA may not directly make up for effects of prolonged sedentary behavior (Ford and Caspersen, 2012), but breaking up prolonged sedentary time (Dempsey et al., 2014; Dunstan et al., 2012b), or replacing daily sedentary time with equal amounts of a physically more active behavior (Aggio et al., 2015), have been observed to associate with lower cardiometabolic risk factors and better cardiovascular health. However, so far the evidence regarding the healthiness of breaking up prolonged sitting suffers from many shortcomings (Chastin et al., 2015a). Observational studies cannot conclude on an association between breaking up sedentary behavior and cardiometabolic risk factors other than BMI, and experimental evidence is most consistent only in suggesting that frequently interrupting sitting improves the postprandial glycemic and insulin response (Chastin et al., 2015a).

2.5.3 ASSOCIATIONS OF SLEEP WITH CARDIOVASCULAR DISEASES

There is growing evidence from epidemiological studies that a habitual sleep duration deviating from the population mean associates in a U-shaped manner with risk of total mortality (Cappuccio et al., 2010; Gallicchio and Kalesan, 2009), with CVD (Sabanayagam and Shankar, 2010), obesity and impaired glucose metabolism (Knutson, 2010; Mezick et al., 2011; Spiegel et al., 2009). Short sleep duration has been associated with increased coronary heart disease and stroke mortality (Cappuccio et al., 2011), while long sleep duration seems to associate with total CVD mortality (Cai et al., 2015; Gallicchio and Kalesan, 2009). In Finnish adults, self-reported short and long sleep duration as compared to mid-range sleep, was found to associate with higher CVD incidence and mortality, but in women only (Kronholm et al., 2011).

Men and women with a high Framingham Risk Score have been reported more likely to have short sleep (Matthews et al., 2011) and poor sleep (Cintra et al., 2012), as measured by polysomnography. Compared to a mid-range sleep, those with short sleep have an increased risk of obesity, impaired glucose metabolism, and hypertension, which furthermore can be related with risk of CVD (Knutson and Van Cauter, 2008; Knutson, 2010; Spiegel et al., 2009). Also long sleep as compared to mid-range sleep has been observed

to associate with unfavorable cardiometabolic risk factor levels (Buxton and Marcelli, 2010; Knutson, 2010). Findings from epidemiological, as well as experimental studies, also suggest a U-shaped association between sleep duration and inflammation, but many findings are contradictory and a full consensus is still lacking (Grandner et al., 2013).

The role of long sleep as a risk factor for CVD is debated since the mechanisms linking long sleep duration with for example abnormal glucose metabolism or poor cardiometabolic health are not understood and have not been explored thoroughly (Anothaisintawee et al., 2016; Knutson and Turek, 2006). It is discussed that long sleep may be a marker of disease or ill health and therefore show relationships with CVD (Badran et al., 2015; Cappuccio et al., 2011; Knutson and Turek, 2006; Stamatakis and Punjabi, 2007). Potential pathways between short sleep and cardiometabolic risk include increased feeling of hunger, lower brain glucose utilization, increases in growth hormone and cortisol releases, and increased sympathetic nervous activity (Knutson, 2010).

There are some controversial findings whether sleep quality is related with cardiometabolic health independently of sleep duration or not (Altman et al., 2012; Bansil et al., 2011). However, disturbed sleep has been observed to be associated with higher odds of poor general health, obesity, high blood pressure, elevated blood glucose and mortality (Buxton and Marcelli, 2010; Grandner et al., 2010; Knutson, 2010). Insomnia or insomnia-related symptoms have been found to precede deaths due to myocardial infarction or coronary heart disease (Schwartz et al., 1999). The severity and the cumulative number of sleep related problems seem to increase the risk of acute myocardial infarction (Laugsand et al., 2011) and coronary heart disease risk (Loponen et al., 2010). Furthermore, the joint association between sleep problems and metabolic disorders with coronary heart disease risk is more than multiplicative (Loponen et al., 2010).

Evening chronotypes are reported more often than earlier chronotypes to suffer from poor (Merikanto et al., 2012) and misaligned sleep, also referred to as social jetlag (Wittmann et al., 2006). In laboratory conditions, circadian misalignment, i.e. living in desynchrony with one's internal clock, predisposes healthy adults to decreased insulin sensitivity, an inverse cortisol profile over the day (Scheer et al., 2009), higher blood pressure and increase in inflammatory biomarkers (Morris et al., 2016). These findings are partly supported by observational studies that have shown misaligned sleep to associate with obesity (Roenneberg et al., 2012), insulin sensitivity, adiposity and higher cholesterol levels (Wong et al., 2015).

Furthermore, in epidemiological studies, evening chronotype has been observed to associate with poor general health (Haraszti et al., 2014; Paine et al., 2006), poor glycemic control in type 2 diabetics (Osonoi et al., 2014) and with type 2 diabetes, BMI, waist circumference and hypertension in a general adult sample (Merikanto et al., 2013). However, results regarding separate risk factors including total cholesterol, LDL cholesterol, glucose tolerance

and systolic blood pressure were on average lower for evening types than they were for morning types, thus complexing the picture as a whole (Merikanto et al., 2013). The role of both our behaviors and our circadian system need to be understood in order to fully predict effects of circadian misalignment on health outcomes (Scheer et al., 2009).

2.5.4 INTERACTION OF PHYSICAL ACTIVITY AND SLEEP FOR CARDIOVASCULAR DISEASES

Many studies of sleep and CVD may control for PA level in the analyses, but there are only few studies that have examined the interaction of PA and sleep with CVD. Among Australian middle-aged and older adults, a U-shaped association between sleep duration and heart disease, stroke, diabetes and elevated blood pressure was observed, with a significant joint association of low PA and short sleep with stroke (Magee et al., 2012). Stroke was significantly more prevalent in those with short sleep duration and not meeting recommended levels of PA, than in those with short sleep duration but meeting PA recommendations (Magee et al., 2012). Evidence from the Netherlands, China and Japan show that clustering of traditional behavioral risk factors (PA, smoking, alcohol consumption, diet) and sleep duration strongly associate with fatal CVD (Eguchi et al., 2012; Hoevenaar-Blom et al., 2014; Odegaard et al., 2011). It has been proposed that almost two thirds of fatal CVD events could theoretically be prevented by adopting sufficient PA, healthy diet, non-smoking, moderate alcohol consumption and sufficient sleep (Hoevenaar-Blom et al., 2014).

A review by Pepin et al. (2014) suggest that PA and sleep can interact to influence fatal or nonfatal CVD risk, but more research simultaneously targeting PA, sedentary behaviors and sleep is needed. The interaction between PA and sleep for CVD mortality has to the best knowledge only been studied in two different cohorts with controversial findings. PA was found to moderate the association between long sleep duration and CVD mortality among Swedish adults (Bellavia et al., 2014), while no significant interaction between PA and sleep was detected in a large U.S. cohort (Xiao et al., 2014). In the U.S. cohort also the interaction between sleep and TV viewing time was analyzed, but the result was non-significant.

According to substitution modelling it has been suggested that PA and sleep have a synergistic effect on cardiometabolic risk factors (Buman et al., 2014b) and that replacing time spent sedentary among persons sleeping less than 7 hours with an equal amount of time either sleeping or in PA, decreases the odds of mortality (Stamatakis et al., 2015). It is evident that time spent in sleep, PA and sedentary behaviors necessarily take up time from one of the other behaviors. Time that is spent as a whole in these behaviors matters for cardiometabolic risk factors including BMI, waist circumference, blood pressure, CRP, and insulin sensitivity (Chastin et al., 2015b). Particularly the positive effects of moderate to vigorous intensity PA on cardiometabolic risk

factors seem to be moderated by the proportion of time spent in sedentary behavior, light intensity PA and sleep. A stronger health enhancing effect of more time in moderate to vigorous PA is more often observed if the proportion of sedentary behavior to low intensity PA is smaller (Chastin et al., 2015b).

Among postmenopausal women the cardiovascular risk profile was more strongly modified by PA than by sleep (Casas et al., 2012). Irrespective of their sleep quality, women with high compared to low PA levels had a better cardiovascular risk profile including a lower BMI, waist circumference, trunk and total body fat, insulin levels, and HDL cholesterol levels. Neither good sleep quality or sufficient duration compensated for the effects of insufficient PA.

2.6 THE RATIONALE FOR THIS STUDY

PA indisputably has an important role in having lower CVD risk and the importance of it is best described by physical inactivity listed among the leading risk factors for CVD (Myers et al., 2015; World Health Organization, 2015). The role of sedentary behaviors (Dempsey et al., 2014; Wilmot et al., 2012), as well as sleep (Ferrie et al., 2011; Jackson et al., 2015) for the risk of CVD have gathered increasing interest during the past decades. Regarding CVD risk, sleep seems to compare in importance with many more established risk factors (Redline and Foody, 2011). The effects of different risk factors on CVD are often nested and complex, with total CVD risk depending on the combination of risk factors (World Health Organization, 2009). Modern society with increasing opportunities to remain sedentary, around the clock requirements of productivity and access to food, light and entertainment, challenges human health (Rajaratnam and Arendt, 2001) and a natural, physically active lifestyle (Archer and Blair, 2011). It is clear from a time-use point of view that engaging in either sleep, PA, or sedentary behavior takes up time from one of the other (Tudor-Locke et al., 2011). This approach has already yielded some first piece of evidence that reveal the importance of PA, sleep and sedentary behaviors upon each other and further on health outcomes (Buman et al., 2014b; Stamatakis et al., 2015). However, there is still to date a considerable gap of knowledge to fill regarding the joint association of PA and sleep with cardiometabolic health and CVD risk.

The prevalence of behaviors and the risks associated with the combination of behaviors need to be studied in epidemiological settings, so that eventually, effective and targeted interventions and public health recommendations can be planned. The clustering of health behaviors has indeed gathered increasing research interest, but a majority of studies to date have approached the issue by co-occurrence or index-based rather than true clustering methods (McAloney et al., 2013). Large population-based samples are often heterogeneous in one way or another, but the source of

heterogeneity is not always observable, particularly with large and complex arrays of data (Collins and Lanza, 2010; Lubke and Muthen, 2005). Behavioral patterns are often complex and heterogeneous and forming subgroups of people is not always explicit. As a complement to general trends and associations that are modeled by more traditional analysis methods such as regression analysis or analysis of variance, modelling the underlying interindividual heterogeneity with a person-oriented method, can help to identify true underlying groups of people based on their patterns of behaviors (Bergman and Trost, 2006; von Eye et al., 2006).

3 AIMS

The purpose of this thesis is to study whether characteristics related to PA and sleep identify people at different risk of CVD in a population-based sample of Finnish adults. In order to model underlying behavioral groups in the sample, latent class analysis as a person-oriented method is used. The aim is also to study the interaction between PA and sleep with CVD mortality. The specific aims of the study are listed below:

1. To study the interrelationships between sleep and PA in a population-based sample using a person-oriented approach (I)

2. To study the operationalization of chronotype by a person-oriented method (II)

3. To study the associations between chronotype, PA and sedentary behaviors among the general adult population using a person-oriented perspective (II)

4. To study the joint association of sleep and PA on cardiometabolic risk factors and total CVD risk (III)

5. To study the interrelationships between a history of sports, PA, sleep and mortality in a population of former athletes (IV)

Aims

4 MATERIAL AND METHODS

4.1 STUDY SAMPLES

The study comprises data from two population studies, the National FINRISK 2012 Study, and the Finnish former elite athlete cohort.

4.1.1 THE NATIONAL FINRISK 2012 STUDY

In substudies I to III data comprise the National FINRISK 2012 Study that is a cross-sectional health examination survey coordinated by the THL in Finland. The FINRISK 2012 Study monitors CVD risk factors in five different regions of Finland (Borodulin et al., 2014b). The study protocol closely follows the recommendations of the World Health Organization MONICA Study (World Health Organization, 1988) and the later recommendations of the European Health Risk Monitoring Project (Tolonen et al., 2002). The study protocol has been repeated in five-year intervals since 1972, when it still was called the North Karelia Project. In 2012, a stratified, random sample of 10,000 Finnish men and women aged 25 to 74 were mailed a health questionnaire together with an invitation to participate in a health examination (Borodulin et al., 2014b). At the health examination site, trained personnel measured weight, height and blood pressure and took a blood draw, and a second health questionnaire was handed out to be returned by mail. All measurements were undertaken in the winter of 2012 with a participation rate of 64.9% (n=6424, men=3041; women=3383).

4.1.2 THE FINNISH FORMER ELITE ATHLETE COHORT

The Finnish former elite athlete cohort (IV), led by Professor Seppo Sarna at the University of Helsinki is a prospective cohort study based on former elite male athletes (N=2448) and their referents (N=1712). The athletes had represented Finland at least once in international or inter-country competitions between the years 1920 and 1965. Athletes represented a variety of different endurance, team-sport and power sport disciplines. The referents were selected among Finnish men who were classified as completely healthy (military class A1, fully fit for ordinary military service) at 20 years of age at the medical examination preceding their conscription (Sarna et al., 1993). The referents were chosen from public archives of the register of men liable for military service and matched on birth cohort and area of residence with the athletes (Sarna et al., 1993).

In 1985, a baseline health questionnaire was mailed to all cohort members still alive (N=2528, 60.8% of the original cohort). The response rate was 80-90% for athletes and 77% for referents. The questionnaire included

demography, anthropometrics, symptoms and diseases, health-related factors and health behaviors such as PA and sleep. A follow-up was done in 1995 and 2001, but these data were not used in this study.

4.2 ETHICAL CONSIDERATIONS

The ethical approval for the National FINRISK 2012 Study (I-III) was given by the Coordinating Ethics Committee of the University Hospital District of Helsinki and Uusimaa. All participants also gave their written, informed consent. The Finnish former elite athlete cohort (IV) study was approved by the Ministry of Social Affairs and Health in Finland and the Statistics Finland, and all subjects gave informed consent by returning the questionnaires. All participants received a cover letter explaining the purpose of the study.

4.3 MEASUREMENTS

Main data in all the substudies were based on self-report on the questionnaires. In substudy III information on measured biomarkers was used and in substudy IV data on mortality was attained from national registers. The questionnaires in the FINRISK 2012 Study and the Finnish former elite athlete cohort were different, but both assessed health behaviors, socioeconomic factors, and health status.

4.3.1 PHYSICAL ACTIVITY
In the FINRISK 2012 Study PA was assessed by six questions. LTPA was assessed by three different questions ($Q_{LTPA}1$, $Q_{LTPA}2$, and $Q_{LTPA}3$) as follows: $Q_{LTPA}1$= "How much do you exercise and stress yourself physically in your leisure time?"; $Q_{LTPA}2$= "How often do you in your leisure time exercise for at least 20 minutes at least mildly sweating?"; and $Q_{LTPA}3$= "How long does your leisure time activity take at a time?" The answers to $Q_{LTPA}1$ were categorized into 1) Inactive (*"In my leisure time, I read, watch TV, and work in the household with tasks which do not make me move much and which do not physically tax me"),* 2) Low LTPA (*"In my spare time, I walk, cycle or exercise otherwise at least 4 hours per week, excluding travel to work"*), and 3) Moderate to high LTPA (including both *"In my spare time, I exercise to maintain my physical condition for at least 3 hours per week",* and *" In my spare time, I regularly exercise several times a week in competitive sports or other heavy sports"*). The response alternatives to $Q_{LTPA}2$ ranged from *"I have a disability/disease which does not enable me to exercise"* and *"less than once a week",* to *"5 times a week or more often"* and responses to

Q$_{LTPA}$3 included alternatives from "*I do not exercise in my free time*" to "*one hour or longer*".

OPA was assessed with one question: "How demanding is your work physically?" with response options categorized as 1) No OPA (Inactive) (*"I work mainly sitting"),* 2) Low OPA (*"I walk quite much in work but do not have to lift or carry heavy objects")* and 3) Moderate to high OPA (*"I have to walk or lift much", and "I do heavy manual labor").* CPA was assessed by the question: "How many minutes do you walk, ride on a bicycle or otherwise exercise to get to work?" There were six response options that were grouped into three categories: 1) Not physically active in commuting (*"I do not work or I use only a motorized vehicle"*) (Inactive), 2) less than 30 minutes CPA (*"Less than 15 minutes daily"*, and *"15-29 minutes daily"*) (low CPA), and 3) 30 minutes or more CPA (*"30-44 minutes daily", "45-59 minutes daily",* and *"over an hour daily"*) (moderate to high CPA). Domestic PA was assessed as follows: "How many minutes, excluding activity at work, commuting or exercise, do you daily walk, cycle or engage in a hobby in your leisure time that requires moving about?" with alternatives of response as follows *"less than 15 minutes per day", "15 - 29 minutes per day", "30 - 44 minutes daily", "45 - 59 minutes daily",* and *"over an hour per day".*

In the Finnish former elite athlete cohort LTPA was assessed by the three following questions: Q1= "Is your PA in leisure time about as tiring on average as: *walking; alternatively walking and jogging; jogging; running*", Q2="What is the mean average duration of your exercise session: *less than 15 minutes; 15 to 30 minutes; 30-60 minutes; 60-120 minutes; more than 2 hours*", and Q3="How many times per month do you participate in physical exercise: *less than once/month; 1 to 2 times per month; 3 to 5 times per month; 6 to 10 times per month; 11 to 19 times per month; 20 times per month or more often*" (Kujala et al., 1999).

The leisure time physical activity index

For the purposes of substudy II, a LTPA index was composed. It was based on all the information of LTPA, CPA and domestic PA on the FINRISK 2012 Study questionnaire. People were divided into "*none or very low PA*", "*low*", "*medium*" or "*high to very high PA*" and this was called the LTPA index. To reach the score of "*high to very high PA*" people had to report moderate to high LTPA for at least 3 hours/week (Q$_{LTPA}$1), or to have a resembling combination of LTPA and CPA, or to be active in commuting for at least 45 minutes/day despite no LTPA.

First, the Q$_{LTPA}$1 was cross tabulated with the CPA question. Those with Q$_{LTPA}$1=1 and less than 30 minutes of CPA were scored as "*none or very low PA*" and those with high LTPA regardless CPA were scored as "*high*" active. Next, the two other LTPA questions (Q$_{LTPA}$2, and Q$_{LTPA}$3) were considered and persons were grouped as "*none or very low PA*" if they either reported less than 15 minutes per week in Q$_{LTPA}$3, or a frequency of only once a week

or less in Q$_{LTPA}$2. Persons with at least 4 times a week and at least 15 minutes or at least 60 minutes and at least twice a week were initially regarded "*Medium*" to "*high active*" for the purpose of the index.

Information on the domestic PA question was utilized so that if a person reported only having domestic PA, but 60 minutes/day or more, he or she was not considered as physically inactive in the final index, despite having not reported any other LTPA or CPA. But, if a person reported only high domestic PA levels, with no LTPA or CPA, this was not regarded sufficient to classify the person as highly active.

The scoring and classification of the index was based on current PA guidelines that adults should aim for at least 150 minutes of moderate intensity PA or at least 75 minutes of vigorous intensity PA per week, or equivalent combinations (World Health Organization, 2010).

The MET-index

For the purposes of substudy IV, the volume of PA was computed based on the three structured questions on participation in LTPA (Kujala et al., 1999). A multiple of the resting metabolic rate, a metabolic equivalent (MET) was assigned to each activity and a MET index (cumulative leisure MET hours per week) was calculated as the product of intensity, duration and frequency of LTPA. The method has been validated against detailed PA interview (Waller et al., 2008). Following the current PA guidelines (Haskell et al., 2007; World Health Organization, 2010) subjects were grouped according to their weekly amount of LTPA into those with sufficient (i.e. achieving 450 MET minutes per week) and insufficient PA (not achieving 450 MET minutes per week).

Sedentary behaviors

In the FINRISK 2012 Study, sedentary behaviors were assessed as average time (hours and minutes) spent sitting on a weekday at the office (occupational sitting), at home in front of the TV (TV sitting), home in front of the computer (computer sitting), sitting in a vehicle (vehicle sitting), or sitting elsewhere (elsewhere sitting). In substudy I, the total time spent in TV sitting and computer sitting was calculated and the sum was categorized into gender-specific thirds (low, moderate and high) of screen time sitting. For the purposes of substudy II, time spent sitting in the different domains was divided into fourths, where one point was given to the highest quartiles. A sum of points from the five domains were combined to an overall sitting index, where total score ranged from 0 to 5 (0= "*does not belong to the highest quartile in any domain of sitting*" and 5= "*belongs to the highest quartile in all domains of sitting*"). For the purpose of the analyses (II) the sitting index was divided into low (score=0), medium (score=1) and high

(score=2-5). The high score included 2-5 domains, as not everyone report sitting in all five different domains, but high sitting in only one domain does not necessarily describe a sedentary lifestyle if for example reported as occupational sitting.

4.3.2   SLEEP

In the FINRISK 2012 Study (substudies I-III), the subjects reported their sleep duration as average sleeping hours during a night and a 24 hour period. For the purposes of substudy I, sleep duration was categorized based upon nocturnal sleeping hours as follows: 1) <6 hours, 2) 6-6.9 hours, 3) 7-7.9 hours, 4) 8-9 hours, and 5) >9 hours. The subjects also reported the time when they usually go to and get up from bed on weekdays and on weekends, respectively. Based upon these times, time in bed was computed for weekdays and weekends separately and a "sleep duration difference" as the difference between time in bed on weekdays and weekends was calculated, and dichotomized into 1) 30 minutes or less and 2) over 30 minutes.

In substudy IV, sleep duration was obtained by asking "How many hours do you usually sleep per 24 hours?" including nine response alternatives (≤6 hours, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, and ≥10 hours). Based upon previous literature (Grandner and Drummond, 2007) and a tentative univariate Cox model for mortality where the sleep duration categories that had a hazard ratio (HR) over 1 (increased risk of mortality) compared to 7 hours sleep were recognized, sleep duration in substudy IV was recoded into ≤6 hours/day (short sleep), 6.5-8.5 hours/day (mid-range sleep) and ≥9hours/day (long sleep).

In substudies I-III perceived satisfaction of sleep was assessed by the question, "Do you think you sleep enough?" Response options were dichotomized into *"Yes, always or often",* and *"No, rarely or I cannot say".* In substudy IV, sleep quality was reported as the usual perceived sleep quality, with response alternatives as follows: *"Well", "Fairly well", "Fairly poorly", "Poorly"* and *"Cannot say",* further dichotomized into *"Good or fair sleep* (including *"fairly poorly"*)" and *"Poor "*, excluding *"Cannot say"*.

Furthermore, the time spent napping (I) was calculated as the difference between self-reported nocturnal sleep and 24-hour sleep duration. Napping was categorized into 1) not napping, 2) napping for 30 minutes or less, and 3) napping longer than 30 minutes. Sleep medications in substudies I-III were reported as having used medications *during the past week; 1-4 weeks ago*; *1-12 months ago*; *over a year ago*; or *never*. Responses were dichotomized into *"No, never"*, and *"Yes, currently using or have used in past"*.

In substudy IV, sleep medications were assessed as days of use within the past 12 months. Those who reported no use or having used during less than 10 days were categorized as *"No sleep medication"* with rest of the responses categorized as *"Sleep medication use"*. In substudy IV, there were 18.6% missing data (no response) on sleep medication use. Of these, 14.5% was re-

classified as non-use because the person reported to sleep well and not to require more than 20 minutes for becoming alert in the morning, whereas the rest had to be excluded.

4.3.3   CHRONOTYPE

Chronotype was initially assessed by six questions on morningness-eveningness preference, modified from the MEQ (Horne and Östberg, 1976). The questions were: 1) "How easy is it for you to get out of bed in the morning?" with 4 responses ranging from "*not easy at all*" to "*very easy*". 2) "How tired are you in the morning?" with 4 responses ranging "*Very tired*" to "*Very rested*". 3) "There are so called morning people and evening people, which are you?" with 4 responses "*definitely morning*", "*more morning-than-evening*", "*more evening-than-morning*", and "*definitely evening*". 4) "What is your physical alertness in the morning?" with 4 responses ranging from "*Good*" to "*Very difficult*". 5) "At what time would you prefer a 2-hour physical task?" with 4 responses "*8:00-10:00*", "*11:00-13:00*", "*15:00-17:00*", and "*19:00-21:00*". 6) "What time would you prefer to start working?" with responses grouped into "*04:00-07:00*", "*08:00*", "*09:00-13:00*", "*14:00-16:00*", and "*17:00-03:00*". Based on these items, the Morningness-Eveningness Score according to Horne and Östberg (1976) (a higher total score for morningness and a lower score for eveningness) was calculated and people were grouped into morning types (scores of 19-28 points), intermediate types (scores of 13-18 points) and evening types (scores of 5-12 points) (Merikanto et al., 2013). The single self-evaluation question from the Horne and Östberg set of questions where participants classified themselves as morning type, more morning-than-evening type, more evening-than-morning type or evening type accordingly was used for comparison purposes in substudy II and as measure of chronotype in substudy IV.

Since determining chronotype based on scoring on a series of questions has been challenged (Adan et al., 2012; Di Milia et al., 2013; Natale and Cicogna, 2002) and also because chronotype is a latent construct and not directly measurable, an empirical operationalization using latent class analysis (LCA) was conducted in substudy I and II. The LCA models latent structures in the data and enables also estimations of the classification error (Collins and Lanza, 2010), something that is not possible with scoring based on classification methods such as the MEQ. This approach will be explained in more detail in the Statistical methods section.

The corrected mid-point of sleep is one suggested measure of chronotype (Roenneberg et al., 2007). It is calculated as the mid-point between sleep onset and awakening during free days corrected for by the average of mid-points of sleep during working days (5 days) and free days (2 days) (Wittmann et al., 2006). In both substudy I and II the corrected mid-point of sleep was calculated, but because times for onset of sleep and awakening

were unavailable the times of going to bed and getting up from bed were used instead. The corrected mid-point of sleep was used to confirm the latent chronotype classes (I,II), and also to evaluate the result between chronotype and PA and sitting in substudy II.

4.3.4   CARDIOMETABOLIC RISK FACTORS

In the FINRISK 2012 Study cardiometabolic risk factors were assessed in a health examination. A trained nurse measured height, weight, waist circumference, and blood pressure, and took a blood draw of the participants. Height was measured to the nearest 0.1 centimeter (cm). Weight was measured in light clothing to the nearest 100 grams with a beam balance scale. Waist circumference (cm) was measured at the midpoint of the lowest rib and iliac crest. BMI was calculated as weight in kg divided by squared height in m and was coded as high if BMI was ≥ 30 kg/m^2. Waist circumference was coded as high for men if ≥ 102 cm and for women if ≥ 89 cm. In substudy IV, self-reported data on height (m) and weight (kg) were used to calculate the BMI and it was further categorized as normal weight when BMI <25 kg/m^2, overweight when BMI 25-29.9 kg/m^2 and obese when BMI ≥ 30 kg/m^2.

In the FINRISK 2012 Study blood pressure was measured three times, using mercury sphygmomanometers, from the right upper arm while the participant was in a seated position, and the average of the second and third measurements was computed.

The blood draw taken in the health examination was analyzed in the laboratory of the THL (Helsinki, Finland) using standardized, validated methods. Serum total cholesterol, HDL cholesterol and triglycerides were analyzed using enzymatic methods (Abbott Laboratories, Abbott Park, Illinois, U.S.A). LDL cholesterol was calculated using the Friedewald algorithm (Bachorik and Ross, 1995). CRP and HbA1$_c$ were determined by immunoturbidimetrics (Abbott Laboratories, Abbott Park, Illinois, U.S.A).

For the analyses of the substudy III, all continuous risk factors were dichotomized based on if they were within recommended levels as suggested by the national Current Care Guidelines and international guidelines (Working group appointed by the Finnish Medical Society Duodecim and the Finnish Association for the Study of Obesity, 2013; Working group appointed by the Finnish Medical Society Duodecim and the Finnish Hypertension Society, 2014; Working group appointed by the Finnish Medical Society Duodecim, the Finnish Society of Internal Medicine and the Medical Advisory Board of the Finnish Diabetes Society, 2016; Working group set up by the Finnish Medical Society Duodecim and Finnish Society of Internal Medicine, 2013; World Health Organization, 2007). Total cholesterol was coded as high if total cholesterol was ≥ 5 mmol/L or if the participant was taking lipid-lowering medication. The use of lipid-lowering medication was assessed in the FINRISK 2012 Study and a person was considered to use

lipid-lowering medication if reported using the medication by a doctor's order. HDL cholesterol was coded as high (i.e. good) if HDL cholesterol was ≥1.00 mmol/L for men, and if HDL cholesterol was ≥1.20 mmol/L for women. LDL cholesterol was coded as high if LDL cholesterol was ≥3.00 mmol/L or if the participant was using lipid-lowering medication. Triglycerides were coded as high if triglycerides were ≥1.70 mmol/L or if the participant was using lipid-lowering medication. Total cholesterol/HDL cholesterol ratio was coded as high if it was >5.00 for men and >4.18 for women. CRP was coded as high if CRP was between 3.00 mg/L and 10.00 mg/L. Those with a CRP ≥10.00 mg/L were excluded from analyses as having an acute infection. $HbA1_c$-% was dichotomized as high when $HbA1_c$-% >6.00 % or if the participant had been diagnosed with diabetes. High blood pressure was determined as systolic blood pressure ≥140 mmHg or as diastolic blood pressure ≥90 mmHg or if the participant was taking blood pressure medication.

The Framingham 10-year Risk Score

To assess total CVD risk in the substudy III, the Framingham 10-year Risk Score was calculated according to D´Agostino et al. (2008). The risk score is developed to assess general CVD risk, based on continuous data on selected risk factors. The risk score is gender-specific and information on age, measured total cholesterol and HDL cholesterol levels, measured blood pressure and in addition, self-reported smoking, diagnosis of diabetes and use of antihypertensives are included for calculation (D'Agostino et al., 2008). In the Framingham Risk Score function coefficients are related to each risk factor with systolic blood pressure among women and age among men getting the highest coefficients. Furthermore, in both genders HDL cholesterol gets a negative coefficient that reflects positively on the score (D'Agostino et al., 2008).

In this study, if a person reported use of blood pressure medication within the past week this was regarded as using antihypertensives for calculation of the risk score. Diabetes classification was based on reported doctor's diagnosis or current use of diabetes medication.

4.3.5 ASSESSMENT OF CONFOUNDING VARIABLES

Employment status was assessed on the FINRISK 2012 Study questionnaire and it was utilized in substudies I to II as dichotomized into employed or not employed, with the latter including all retired, unemployed and homemakers irrespective of their reason for unemployment. In the Finnish former elite athlete cohort (IV) occupational data was collected partly from the Population Register Centre of Finland and partly from the questionnaire. Occupational groups were classified into the following main

categories: executives, white collar, blue collar, unskilled workers and farmers. Each person was classified according to the occupation practiced for the longest period (Fogelholm et al., 1994).

Education was assessed in years and the response was divided into thirds by birth cohort for the purpose of substudies I to III. Information about smoking was categorized as non-smoking, former smoker since ≤6 months, former smoker since >6 months, and smoking (I, III) and further in the substudy II smoking was dichotomized into non-smoker and current smoker. In substudy IV, a detailed smoking history was assessed (Kaprio and Koskenvuo, 1988) and the respondents were classified into four categories: never, occasional, former (ex-), and current smokers.

Alcohol consumption as such was assessed as portions of alcohol beverages consumed during the past week (substudies I-III) or as quantity and frequency (substudy IV) and was further transformed into grams of alcohol per kg of weight (substudy III) and into grams of pure alcohol per month (substudy IV), with a standard drink containing 12 grams of alcohol as previously reported (Romanov et al., 1987). In substudy IV, the respondents were further categorized as abstainers, occasional to moderate users (no more than 14 drinks per week) and heavy users (on average more than 2 drinks a day) (Järvenpää et al., 2005). Based on the food frequency questionnaires of the FINRISK 2012 Study, a dietary index describing healthiness of the diet including alcohol consumption was calculated for the purposes of substudy II (Kanerva et al., 2013).

Menopausal status of women in substudy III was coded as those with normal menstruation, those who were postmenopausal with hormone replacement therapy, and those who were postmenopausal without hormone replacement therapy. Postmenopausal was defined as having no regular menstruation within the last 12 months.

In substudy II, depression was coded as none, mild, moderate, and severe based on three dichotomous (yes, no) questions assessing: 1) a doctor's diagnosis of depression, 2) depressive mood during a period of at least two weeks within the past year, and 3) lack of interest in most things during a period of at least two weeks within the past year. Depression was not directly assessed in the Finnish former elite athlete cohort's 1985 questionnaire, but life satisfaction was measured with Allardt's scale containing the items "interestingness of life", "life happiness", "life easiness" and "loneliness" (Koskenvuo et al., 1979). A high score indicates high dissatisfaction. Life satisfaction has previously been shown to correlate with depression in this cohort (Bäckmand et al., 2001).

For the FINRISK 2012 sample, prevalent CVD was coded based on self-reported doctor's diagnosis of myocardial infarction, stroke, bypass surgery, angioplasty, angina pectoris or heart failure. In substudy IV, for the Finnish former elite athlete cohort, a dichotomized health status variable (having a history of disease; not having a history of disease) was composed based on self-reported and physician-diagnosed chronic diseases in 1985, including

coronary heart disease (coronary heart disease, angina pectoris), pulmonary disease (chronic bronchitis, emphysema, asthma), diabetes, arthritis (rheumatoid arthritis, osteoarthritis), Parkinson's disease and cancer. Data on cancer diagnoses (yes/no) were obtained as International Classification of Diseases (ICD) codes (ICD-8 from 1970 to 1985) to neoplasms of all organs (ICD 140-239) from the Finnish Cancer Registry and the hospital discharge reports.

4.4 STUDY DESIGN AND INCLUSION CRITERIA

The National FINRISK 2012 Study was a cross-sectional sample, with a participation rate of 64,9% (n=6424). Analyses in substudies I and III were gender specific and included those with no reported CVD (including myocardial infarction, stroke, bypass surgery, angioplasty, angina pectoris, and heart failure) (n=5858), who also returned the second health questionnaire, with the final sample in the substudy I being 4,470 (1,947 men and 2,523 women). In substudy III only those without acute infection and information on all dependent variables were included (n=4031). In substudy II there were 4904 (76%) of the initial 6424 participants who provided information for the chronotype. A part of the analyses in substudy II further excluded those not participating in working life (n=1886).

The Finnish former elite athlete cohort is a prospective study as described earlier. All subjects who were alive at the start of the follow-up on January 1, 1985, who answered the baseline questionnaire, and were not deceased by cancer within the first two years of follow-up (between January 1, 1985 and December 31, 1986), who did not answer "cannot say" to the sleep quality question, were not shooters, and also provided information on other variables of interest were included in the analyses (n=1660).

4.5 STATISTICAL METHODS

The main statistical analyses for this thesis included LCA (I,II), binomial (I,III) and multinomial (II) logistic regression analysis, analysis of variance (ANOVA) (III) and Cox proportional hazards model (IV). Descriptive statistics include means and standard deviations (SD) for continuous and frequencies for categorical variables, respectively. Differences between PA and sleep Profiles or former athletes and referents in distributions of categorical variables were tested by chi-square test and between means by ANOVA.

As a first step of analysis in substudy I the available PA and sedentary behavior variables were regressed on all sleep variables using logistic models predicting high PA and sitting, respectively. Models were adjusted for age, BMI, education, employment status, alcohol, and smoking. Based on these

models, the final set of PA, sitting and sleep variables were chosen to be the observed indicator variables included in the LCA modelling.

As a primary step of analyses in substudy III, independent associations between each indicator variable of the LCA and the cardiometabolic risk factors were studied by logistic regression. Then the associations between membership in PA and sleep Profiles and cardiometabolic risk factors were determined both by ANOVA (results not shown) and logistic regression models, with posterior probabilities for membership to Profiles as weights to get more accurate estimates between the Profiles and the cardiometabolic risk factors. In the ANOVA models, the risk factors were treated as continuous and in logistic models the risk factors were dichotomized into high and low as described previously, and the most prevalent latent class PA and sleep Profiles (Profiles 1) in men and women were chosen as reference categories. Models were adjusted for age, education level, alcohol consumption, and smoking. In women, models were also adjusted for menopausal status.

Differences between the PA and sleep Profiles in the Framingham 10-year Risk Score (III) was determined by weighted analysis of covariance using Bonferroni adjustment for multiple comparisons, adjusting for age, education level, alcohol consumption, smoking, BMI, and menopausal status in women.

Multinomial logistic regression analysis, weighted by the posterior probabilities of the latent chronotype classes was used to study the associations of chronotype with LTPA index and sitting index (II). Sleep duration with 7-7.9 hours as the reference group was included in all models, and the interaction between sleep and chronotype was tested, but not included in the final models, because it was not statistically significant. Final models were further adjusted for age, gender, education, smoking, diet score, BMI, prevalent CVD, and depression.

Significance level in all substudies was set at $p < 0.05$. Statistical analyses were performed in SPSS (IBM SPSS statistics v.22, Armonk, NY) (II,III) and SAS version 9.3 (SAS Institute Inc., Cary, NC) (I,II, IV).

4.5.1 LATENT CLASS ANALYSIS

For the purpose of identifying latent PA and sleep clustering (I), as well as latent chronotypes (I,II) in the sample, LCA was utilized. LCA is a latent variable model looking for true, underlying subgroups of individuals in the sample, with the same kind of individual characteristics based on a set of measured variables (Collins and Lanza, 2010; Nagin, 2005). For each person, a probability to belong to every latent class is estimated based on item-response probabilities for the measured variables, conditional on latent class. The highest probability for a person's class membership describes the most likely latent class for this person. The number of latent classes represents the number of different subpopulation clusters in the sample (Collins and Lanza,

2010; Lanza et al., 2007; Lubke and Muthen, 2005) and the model also provides estimates or likelihoods of the prevalence of the latent classes. The class prevalence likelihoods also represent estimations of classification error (Collins and Lanza, 2010). The LCA does not focus on combinations between variables but on similarities in individual response patterns.

The PROC LCA for SAS (Lanza et al., 2007; University Park: The Methodology Center, Penn State, 2013) command procedure was used to estimate model parameters, with all items for the LCA being categorical. Data on questionnaire items was assumed to be missing at random, and was handled within an expectation-maximization algorithm. The expectation-maximization algorithm produces full information maximum likelihood estimates for parameters (Lanza et al., 2007).

In substudy I, the PA and sleep Profiles were based on class-specific item-response probability patterns on six different sleep items (including chronotype), four different PA items, and one employment item, with response alternatives ranging from two to five, resulting in 77 760 possible response patterns to the items. To determine the variables that were to be included in the LCA, available sleep items were regressed on PA and sedentary behaviors variables and those predicting PA and sedentary behavior were chosen. The employment variable was also included in the LCA, because CPA and OPA that are present only for those working, were considered.

LCA models with one through five classes were fitted to the data in order to find the optimal number of latent classes. Gender was included as a grouping variable for the LCA and measurement invariance between genders was tested by fitting a model where all item response probabilities were free to vary and another where item response probabilities were constrained to be equal across genders. The difference in G^2 statistic was statistically significant, suggesting that measurement invariance could not be assumed to hold across genders. Thus separate models for genders were created.

Similarly, in order to operationalize chronotype first in substudy I and later in substudy II, the six psychometrically justified questions derived from the original 19-item Horne and Östberg MEQ (Hätönen et al., 2008) were used as indicator variables in LCA models. Chronotype LCA models with classes from 1 to 6 in the substudy I and 1 to 7 in the substudy II were fitted to the data.

Due to high degrees of freedom in the models, the G^2 statistic does not follow the chi-squared distribution and, consequently, the p-value for absolute model fit cannot be calculated (Collins and Lanza, 2010). Therefore, the choice of the best model in all LCA analyses was based on the Bayesian information criterion (BIC), where the smallest value represents the most optimal balance between the absolute model fit and parsimony, taking into account the sample size and number of freely estimated parameters. Model entropy and identification percentage were also considered where entropy close to 1 and an identification percentage closer to 100% describes better

model homogeneity. Furthermore, information about average posterior probabilities for the latent classes, that describe class separation were also considered. As a rule, average posterior probabilities over 0.7 indicate good class separation (Nagin, 2005). Finally, the decision was also based upon the interpretability and prevalence of the latent classes.

In substudy I the decision of the best PA and sleep model stood between the three and four class models, and, regarding the criteria mentioned above the four class model was chosen as the final. Likewise, based on above mentioned criteria, the choice of best chronotype model in the substudy I fell on the four class model. Here, to confirm the choice of the four chronotype classes, the distributions in midpoint of sleep, a suggested measure of chronotypes (Roenneberg et al., 2007) were compared between the four classes. The four classes differed, as was expected, in their midpoint of sleep and this was regarded as additionally supportive for the choice of a four-class chronotype classification in substudy I.

In substudy II, the choice of the best model for chronotype, based as also previously upon information criteria, model entropy, average posterior probabilities and interpretability, stood between the 4-, 5- and 6-class solutions where the 5-class model was considered as the final. The 4-class model which, had been the most suitable model in substudy I and represented what can be thought of as a very traditional categorization of the chronotype, was carried along into some further analyzes also in substudy II. These analyses included studying the translocation of persons between the 4-class and 5-class models, and to support the associations between chronotype and PA and sitting.

4.5.2 MORTALITY FOLLOW-UP

All residents of Finland have a unique personal identity code, the social security number. This enables registry linkage of data in research settings. Personal identifiers and possible dates of emigration or death for the Finnish former elite athlete cohort were obtained from the Population Register Centre of Finland. Information on cause of death was obtained using the national Causes of death register at Statistics Finland with the ICD codes used for classification (the 8th version in 1969-1986: codes 1-779, the 9th version in 1987-1995: codes 1-779, the 10th version in 1996: codes A-R, S-Y).

Cox proportional hazards model with age as the time variable and age at baseline in 1985 as the entry, was used to estimate adjusted HRs and 95% confidence intervals (CI) of total (all causes) and CVD mortality with follow-up until December 31, 2011. In models for CVD mortality, death of any other reason was treated as censoring. The proportional hazards assumption for each exposure was tested for by including an interaction with time in crude, univariate models. All included variables satisfied the assumption.

Sleep duration and sleep quality were regarded as the main explanatory variables and the independent unadjusted crude as well as adjusted

associations of sleep duration and sleep quality with total and CVD mortality were initially tested stratified by history of sports and in the full sample. Secondly, in the full sample, sleep duration, sleep quality and PA were included as concurrent independent predictors in a multivariable Cox model, adjusting for following covariates: history of sports, occupational status, smoking, alcohol use, BMI, and chronotype, sleep medication, and history of chronic disease.

The interactions between sleep duration and sleep quality with history of sports and history of chronic disease were not significant for either total or CVD mortality. The unadjusted multiplicative interactions between sleep duration and PA and between sleep quality and PA regarding all-cause mortality (p<0.001 and p=0.034, respectively) and CVD mortality (p=0.005 and p=0.085, respectively) were also tested. According to the aim of the substudy IV, the combination of sleep duration and PA level was recoded as follows: short sleep + insufficient PA; short sleep + sufficient PA; long sleep + insufficient PA; long sleep + sufficient PA; mid-range sleep + insufficient PA; and mid-range sleep + sufficient PA. The combination of sleep quality and PA level was recoded as follows: poor sleep + insufficient PA; poor sleep + sufficient PA; good sleep + insufficient PA; and good sleep + sufficient PA. Cox proportional hazards models for total and CVD mortality were analyzed with the combination of sleep duration as well as sleep quality and PA as main exposure, with the mid-range sleep+sufficient PA or good sleep+sufficient PA as the reference, rerspectively. Models were adjusted for history of sports, occupational status, smoking status, alcohol use, BMI, chronotype, sleep medication, and history of chronic disease.

Additive interaction was estimated by the relative excess risk due to interaction (RERI) with corresponding 95% CI using an Excel spreadsheet created by Knol and VanderWeele (2011) available as a supplement to their article. For the purpose of the additive interaction analyses short sleepers with insufficient PA, short sleepers with sufficient PA, and mid-range and long sleepers with insufficient PA were compared to mid-range and long sleepers with sufficient PA, adjusting for all covariates as before.

5 RESULTS

5.1 PHYSICAL ACTIVITY AND SLEEP PROFILES

According to the LCA, men and women in the FINRISK 2012 data most likely form four different subgroups that can be identified by different PA and sleep behavior patterns or Profiles. In table 2 the item-response probabilities that can range from 0 to 1 in each latent class are shown for men and in table 3 for women, respectively. Within each latent class, a certain pattern of responses is most likely or very unlikely to occur, respectively. Between the latent classes, certain class-specific item-response probabilities characterize the specific classes as compared to the others. These, between-class item-response patterns are hereafter referred to as PA and sleep Profiles or only Profiles. A short description of each Profile is given below.

In men, the first and most prevalent Profile (45%), called "*Physically active, normal range sleepers*" is characterized by working status, low CPA, moderate-to-high LTPA, low screen time sitting, no napping, satisfaction with one's sleep, a sleep duration between 7 and 7.9 hours and not taking sleep medications.

In men, the second Profile (30.2%) called "*Lightly active, morning types with normal range sleep*" is characterized by not working and furthermore by inactivity in both CPA and OPA, low LTPA, satisfaction with one's sleep, sleeping longer during weekend days, not using sleep medication and being definitely morning type.

The third Profile in men is called *"Occupationally active, evening type short sleepers"* (20%) and is characterized by working, moderate-to-high OPA, moderate screen time sitting, sleeping longer during weekend days, and being evening type.

The "*Physically inactive, poor sleepers*" is the least prevalent, fourth Profile in men (4.8%). This Profile is characterized by not working, inactivity in CPA and OPA and LTPA, high screen time sitting, long naps, dissatisfaction with one's sleep, not sleeping longer during weekend days, sleep duration of less than 6 hours, use of sleeping medication and evening type.

Table 2   *Estimated prevalence and item response probability patterns for latent class sleep and physical activity Profiles in men. For each Profile, the characterizing highest probabilities in all variables are bolded and in italic. Furthermore, if an item response probability distinguishes the Profile from the others, the value is bolded and highlighted.*

Men		Profile 1 (45%)	Profile 2 (30%)	Profile 3 (20%)	Profile 4 (5%)
Variable	Response alternatives				
CPA	*Inactive*	***0.51***	***1.00***	***0.56***	***1.00***
	Low	**0.37**	0.00	0.32	0.00
	Moderate to high	0.12	0.00	0.12	0.00
OPA	*Inactive*	***0.42***	***1.00***	0.33	***1.00***
	Low	0.25	0.00	0.26	0.00
	Moderate to high	0.33	0.00	***0.42***	0.00
LTPA	*Inactive*	0.15	0.11	0.29	**0.34**
	Low	0.42	***0.64***	***0.39***	***0.50***
	Moderate to high	***0.43***	0.25	0.32	0.15
Screen time sitting	*Low*	***0.44***	0.18	0.32	0.19
	Moderate	0.34	0.34	**0.38**	0.15
	High	0.22	***0.48***	0.30	***0.66***
Napping	*0 hours*	***0.75***	***0.51***	***0.51***	***0.54***
	≤0.5 hours	0.17	0.18	0.19	0.10
	>0.5 hours	0.09	0.31	0.30	**0.36**
Do you sleep enough?	*No*	0.03	0.04	***0.55***	***0.75***
	Yes	***0.97***	***0.96***	0.45	0.25
Workday-weekend sleep duration difference	*None*	0.42	**0.83**	0.27	**0.83**
	>0.5 hours	***0.58***	0.17	***0.73***	0.17
Sleep duration	*<6 hours*	0.00	0.01	0.13	**0.32**
	6-6.9 hours	0.05	0.10	***0.42***	***0.40***
	7-7.9 hours	**0.46**	0.35	0.39	0.13
	8-9 hours	***0.47***	***0.48***	0.07	0.09
	>9 hours	0.02	0.06	0.00	0.05
Sleep medication	*No*	**0.85**	**0.80**	***0.76***	0.34
	Yes	0.15	0.20	0.24	***0.66***
Chronotype	*Evening*	0.12	0.04	**0.26**	**0.27**
	More evening-than-morning	***0.31***	0.34	***0.30***	0.15
	More morning-than-evening	0.26	0.20	0.29	***0.29***
	Morning	***0.31***	***0.42***	0.15	***0.29***
Working status	*Not working*	0.00	**1.00**	0.00	**0.98**
	Working	**1.00**	0.00	**1.00**	0.02

CPA: commuting physical activity, OPA: occupational physical activity, LTPA: leisure time physical activity

The most prevalent, first Profile in women (47%) is called "*Physically active, good sleepers*" and it is characterized by working status, low OPA, moderate-to-high LTPA, moderate screen time sitting, no napping, being satisfied with one's sleep, and not using sleeping medication.

The second Profile in women (24.8%) called "*Lightly active, normal range sleepers*" is characterized by not working, inactivity in CPA and OPA, low LTPA, being satisfied with one's sleep, not sleeping longer during weekend days, sleep duration of 8-9 hours, and morning type.

The third Profile in women is called "*Occupationally active, unsatisfied evening type sleepers*" (17.7%) and is characterized by working, moderate-to-high OPA, dissatisfaction with one's sleep, sleeping longer during weekend days, sleep duration of 7 to 7.9 hours, and evening type.

The "*Physically inactive, short sleepers*" is the least prevalent, fourth Profile in women (10.7%), characterized by not working, inactivity in CPA and OPA and LTPA, high screen time, long napping, sleeping less than 6 hours, and using sleeping medication.

Table 3   *Estimated prevalence and item response probability patterns for latent class sleep and physical activity Profiles in women. For each Profile, the characterizing highest probabilities in all variables are bolded and in italic. Furthermore, if an item response probability distinguishes the Profile from the others, the value is bolded and highlighted.*

Women		Profile 1 (47%)	Profile 2 (25%)	Profile 3 (18%)	Profile 4 (11%)
Variable	Response alternatives				
CPA	*Inactive*	0.38	***0.99***	0.38	***0.99***
	Low	*0.41*	0.00	*0.40*	0.00
	Moderate to high	0.20	0.01	0.22	0.01
OPA	*Inactive*	*0.41*	***0.96***	*0.43*	***0.97***
	Low	***0.38***	0.02	0.30	0.03
	Moderate to high	0.21	0.01	***0.27***	0.00
LTPA	*Inactive*	0.17	0.15	0.28	***0.35***
	Low	*0.47*	***0.60***	*0.43*	*0.51*
	Moderate to high	***0.36***	0.24	0.29	0.14
Screen time sitting	*Low*	*0.48*	0.21	*0.45*	0.19
	Moderate	***0.33***	0.26	0.25	0.22
	High	0.19	*0.53*	0.29	*0.59*
Napping	*0 hours*	***0.75***	*0.70*	*0.62*	*0.60*
	≤0.5 hours	0.14	0.15	0.18	0.12
	>0.5 hours	0.11	0.16	0.21	***0.28***
Do you sleep enough	*No*	0.03	0.00	*0.69*	*0.65*
	Yes	***0.97***	***1.00***	0.31	0.35
Workday-weekend sleep duration difference	*None*	0.38	***0.87***	0.23	***0.85***
	>0.5 hours	*0.62*	0.13	***0.77***	0.15
Sleep duration	*<6 hours*	0.00	0.00	0.11	***0.17***
	6-6.9 hours	0.05	0.05	0.31	*0.30*
	7-7.9 hours	0.37	0.29	***0.47***	0.26
	8-9 hours	*0.54*	*0.59*	0.10	0.19
	>9 hours	0.04	0.06	0.01	0.08
Sleep medication	*No*	***0.80***	*0.71*	*0.60*	0.41
	Yes	0.20	0.29	0.40	*0.59*
Chronotype	*Evening*	0.15	0.08	***0.40***	*0.33*
	More evening-than-morning	*0.31*	*0.40*	0.23	0.32
	More morning-than-evening	0.25	0.16	0.25	0.18
	Morning	0.29	***0.36***	0.12	0.17
Working status	*Not working*	0.01	*0.98*	0.01	*0.93*
	Working	*0.99*	0.02	*0.99*	0.07

CPA: commuting physical activity, OPA: occupational physical activity, LTPA: leisure time physical activity

5.2 BACKGROUND CHARACTERISTICS OF THE PHYSICAL ACTIVITY AND SLEEP PROFILES

There were significant differences between men and women in the substudy I sample regarding age, nocturnal sleeping hours, and PA. The mean age of men was 52 years (SD ±14 years) and women 51 years (SD ±14 years), respectively (p<0.001). Men slept on average 12 minutes less than women (7.4 hours vs. 7.6 hours, p<0.001) and more often reported high LTPA as well as high OPA than women (34% vs. 29% and 23% vs. 7%, respectively). Women more often reported CPA of at least 30 minutes per day (13% vs. 8%), and more dissatisfaction with their sleep than the men did (20% vs. 17%).

Between the PA and sleep Profiles in men, overall differences were observed in age, educational years, alcohol consumption, and smoking (Table 4). Members in Profiles 1 and 3 were younger than members in Profiles 2 and 4, and they had on average more educational years than members in Profiles 2 and 4. Highest prevalence of current smoking, as well as the highest alcohol consumption was observed for members in Profile 3. No significant differences were observed in weight between members of the Profiles.

Table 4 *Background characteristics of men in the four PA and sleep Profiles. Results are given as means (± SD) or prevalences (%). Overall differences between Profiles are tested by ANOVA and Chi square test, respectively.*

Men	"Physically active, normal range sleepers"	"Lightly active, morning types with normal range sleep"	"Occupationally active, evening type short sleepers"	"Physically inactive, poor sleepers"	Results of statistical testing for differences between Profiles
Profile number	1	2	3	4	
Age, mean (years)	46.1 (SD ±11.5)	64.3 (SD ±8.5)	44.7 (SD ±11.1)	60.4 (SD ±10.6)	F=379; df=3; p<0.001
Education, mean (years)	14.2 (SD ±3.6)	11.2 (SD ±3.8)	13.7 (SD ±3.4)	11.5 (SD ±4.0)	F=81.9; df=3; p<0.001
Weight, mean (kg)	85.1 (SD ±13.7)	84.8 (SD ±13.7)	85.3 (SD ±13.7)	86.8 (SD ±15.2)	F=0.496; df=3; p=0.685
Alcohol, mean (g/kg/week)	1.0 (SD ±1.2)	0.8 (SD ±1.4)	1.2 (SD ±1.7)	0.9 (SD ±1.3)	F=4.6; df=3; p=0.003
Current smoker	18.6%	15.8%	24.7%	22.1%	X^2=39.5; df=9; p<0.001

In women, overall differences between the Profiles were observed in age, educational years, weight, alcohol consumption, and menopausal status (Table 5). Members in Profiles 1 and 3 were on average younger than members in Profiles 2 and 4, they had more educational years, and consumed on average more alcohol than members in Profiles 2 and 4. The highest mean weight was observed for members in Profile 4.

Table 5 *Background characteristics of women in the four PA and sleep Profiles. Results are given as means (± SD) or prevalences (%). Overall differences between Profiles are tested by ANOVA and Chi square test, respectively.*

Women	"Physically active, good sleepers"	"Lightly active, normal range sleepers"	"Occupationally active, unsatisfied evening type sleepers"	"Physically inactive, short sleepers"	Results of statistical testing for differences between Profiles
Profile number	1	2	3	4	
Age, mean (years)	45.2 (SD ±11.0)	61.6 (SD ±12.2)	45.6 (SD ±11.1)	58.1 (SD ±13.7)	F=299.3; df=3; p<0.001
Education, mean (years)	14.9 (SD ±3.6)	12.1 (SD ±4.1)	14.7 (SD ±3.5)	12.6 (SD ±4.2)	F=83.4; df=3; p<0.001
Weight, mean (kg)	69.6 (SD ±13.4)	71.2 (SD ±12.9)	69.5 (SD ±14.0)	74.4 (SD ±16.4)	F=9.0; df=3; p<0.001
Alcohol, mean (g/kg/week)	0.6 (SD ±0.9)	0.4 (SD ±0.7)	0.6 (SD ±1.0)	0.5 (SD ±1.0)	F=7.3; df=3; p<0.001
Current smoker	15.0%	12.6%	16.4%	17.5%	X^2=7.0; df=9; p=0.638
Not in menopause	67.6%	29.0%	65.0%	38.2%	X^2=265; df=6; p<0.001

5.3 OPERATIONALIZATION OF CHRONOTYPE BY LATENT CLASS ANALYSIS

For the purposes of forming the latent PA and sleep Profiles in substudy I, a LCA for chronotype was first conducted. This analysis revealed four underlying chronotype groups within the sample. The first chronotype (17.5%) was characterized by likelihood for morning tiredness and self-reported eveningness, and a preference to work hours between 14 and 16 o´clock. This group was called *"evening types"*. The second chronotype (26.9%) was characterized by likelihood for strong morning alertness and self-reported morningness, called the *"morning types"*. The third latent chronotype (25.3%) was characterized by likelihood for self-reported more morningness than eveningness, with fair morning alertness. This group was called *"more morning-than-evening types"*. The fourth chronotype (30.2%)

was characterized by likelihood for self-reported eveningness more than morningness and poor morning alertness, but still feeling quite rested and able to easily get up in the morning. These were called the "*more evening-than-morning types*". As was expected, the corrected midpoint of sleep in the four latent chronotypes differed, as follows: morning types, 2:49 a.m.; more morning-than-evening types, 3:14 a.m.; more evening-than-morning types, 3:45 a.m.; and evening types, 4:25 a.m.

In substudy II, where chronotype was operationalized in a slightly larger sample than in substudy I (substudy II including also individuals with a CVD history), a 5-class LCA model was chosen as the final one. This model suggested a division of chronotype into five latent groups, where one "*tired, more evening type*" and one "*rested, more evening type*" were identified.

The characteristics of the "*tired, more evening types*" (17%) included not that easy to get out of bed in the morning, to be somewhat tired and have a not that good alertness in the morning and rate one-self as more evening-than-morning type, whereas the "*rested, more evening types*" (28%) were characterized by having quite easy to get up from bed in the morning, to be somewhat rested, but not having that good alertness in the morning, to rate oneself as more evening-than-morning type.

The three other classes that were identified by the 5-class chronotype model included "*morning types*", "*rested, more morning types*", and "*evening types*". The "*morning types*" (23%) were characterized by high likelihoods of having very easy to get out of bed in the morning, to be very rested and alert in the morning, and to rate oneself as definitely morning type. The "*rested, more morning types*" (24%) were characterized by having quite easy to get up from bed in the morning, to be somewhat rested and have a moderate alertness in the morning, to rate oneself as more morning-than-evening type and prefer morning working hours. The "*evening types*" (8%) were characterized by not that easy to get out of bed in the morning, to be somewhat tired and having very poor alertness in the morning, to report oneself as definitely evening type and to prefer afternoon working hours.

The mean corrected midpoint of sleep in the five latent chronotypes differed, as follows: *morning types*, 02:48 a.m.; *rested, more morning types*, 03:09 a.m.; *rested, more evening types*, 03:37 a.m.; *tired, more evening types*, 03:50 a.m., and *evening types*, 04:40 a.m. Studying the differences between a possible 4-class LCA model and the chosen 5-class LCA model in substudy II, it was observed that 56% of those who in the 5-class model most likely placed in the "*tired, more evening type*" originated in the "*evening type*" and 19% in the "*more evening-than-morning type*" in the 4-class LCA model.

5.4 ASSOCIATIONS OF CHRONOTYPE WITH PHYSICAL ACTIVITY AND SITTING

A higher proportion of none to very low LTPA, and high sitting were observed in the "*tired, more evening types*" and "*evening types*" than in the other three chronotypes when comparing the distribution of the LTPA and sitting indexes in the latent chronotypes in substudy II. When participants in working life were studied, similar associations were observed. As a comparison, similar crude associations between chronotype and PA were also observed for different operationalizations of chronotype (using 4 latent classes, a self-reported single-question chronotype, a MEQ-based classification, or the mid-point of sleep).

As compared to the "*morning types*", all other of the five latent chronotypes had higher odds of none to very low or low LTPA, than high LTPA, with the highest odds of none to very low LTPA in the "*evening type*" (odds ratio [OR] 3.01, 95% CI 2.00-4.53) and the "*tired, more evening type*" (OR 2.70, 95% CI 1.91-3.81), and of low LTPA in the "*tired, more evening type*" (OR 1.79, 95% CI 1.34-2.39). The associations were adjusted for sleep duration, age, gender, education, smoking, diet, BMI, prevalent CVD, and depression. Among those in working life only, all other chronotypes compared to the "*morning types*" were associated with higher odds of none and very low LTPA, than high LTPA, but only the "*tired, more evening types*" also showed higher odds of low LTPA (OR 1.49, 95% CI 1.05-2.10) than high LTPA as compared to the "*morning types*".

Only *"Evening types"* compared to "*morning types*" were significantly associated with higher odds of high rather than low sitting (OR 1.69, 95% CI 1.19-2.41), adjusting for sleep duration, age, gender, education, smoking, diet, BMI, prevalent CVD, and depression. Being a "*rested, more morning type*", compared to being "*morning type*", was associated with lower odds of both medium (OR 0.78, 95% CI 0.64-0.96) and of high (OR 0.77, 95% CI 0.60-0.99) than low sitting.

5.5 JOINT ASSOCIATIONS OF PHYSICAL ACTIVITY AND SLEEP WITH CARDIOMETABOLIC RISK FACTORS

In men there were only few significant differences between the PA and sleep Profiles in odds of high cardiometabolic risk factor levels (III). In unadjusted models, compared to the "*Physically active, normal range sleepers*" (the Profile 1), the "*Lightly active, morning types with normal range sleep*" (the Profile 2) and the "*Physically inactive, poor sleepers*" (the Profile 4) were associated with higher odds of high blood pressure, high triglycerides, high HbA1$_c$, high BMI, and a large waist circumference. Furthermore, membership in Profile 2 was significantly associated with higher odds of high total cholesterol and high LDL cholesterol when compared to membership in Profile 1. However, after adjustments for age, smoking, alcohol consumption and education, as compared to membership in the "*Physically active, normal range sleepers*" Profile 1, only the association of membership in "*Physically inactive, poor sleepers*" Profile 4 with high HbA1$_c$ remained significant (Table 6).

In women, most associations between membership in Profiles and high cardiometabolic risk factor levels were observed for membership in Profile 2 and Profile 4, as compared to Profile 1, respectively (Table 7). As compared to the "*Physically active, good sleepers*" (Profile 1), the "*Lightly active, normal range sleepers*" (Profile 2) and the "*Physically inactive, short sleepers*" (Profile 4) both were associated with higher odds of high total cholesterol, high LDL cholesterol, high triglycerides, high total cholesterol/HDL cholesterol ratio, high HbA1$_c$, high blood pressure, high BMI and a large waist circumference. Membership in Profile 4 was also associated with higher odds of high CRP and lower odds of high HDL cholesterol levels when compared to membership in the Profile 1. Some of the associations were attenuated already when introducing age in the models, but after full adjustments for smoking, alcohol consumption, education, and menopausal status, membership in Profile 2 remained associated with higher odds of high total cholesterol, high LDL cholesterol, and high triglycerides. Also, membership in Profile 4 remained associated with higher odds of elevated blood pressure, high triglycerides, high HbA1$_c$, high CRP, high BMI, and large waist circumference, and lower odds of high HDL cholesterol, as compared to membership in Profile 1.

Table 6   Odds ratios (and 95% CI) for high cardiometabolic risk factor levels as compared to membership in the "Physically active, normal range sleepers" among men. The statistically significant associations are bolded.

PA and sleep Profile	Total Cholesterol ≥5 mmol/L	HDL Cholesterol ≥1.0 mmol/L	LDL Cholesterol ≥3.0 mmol/L	Total/HDL Cholesterol >5	Triglycerides ≥1.7 mmol/L	Blood Pressure ≥140/90 mmHg	HbA1$_c$ >6.0%	CRP 3.0–10.0 mg/L	BMI ≥30.0 kg/m²	Waist Circumference ≥102 cm
"Physically active, normal range sleepers"	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
"Lightly active, morning type with normal sleep"	0.72 (0.51-1.01)	0.94 (0.58-1.52)	0.82 (0.59-1.14)	1.16 (0.87-1.56)	1.13 (0.84-1.50)	1.19 (0.88-1.60)	1.54 (0.95-2.51)	0.92 (0.62-1.36)	1.05 (0.75-1.49)	1.16 (0.86-1.56)
"Occupationally active, evening type short sleepers"	0.95 (0.72-1.25)	0.88 (0.57-1.35)	1.06 (0.81-1.40)	1.01 (0.76-1.34)	1.14 (0.87-1.49)	0.90 (0.69-1.17)	1.13 (0.65-1.96)	0.99 (0.69-1.44)	1.23 (0.89-1.69)	1.14 (0.86-1.52)
"Physically inactive, poor sleepers"	0.58 (0.33-1.02)	0.71 (0.33-1.51)	0.70 (0.40-1.24)	1.23 (0.74-2.04)	1.08 (0.65-1.78)	0.87 (0.52-1.47)	**2.17 (1.09-4.35)**	1.18 (0.63-2.22)	1.32 (0.75-2.32)	1.56 (0.95-2.58)

Note: Criteria for high Total Cholesterol, LDL cholesterol, Triglycerides, and Blood Pressure also included the use of medication and for high HbA1$_c$ the diagnosis of diabetes. Models adjusted for age, education level, alcohol consumption, and smoking. HDL: high density lipoprotein, LDL: low density lipoprotein, HbA1$_c$: glycated hemoglobin, CRP: C-reactive protein, BMI: Body mass index

Table 7 Odds ratios (and 95% CI) for high cardiometabolic risk factor levels as compared to membership in the "Physically active, good sleepers" among women. The statistically significant associations are bolded.

PA and sleep Profile	Total Cholesterol ≥5 mmol/L	HDL Cholesterol ≥1.2 mmol/L	LDL Cholesterol ≥3.0 mmol/L	Total-/HDL Cholesterol >4.18	Triglycerides ≥1.7 mmol/L	Blood Pressure ≥140/90 mHg	HbA1c >6.0%	CRP 3.0–10.0 mg/L	BMI ≥30.0 kg/m²	Waist Circumference ≥89 cm
"Physically active, good sleepers"	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
"Lightly active, normal range sleepers"	**1.67** (**1.22-2.30**)	0.96 (0.64-1.46)	**1.46** (**1.10-1.94**)	1.12 (0.82-1.54)	**1.39** (**1.04-1.88**)	1.21 (0.92-1.58)	1.56 (0.91-2.67)	1.20 (0.89-1.62)	1.04 (0.78-1.39)	1.05 (0.82-1.35)
"Occupationally active, unsatisfied evening type sleepers"	0.90 (0.70-1.15)	0.90 (0.61-1.35)	0.92 (0.72-1.17)	1.06 (0.76-1.47)	1.08 (0.78-1.49)	1.05 (0.80-1.37)	1.32 (0.73-2.41)	0.94 (0.69-1.28)	1.07 (0.79-1.43)	0.87 (0.68-1.12)
"Physically inactive, short sleepers"	1.00 (0.69-1.46)	**0.57** (**0.36-0.90**)	1.06 (0.74-1.51)	1.21 (0.82-1.77)	**1.48** (**1.03-2.12**)	**1.49** (**1.06-2.10**)	**2.21** (**1.22-3.99**)	**1.82** (**1.28-2.58**)	**1.49** (**1.05-2.10**)	**1.56** (**1.14-2.13**)

Note: Criteria for high Total Cholesterol, LDL cholesterol, Triglycerides, and Blood Pressure also included the use of medication and for high HbA1c the diagnosis of diabetes. Models adjusted for age, education level, alcohol consumption, smoking and menopausal status. HDL: high density lipoprotein, LDL: low density lipoprotein, HbA1c: glycated hemoglobin, CRP: C-reactive protein, BMI: Body mass index

5.6 ASSOCIATIONS OF MEMBERSHIP IN PHYSICAL ACTIVITY AND SLEEP PROFILES WITH 10-YEAR CARDIOVASCULAR DISEASE RISK

Figure 1 shows the differences in the Framingham 10-year Risk Score between the PA and sleep Profiles in men and women, respectively. In men the membership in Profiles 2 and 4 was associated with a significantly higher risk score than membership in the Profiles 1 and 3, in both age-adjusted and fully adjusted models. The highest 10-year CVD risk score was observed for membership in Profile 4 in men.

In women, the Framingham 10-year Risk Score was highest for membership in Profile 2, differing from all other Profiles also in the fully adjusted models. Throughout the models was also membership in Profile 4 associated with a significantly higher risk score than in Profiles 1 and 3. Overall, women had consistently lower Framingham Risk Scores than men.
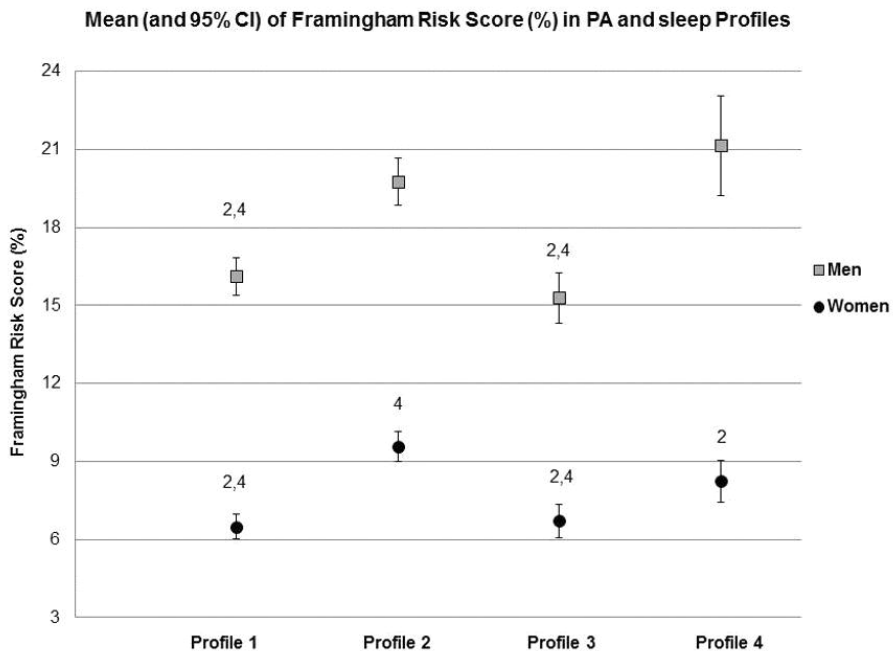
Figure 1. Comparison of Framingham Risk Score (%) between PA and sleep Profiles in men (squares) and women (circles), respectively. Adjusted for age, education, alcohol, smoking, BMI, and menopause (in women). Numbers in the figure indicate the Profile compared to which there was a statistically significant difference by pairwise comparisons in ANOVA.

5.7 INTERACTION BETWEEN PHYSICAL ACTIVITY AND SLEEP IN RELATION TO MORTALITY

In substudy IV, former athletes less often reported short (7.1% vs. 10.1%) and poor sleep (8.7% vs 14.0%), but more often sufficient LTPA (74.4% vs. 46.5%) as compared to non-athlete men. Nevertheless, the interaction between history of sports and sleep duration or sleep quality regarding mortality was not significant and neither in former athletes or referents the sleep duration nor sleep quality were independently associated with mortality. In all subjects, a crude association between short sleep duration (HR 1.28, 95% CI 1.01-1.61), poor sleep quality (HR 1.31, 95% CI 1.07-1.61) and low LTPA (HR 1.30, 95% CI 1.13-1.49) with all-cause mortality was observed. Regarding CVD mortality, only insufficient LTPA level was found significant in unadjusted models (HR 1.41, 95% CI 1.16-1.73). In multivariable models including information about history of sports as well as occupational status, smoking status, alcohol consumption, BMI, chronotype, sleep medication, and history of chronic disease, the independent associations between sleep, PA and mortality were attenuated.

A significant, unadjusted multiplicative interaction between sleep duration and LTPA in relation to both all-cause and CVD mortality risk was observed. The combination of short sleep and insufficient LTPA was associated with higher all-cause mortality (HR 1.41, 95% CI 1.00-1.99) and CVD mortality (HR 1.82, 95% CI 1.16-2.85), as compared to having mid-range sleep and sufficient LTPA, in fully adjusted models. Furthermore, the positive RERI (RERI =0.92, 95% CI: 0.04-1.80) suggested a significant additive interaction between sleep duration and LTPA in relation to CVD mortality.

The combination of poor sleep quality and insufficient LTPA was related to increased all-cause mortality (HR 1.37, 95% CI 1.00-1.87), but not to CVD mortality after adjustments. The additive interaction (RERI 0.34, 95% CI: -0.13 – 0.82) between sleep quality and PA in relation to all-cause mortality was not significant.

Results

6 DISCUSSION

This thesis aimed to study the interrelationships between PA, sleep and CVD risk. The main findings to the specific aims of the study are:

1. Using LCA, a person-oriented method, and combining information on several PA and sleep variables, four different latent classes characterized by different PA and sleep Profiles among initially CVD free adults in Finland were identified. Small gender differences between the Profiles were observed, but mainly the Profiles had similar characteristics in men as in women. Employment status, OPA and LTPA, screen time sitting, self-rated sleep sufficiency, sleep duration and chronotype were all important characteristics differentiating the four Profiles.
2. Studying the operationalization of chronotype in the population-based sample, it was observed that chronotype classes are characterized by differences in morning- and evening preference and also morning tiredness.
3. Evening chronotype and being more evening-than-morning oriented and feeling tired in the morning, was related with higher odds of very low and low LTPA as compared to morning-type and high PA. Evening type also associated with high sitting.
4. The estimated 10-year CVD risk differed between the PA and sleep Profiles in both genders, but associations between membership in the Profiles with separate cardiometabolic risk factors were statistically evident only in women.
5. A combination of short sleep and low LTPA predicted a higher all-cause and especially CVD mortality, in a population of former athlete men and their referents.

6.1 INTERRELATIONSHIPS BETWEEN PHYSICAL ACTIVITY AND SLEEP

High LTPA, mid-range sleep, and satisfaction with one's sleep characterize the most prevalent PA and sleep Profiles in both men and women. These Profiles were estimated to comprise of 45% and 47% of men and women, respectively. On the other hand, the least prevalent PA and sleep Profile represented a combination of likelihoods for leisure time physical inactivity, having high screen time sitting, and short as well as self-reported insufficient sleep. The estimated prevalence of these PA and sleep Profiles were 5% and 11% in men and women, respectively.

All Profiles represent underlying groupings of men and women, representative of the general, apparently CVD free adult population in Finland. The characteristics emerging in the Profiles are supported by earlier research. First of all, employment status as a marker of socioeconomic status is known to be related with both PA and sleep (Bauman et al., 2012; Kronholm et al., 2006). The PA and sleep Profiles generated in this study are differentially characterized by employment status and there were two Profiles characterized by « working » and two by « not working ». Differences in PA and sleep further differentiated both the « working » and the « not working » Profiles, creating four different class Profiles.

Epidemiological studies have previously observed physically active persons to report better sleep quality (Laugsand et al., 2011; Soltani et al., 2012; Wu et al., 2015) and more often mid-range sleep duration than physically inactive persons (Kronholm et al., 2006; Stranges et al., 2008; Tu et al., 2012; Yoon et al., 2015). On the other hand, sleep durations deviating from the mid-range of 7 to 8 hours have been observed to associate with low PA levels (Grandner and Drummond, 2007; Grandner et al., 2010; Patel et al., 2006). Persons that report frequent insufficient sleep (Strine and Chapman, 2005) or insomnia-related symptoms (Haario et al., 2012) tend to engage in less LTPA.

The estimated prevalences of the Profiles were slightly different between genders, and there were some small gender differences also in the characteristics of the PA and sleep Profiles. As reported in earlier literature, Finnish women engage more than men in CPA (Borodulin et al., 2016; Mäkinen et al., 2009) which was also seen in the Profiles as higher likelihoods of CPA overall within the Profiles of women than men. Likewise, women more often than men have longer sleep duration (Kronholm et al., 2006) but are dissatisfied with their sleep quality or report insomnia-like symptoms (Ohayon, 2002). Long sleep did not strongly differentiate the Profiles in either men or women but self-reported sleep sufficiency did. It was observed that there was an equally high likelihood of self-reported insufficient sleep in Profile 3 and Profile 4 among women, but in men the clearly highest likelihood of insufficient sleep was observed in Profile 4.

The Profiles identified in the substudy I are in line with previous findings indicating important relationships between PA and sleep. Importantly, the study adds a person-oriented perspective to the issue of PA and sleep behavior clustering, a more novel approach in epidemiological studies. Even if many studies mention the clustering of behaviors, there is diversity in the used methods of clustering (McAloney et al., 2013; Noble et al., 2015). The use of actual clustering methods that model underlying associations between health-related behaviors is less common than studying the health behaviors in isolation or using approaches of co-occurrence or only selected combinations of behaviors (Conry et al., 2011; McAloney et al., 2013). Furthermore, both PA and sleep have seldom been included among the studied health behaviors (Noble et al., 2015).

Large populations and samples rarely are homogeneous in all aspects and identifying clusters or subpopulations can be demanding because the array of data can be complex and the source of heterogeneity is not always observable (Collins and Lanza, 2010; Lubke and Muthen, 2005). The observed or unobserved source of heterogeneity is an important aspect that separate different cluster analyses methodologically (Lubke and Muthen, 2005). Furthermore, a distinction between variable-oriented and person-oriented methods can be made. In variable-oriented methods the focus is on modelling associations between variables, whereas in person-oriented approaches the focus is on individuals and inter-individual variation (Bergman and Trost, 2006; Collins and Lanza, 2010; von Eye et al., 2006). Person-oriented modelling looks at the individual as a totality made up of inseparable components that form patterns of behavior or traits, whereas variable-oriented modelling sees the world as linear variables and the individual as a sum of variables (Bergman and Trost, 2006). In empirical research, theories are many times made up of complex interactions, mutual causality, and nonlinear relations that are not properly accounted for in variable-oriented modelling (Bergman and Trost, 2006).

There are some previous large-scale studies that have included both PA and sleep among the health behaviors under study for clustering. In Belgian adults one "healthy" and one "unhealthy" behavioral cluster was identified using cluster analysis, where information on smoking, alcohol consumption, hours of sleep, OPA and LTPA were included. Only among the oldest participants (50-60 years) the two clusters differed in terms of sleep, but generally sleep was not an important discriminating factor in the clusters (de Bourdeaudhuij and van Oost, 1999). In a large sample (n=4271) of Spanish adults, Guallar-Castillon et al. (2014) studied the interrelationship between PA, sedentary behavior and sleep using factor analysis. They found that sleep was negatively loaded on the factor that the authors called "seated for watching TV and daytime sleeping", characterized by high time spent watching TV, daytime napping and shorter nighttime sleep.

Of these two previous studies, the Spanish study is more alike to the substudy I in terms of the studied behaviors, whereas the Belgian study is more similar methodologically. Cluster analysis and LCA are both person-oriented methods and methodologically closely related, with a key difference being that cluster analysis is based on continuous data and LCA includes categorical data (Collins and Lanza, 2010; Lubke and Muthen, 2005). Factor analysis differs from LCA in that it is a variable- and not person-oriented method (Collins and Lanza, 2010).

The PA and sleep Profiles identified in substudy I share many similarities with latent behavioral classes reported among Finnish adolescents (Heikkala et al., 2014). The authors also found four different latent classes that were characterized by different patterns including PA, sitting and sleep (Heikkala et al., 2014). In both genders, the most prevalent latent class (51% and 66.5% in boys and girls, respectively) was characterized by likelihood of high PA,

favorable sleep duration, and low time spent sitting, like in the Profiles identified in the substudy I of this thesis. However, almost a third of the boys (26.7%) were estimated to be members of a latent class that was characterized by the highest likelihood of long daily time spent sitting, physical inactivity and short sleep duration. A substantially lower percentage (11.8%) of girls than boys were most likely members of the most unhealthy behavioral class characterized among girls by the likelihood of short sleep, low PA, long time spent sitting and current smoking. These behavioral classes in adolescents are much like the Profiles identified in this adult sample. It seems that PA, sedentary behavior and sleep tend to cluster similarly in adults and in adolescents. Interestingly though, a higher percentage of women than men most likely went with the class of poor behaviors, contrary to what was observed in adolescents.

The findings in the substudy IV indicate that former athletes more likely have what is considered sufficient and good sleep than do the non-athletic men. This is in line with findings that show former athletes to engage in healthy lifestyle in aspects of PA and diet also later in life (Fogelholm et al., 1994). It is commonly thought that active athletes who live a disciplined and healthy life in many aspects, also have good and sufficient sleep. Findings however do not support these beliefs, as insufficient or poor sleep can be quite common in active athletes (Lastella et al., 2015). So far the literature has not shown what happens to an athlete's sleep after ending their active career, but the findings in substudy IV indicate more favorable sleep in former athlete men than non-athletes.

6.2   THE ROLE OF CHRONOTYPE

6.2.1   OPERATIONALIZATION OF CHRONOTYPE BY A PERSON-ORIENTED METHOD

As described earlier, the person-oriented analysis aims to model underlying subgroups of people with the same kind of individual characteristics (Collins and Lanza, 2010). Chronotype is a measure of our inherent circadian clock (Adan et al., 2012) and thereby a true latent feature. Many ways to operationalize chronotype exist, but the shortcomings of widely used questionnaire-based indexes and sum-scores include the choice of proper cut-off values and the impossibility to conclude on more specific characteristics behind the score (Adan et al., 2012; Natale and Cicogna, 2002). Using predefined classification scores, one also have to assume that the operationalization is valid for the sample studied, while it remains unknown what the best classification for the specific sample would be. Furthermore, the evening type has repeatedly been shown to associate with an increased risk of disease (Merikanto et al., 2013; Merikanto et al., 2014) and poor health behaviors (Kanerva et al., 2012; Konttinen et al., 2014;

Wittmann et al., 2010), but as shown by the study of Konttinen et al. (2014) not only the circadian preference but also other dimensions of chronotype are important to understand and consider for the consequences to physical and mental health.

Therefore, in substudies I and II chronotype was operationalized by means of the LCA. LCA provides a classification based on the underlying structures in the data at hand, together with a possibility to evaluate the classification error as the class prevalences represent likelihoods (Collins and Lanza, 2010). In substudy I, a 4-class operationalization was determined to best describe the sample, but in substudy II operationalization was done with a slightly larger sample (including also those with pre-existing CVD), and five latent chronotypes were identified. The self-rated morning-evening preference, that also as a single item has been used to operationalize the chronotype, was as expected a clear differentiating item between the chronotypes. However, also the rating of morning tiredness was a clear characteristic of the LCA chronotypes, and in substudy II this item clearly differentiated between the two more evening oriented classes. The findings support that also morning tiredness is an important dimension of the chronotype to recognize, in addition to morning and evening preference (Konttinen et al., 2014; Natale and Cicogna, 2002; Randler and Vollmer, 2012; Zickar et al., 2002).

The latent chronotype classes in substudy II as well as in substudy I were validated by calculating the average of the corrected midpoint of sleep in each class. The corrected midpoint of sleep is a measure of the timing of the sleep that considers both weekday and weekend sleep (Roenneberg et al., 2007). As evening types have been demonstrated to sleep longer during days off (Wittmann et al., 2006), considering bedtimes over the whole week are thought to be a more realistic measure of the actual sleep timing and more precisely its midpoint (Roenneberg et al., 2007). The midpoint of sleep was indeed different between the four as well as the five latent chronotypes, with a later midpoint in each more evening oriented class and the latest midpoint of sleep in definitely evening types.

6.2.2 ASSOCIATIONS BETWEEN CHRONOTYPE AND PHYSICAL ACTIVITY

In the PA and sleep Profiles, chronotype emerged as a differentiating characteristic between the Profiles. When studying associations between chronotype and PA and sedentary behavior more closely in substudy II, it was observed that "*evening type*", but also "*tired, more evening type*", persons reported less LTPA and to some extent more sitting, than did "*morning type*", persons.

Chronotype emerged in the PA and sleep Profiles as a characteristic of the Profiles. For women, the likelihood of evening type was a feature of Profile 3 the "*Occupationally active, unsatisfied evening type sleepers*", whereas in

men the evening type was as likely found in Profile 3 as in Profile 4. The likelihood of evening type in Profile 3 among women was clearly the highest among all Profiles in both genders. The association between gender and chronotype was not confirmed in a large sample (n=2526) of New Zealanders (Paine et al., 2006), but in Finland it was, and a higher prevalence of evening chronotype in women than men has earlier been observed (Merikanto et al., 2012). The high likelihood of evening type in Profile 3 in women can reflect a higher prevalence of night or shift work among members of this Profile, supported by the fact that also the likelihood of moderate to high OPA was characteristic of this Profile. Shift work is common in many manual occupations (Wright et al., 2013a) and evening type persons may be selected to shift- and night work more often than morning type persons (Hublin et al., 2010; Paine et al., 2006). However, data of possible shift work were not available and thus this hypothesis cannot be further verified.

It is also important to consider and understand the role of subjective morning tiredness not only as a differentiating feature of chronotype, but as a dimension with consequences on behavior. Findings in substudy II support earlier conclusion made by Konttinen et al. (2014) who observed that circadian preference and also morning tiredness are important, even if partly correlated, dimensions of the chronotype. They performed a structural equation modelling for operationalization of chronotype and they found an association between higher morningness, morning alertness and lower depression and emotional eating. When they considered the morningness and morning alertness in the same model, the association between morningness and depression and emotional eating was reversed, suggesting that morning tiredness associated stronger with depression and emotional eating than did the circadian preference (Konttinen et al., 2014).

The associations between chronotype and PA and sitting observed in substudy II were independent of sleep duration, depression and pre-existing CVD. This suggests that a later timing of sleep and feeling tired in the morning are important personal characteristics to understand and to consider for targeted health-promotion. The associations between chronotype and PA has rarely been studied previously in population-based adult samples. Evening type and low PA or high sedentary behaviors have been shown to be associated in children and adolescents (Schaal et al., 2010; Urban et al., 2011). In adults, other unhealthy behaviors such as smoking (Broms et al., 2012), alcohol consumption (Wittmann et al., 2010), emotional eating (Konttinen et al., 2014) and unhealthy diet (Kanerva et al., 2012) have been found to relate with a later chronotype.

The chronotype reflects our inherent circadian rhythm (Adan et al., 2012), which itself also gets feedback and is affected by PA during the day (Borbely et al., 2016; Yamanaka et al., 2006). Thus, promoting regular PA to evening type persons can benefit them in many aspects. There may be no harm in evening time exercise as is commonly believed (Buman et al., 2014a; Chennaoui et al., 2015); and on the contrary, there can be substantial health

benefits to be found, especially for evening type persons. As a treatment also for poor sleep (Passos et al., 2012) which often occurs in later chronotypes (Merikanto et al., 2012), PA has shown good results. It can however be more difficult to get evening type persons to engage in PA, as demonstrated in adolescents who if they were to be evening types, less likely believe PA to be an efficient means to cope with sleepiness and seldom engage in PA to cope with sleepiness (Digdon and Rhodes, 2009).

Social jetlag may be a reason for low PA and high sedentary behavior in evening chronotypes, but so far the causal relationship has not been confirmed. Social jetlag associate with physical inactivity and with late chronotype (Rutters et al., 2014). The social schedule force evening chronotypes more likely than earlier chronotypes to live in desynchrony with their natural circadian rhythm, resulting in what is called social jetlag (Roenneberg et al., 2007; Wittmann et al., 2006). Low amounts of natural sunlight and also the exposure to artificial light at late hours, predispose to desynchronized circadian schedules and the desynchrony seems to be greater in the evening than in the morning types (Wright et al., 2013b). Already at a young age the presence of a TV or computer in the bedroom associate with greater weekday-weekend discrepancy in sleep duration (Nuutinen et al., 2013). In substudy I, the discrepancy in the weekday-weekend sleep was most likely in the members in Profile 3 in both genders.

6.3 JOINT ASSOCIATIONS BETWEEN PHYSICAL ACTIVITY AND SLEEP WITH CARDIOVASCULAR DISEASE RISK

In substudy III, the membership in PA and sleep Profiles was associated with cardiometabolic risk factors among women, but very little among men, when information on smoking, alcohol consumption, and socioeconomic status also was considered. Both the "*Lightly active, normal range sleepers*" and the "*Physically inactive, short sleepers*" in women showed many associations with high cardiometabolic risk factor levels. However, in both genders the Profiles were different in their Framingham 10-year Risk Score, indicating a different total CVD risk between the Profiles. Looking at CVD mortality (substudy IV), neither sleep or PA alone, but jointly they showed a significant connection with higher all-cause and CVD mortality independent of a history of sports.

Full understanding is still wanting regarding the interaction between PA and sleep with cardiometabolic risk factors, even though there are several large-scale studies that have studied PA, sleep and sedentary behaviors as predictors of cardiometabolic risk factors (Pepin et al., 2014). The studies have mainly controlled for either PA or sleep as a covariate for the other in modelling, and only few have also studied the interaction of the behaviors.

Nevertheless, the main conclusion to be made based upon these previous studies is that PA is associated with improved cardiometabolic risk factor profile even when adjusting for sleep, and that sleep duration can associate with cardiometabolic risk factors differently at different PA levels (Pepin et al., 2014). The findings in substudy III are in line with the previously reported independent associations between PA, sleep and cardiometabolic risk factors, but also provide new insight to the issue as actual clustering of the behaviors and the joint association with cardiometabolic risk factors was observed from a person-oriented perspective.

In substudy III, the first step in modelling was a variable-centered approach where the association of each PA and sleep variable with each cardiometabolic risk factor was studied. This resulted in a large contingency table with a number of associations to be interpreted. Most associations occurred as expected and described in previous literature, but taken together, the generalization and interpretation of the information would have been problematic. Importantly, as the PA and sleep Profiles identify inter-individual variation, having membership in the Profiles as the predictor of cardiometabolic risk factors and total CVD risk, made the results generalizable to persons instead of combination of variables. It was, based on the first variable-centered analyses, expected that having a Profile where likelihoods of unfavorable behaviors occur, would be more prominently associated with cardiometabolic risk factors.

In women, profiling by PA and sleep distinguishes those with unfavorable levels in many cardiometabolic risk factors. The observed associations between the "*Physically inactive, short sleepers*" in women and high blood pressure, high triglycerides, high HbA1$_c$, high CRP, high BMI, large waist circumference and lower OR for high HDL cholesterol, does reflect the same associations that have been observed in previous variable-centered studies for the independent behaviors. The impact of PA is convincing for higher HDL cholesterol and lower triglyceride levels (Ahmed et al., 2012) and improved glucose metabolism (Roberts et al., 2013). Cross-sectional and longitudinal evidence also support an association between PA and lower inflammation (Ahmed et al., 2012; Roberts et al., 2013), smaller BMI and lower waist circumference (Glazer et al., 2013; Waller et al., 2008). The risks associated with short sleep include obesity, impaired glucose metabolism, and hypertension (Knutson and Van Cauter, 2008; Knutson, 2010; Spiegel et al., 2009). The results for women in Profile 4 support the idea that PA and sleep are synergistic in relation to cardiometabolic risk factors. This has also been shown earlier by substitution modelling (Buman et al., 2014b; Pepin et al., 2014).

Membership in Profile 2 showed associations with high total cholesterol, high LDL cholesterol, and high triglycerides as compared to membership in Profile 1 among women. As the dichotomized variables included information on medication use, this can be a cause for the observed associations considering these risk factors. Members of Profile 2 were on average 62 year

olds and can have been prescribed with lipid lowerers earlier in life which, if in current use, places them in the high risk category for total cholesterol, LDL cholesterol and triglycerides. Being on medication for high cholesterol or blood pressure indicates a less ideal level of the respective risk factor (Lloyd-Jones et al., 2010; Working group set up by the Finnish Medical Society Duodecim and Finnish Society of Internal Medicine, 2013) further related with an substantial lifetime CVD risk (Lloyd-Jones, 2010).

Whereas the cardiometabolic risk factors describe one dimension of risk each, the Framingham Risk Score indicates an estimated risk of total CVD, including also information about age, smoking, and medications. In men, smoking and alcohol consumption and the demographic background related with the PA and sleep Profiles attenuated the independent association of membership in the PA and sleep Profiles with cardiometabolic risk factors. Nevertheless, in the Framingham Risk Score, differences between the Profiles were observed. The estimated total CVD risk was higher in the "*Physically inactive, poor sleepers*" as compared to the "*Physically active, normal range sleepers*". Both PA (Myers et al., 2015) and good quality sleep (Jackson et al., 2015) are related with a lower CVD risk, and furthermore, low socioeconomic status correlates with health behavior clustering (Berrigan et al., 2003; Poortinga, 2007) and CVD risk (Kestilä et al., 2012; Laaksonen et al., 2008). It has also been shown that health behaviors account for a great proportion of the association between educational level and CVD mortality in men (Laaksonen et al., 2008). Members in the "*Physically inactive, poor sleepers*" were likely unemployed and had lower mean educational years compared to "*Physically active, normal range sleepers*". Consequently, in men the observed association between Profile 4 and Framingham Risk Score can likely reflect general clustering of poor health behaviors and thereby a high CVD risk for members of this Profile.

The mean age of members in the Profiles in both men and women is very different. Age is an important correlate of both PA and sleep, where younger age correlates with higher PA, less insomnia-like problems, but not necessarily lower dissatisfaction with sleep (Bauman et al., 2012; Ohayon, 2002). The mean age in different Profiles in men and women varies greatly and a higher age clearly associates with Profiles 2 and 4, but age does not make up a characteristic of the Profiles. Age is also a significant risk factor for CVD and it is possible that the different age distribution in the Profiles account for some of the observed differences, particularly in the Framingham Risk Score between the Profiles. However, age was adjusted for in all final models, attenuating both the results for individual risk factors and general CVD risk particularly in men, but not fully explaining all associations.

Gender differences in the associations between membership in Profiles and cardiometabolic risk factors can be due to the small differences in the behavioral characteristics of the Profiles in men and women (discussed in chapter 6.1.). It has for example been observed that the dose-response association between total PA and CVD risk is stronger in women than in men

(Sattelmair et al., 2011). In a previous Finnish population-based study, Kronholm et al. (2011) concluded on an independent association between sleep duration and CVD risk among women but not men. Variation in the same self-reported behaviors between the genders can result in different observed relationships between the behavior and the outcome. It is also possible that physiological differences such as women having lower muscle-mass and resting energy expenditure than men, hormonal functions and the genetic variance account for gender differences and the effects of PA and sleep behaviors. Furthermore, even if the results for men were not statistically significant, the OR for many risk factors were in the same direction and of similar magnitude as in women, suggesting that some of these associations can have been affected by the lower sample size in men.

6.3.1 INTERACTION BETWEEN PHYSICAL ACTIVITY AND SLEEP FOR CARDIOVASCULAR MORTALITY

Substudy IV shows that being physically inactive in leisure time and having concomitant short or poor sleep, one is at higher risk of CVD mortality, regardless a history of sport.

Few longitudinal studies have assessed the interaction between PA and sleep with mortality (Pepin et al., 2014). Previously Xiao et al. (2014) and Bellavia et al. (2014) have studied the interaction between sleep and PA with mortality. The findings in these two studies were contradictory where one found a significant interaction but the other did not. These two studies were conducted in samples more representative of the general population including both men and women, and therefore are not directly comparable to the findings in substudy IV. Furthermore, in some large population-based studies, the clustering of behavioral risk factors, including also PA and sleep duration has strongly been associated with fatal CVD (Eguchi et al., 2012; Hoevenaar-Blom et al., 2014; Odegaard et al., 2011).

The interaction of LTPA and sleep duration in predicting CVD mortality was evident on both a multiplicative and additive scale. The RERI was calculated for the synergistic association of insufficient PA and short sleep with mortality. The RERI symbolizes the additive risk i.e. whether the risk associated with two behaviors is higher than the sum of the two behaviors separately (Knol and VanderWeele, 2011). Additive interaction was confirmed by the analysis, further strengthening the idea of a joint, synergistic association between low PA and short sleep with CVD risk.

There was no significantly increased risk of mortality for long sleep and low PA in the current study. Bellavia et al. (2014) who particularly observed that long sleep associate with mortality among subjects with low physical activity, did not control for depression. In substudy IV, life satisfaction that previously has been shown to correlate with depression (Bäckmand et al., 2001) was not found to impact the non-significant association between long

sleep and mortality. Adjusting the Cox proportional hazards models for life satisfaction score also did not significantly impact on the hazard ratios and the interpretational outcome of the models, and was left out from the final models.

The interaction of sleep quality and LTPA with all-cause mortality was also significant, but not as strong as the interaction of sleep duration and PA with mortality. Sleep quality and sleep duration are correlated yet distinct characteristics of sleep (Altman et al., 2012; Grandner and Drummond, 2007) and both deserve to be acknowledged. Nevertheless, results of the substudy IV indicate that in regards of CVD mortality, sleep duration is a stronger predictor. Similar conclusions were drawn by Hublin et al. (2007). The role of sleep quality for cardiovascular health should, however, not be neglected because occasional sleep problems are continuingly increasing among the working aged population (Kronholm et al., 2016).

6.4 METHODOLOGICAL CONSIDERATIONS

There are several methodological considerations in this work. A strength of the study is the data that include the large population-based sample of adults and the unique prospective cohort of former elite level male athletes. The results of substudies I and III are generalizable to initially CVD free, general adult population in Finland. The FINRISK 2012 sample can be held representative of the adult population in Finland despite the moderate response rate (64%). The response is still among the highest in European comparison (Mindell et al., 2015).

Generally, participation in health surveys is higher in women, with higher age groups and in those with a higher socioeconomic status (Mindell et al., 2015; Tolonen et al., 2006). These facts may have attenuated the results also in this study, as there were fewer men than women participating. This can further be reflected in the low estimated prevalence of the *"Physically inactive, poor sleepers"* in men, and in the number of non-significant associations with cardiometabolic risk factors in men. Furthermore, those excluded based on missing data in substudies III and IV were less active and had poorer sleep than the included, possibly resulting in some attenuation in the results.

The Finnish former elite athlete cohort consists of former elite-level male athletes who between the years 1920 and 1965 had represented Finland at least once at the Olympics, the World or European championships or athletic contests between two or more countries, and of non-athletic subjects who all were classified as completely healthy at the medical examination preceeding their military service in Finland (Sarna et al., 1993). This cohort offers a unique opportunity to study the relationships of a background in competitive sports and later-life health behaviors including both sleep and PA with health outcomes.

The Finnish former elite athlete cohort has extensive measures on health related variables, including measures of sleep, PA, and chronotype, together with a long register-based mortality follow-up which is a strength for the study. In the Finnish former elite athlete cohort was also the history of PA possible to include in analyses that was not possible in the FINRISK data. The mortality follow-up started for the athletes when they still were active and for the referents at the time of their medical examination (Kettunen et al., 2015). However, the first health questionnaire was mailed in 1985 to all subjects still alive at that time and this is a weakness as no information about health behaviors during the actual career of the former athletes is available. Another limitation of the cohort is that it comprises only male athletes and the results are not generalizable to women.

In substudy IV it was possible to assess causality to some extent, even though data on the predictors origin in only one point in time. The change in PA and sleep over time was not studied in this thesis and the effect on the results of possible changes in behaviors cannot be evaluated. In a cross-sectional study (I,II,III) conclusions about causality cannot be drawn. There is also no rationale trying to conclude on causality between the behaviors in the PA and sleep Profiles because of the nature of the person-oriented approach. The components of the Profiles act as a whole and the effect of a single component cannot be isolated and kept constant as in for example regression modelling (Bergman and Trost, 2006). Reverse causality was tried to minimize by excluding persons with previous CVD in substudies I and III, and controlling for a history of disease in models in substudies II and IV.

The FINRISK data is of high quality including several measurements and laboratory analysis according to standardized protocols. Several measured biomarkers are available and thorough statistical testing is possible. Adjustments in models were chosen to include established factors that are known to confound the associations between health behaviors and cardiovascular health in population-based data, where the information was available. Therefore diet was not included in analyses of substudy III, because the data for the dietary index was not yet at hand. Other important covariates such as depression (II, IV), menopausal status (III), or BMI (III, IV) were chosen based on important associations observed in previous literature with both the behavior and outcome under study. Nevertheless, there always remains a possibility of residual confounding i.e. not all confounding factors are measured and included.

The cardiometabolic risk factors in substudy III were dichotomized and not used as continuous variables in final models. Models were also tested with continuous data on cardiometabolic risk factors, but the results did not differ significantly from the reported ones. The categorical variables were chosen because they allowed for the information on medication use to be included within the outcome of high risk. For example, the American Heart Association's definition of ideal cardiovascular health includes the use of

medication to attain ideal levels of cholesterol, blood pressure and fasting glucose (Lloyd-Jones et al., 2010).

6.4.1 SELF-REPORTED DATA

A methodological weakness of the study is the use of self-report methods. Self-report methods are accepted in large population-based studies, but using devices to objectively measure activity would, in addition, provide valuable information about the intensity and timing of PA, breaks in sedentary behavior and the peacefulness of sleep. That kind of information would deepen our understanding of the behaviors. Measuring PA and sleep objectively has already become fairly easy and the devices and instruments are cheaper to purchase. The use of devices for the objective assessment of PA and sleep is becoming more common also in population-based research. Features of PA, sedentary behavior and sleep that can be captured with devices may reveal important information related to health outcomes and be a future subject to study.

The questions on PA in the FINRISK 2012 study were established over the years and have shown good criterion validity against mortality and morbidity (Hu et al., 2007). In the working age population the questions also show moderate correlation against accelerometer counts (Fagt et al., 2011). The questions do not however provide sufficient information for a more precise calculation of MET-values to be done, similar to what was done in the Finnish former elite athlete cohort. This method has previously been validated against detailed PA interview (Waller et al., 2008). In the substudy II, a LTPA index was created to include information on domestic PA as well. The index scoring and classification of people was based on current PA guidelines for adults and the final index was also evaluated against self-reported fitness.

Sedentary behaviors were self-reported as time spent sitting in five different domains. Sitting is the most typical sedentary behavior and TV time the most common domain of sedentary time to be assessed by self-report (Rhodes et al., 2012). Particularly for more precise assessment of breaks in sedentary time, but also in regards to the amount of sedentariness, to the related posture and timing of the behavior, the use of devices for objective measurement can provide valuable information.

Sleep is the behavior that is still the most difficult to assess objectively by devices. There are accelerometers developed to capture sleep, and wrist accelerometry have provided a good means to measure sleep in field settings (Ancoli-Israel et al., 2003; Marino et al., 2013). The role of self-estimated sleep quality and sufficiency of sleep can however be problematic to assess by accelerometry (Krystal and Edinger, 2008). The sleep questions in FINRISK 2012 study assessed the time of going to bed and rising from bed and also a subjective estimate of sleep duration, that provided the possibility to calculate a separate time in bed variable, and the corrected midpoint of sleep.

All sleep questionnaire and measurement items in the Finnish former elite athlete cohort have also previously been used in the 1981 survey of the Finnish Twin cohort (Hublin et al., 2007; Koskenvuo et al., 2007).

6.4.2   THE LATENT CLASS ANALYSIS

As a method, the LCA has considerable strengths, such as the possibility to use a large set of variables to construct meaningful and sample-specific grouping of people. Health behaviors are highly individual, but interindividual heterogeneity is seldom modelled or considered in large-scale studies using variable-oriented methods. With large data sets and many variables of interest, it can be demanding to interpret large contingency tables with a high number of possible behavioral combinations; and to describe behavioral combinations (McAloney et al., 2013).

Ideally, variable-oriented and person-oriented modelling complete each other and provide a more comprehensive view on the issue (Bergman and Trost, 2006; von Eye et al., 2006). In this thesis, both approaches have been used. In substudy I, as the aim was to study the interrelationship between PA and sleep, first steps of modelling were based on logistic regression models where the associations between PA, sedentary behavior and sleep variables were assessed. Out of these models (results not shown) it was concluded that the relationships between different domains of PA, and sitting and sleep variables were not systematic, with some gender differences also observed. It would have been demanding to form any meaningful subgroups of people based on all this information, using any traditional variable-centered method. With the help of the person-oriented approach of LCA it was possible to combine the broad data on PA and sleep and form an interpretable and more generalizable model describing the underlying clustering of the behaviors.

Employment status was included as a variable in the PA and sleep Profiles since also OPA and CPA were to be included. This resulted in the employment status to differentiate the Profiles strongly, leaving the information in the PA variables OPA and CPA to more accurately identify the class profiles. If the employment status would not have been included, the information in the OPA and CPA variables would more strongly have differentiated the Profiles but not necessarily have reflected the true information in these variables since those not working also have no CPA or OPA.

The LCA is based on probabilities and each person has a probability of membership in every latent class (Collins and Lanza, 2010). The average posterior probabilities of class membership were used to evaluate the average probability of membership for each Profile. The average posterior probabilities for the Profiles varied for men between 0.85 and 0.97 and for women between 0.87 and 0.97. The average posterior probabilities are counted based on every persons probability of membership in that specific

latent class. An average posterior probability of 0.7 can be considered to describe good class separation (Nagin, 2005), i.e. the average likelihood of membership is more certain than uncertain. The probabilistic nature of membership in the latent classes were accounted for in subsequent analyses (II, III) by weighing the models by the probability of membership in each class.

The LCA method also includes subjective decisions such as choice of the best model and interpretation of class profiles to be made. However, statistical criteria are available to support and to justify the decisions. Nevertheless, it is acknowledged that the result of the LCA always reflects the choices made by the researcher. One such choice is also the choice of variables included in the LCA. Many studies using LCA with categorical variables utilize dichotomous variables in their models in order to facilitate the interpretation of the class profiles. In this study it was chosen to have several response categories as many items such as sleep duration would loose important information if dichotomized. This resulted in a more multidimensional interpretation of the Profiles. As discussed earlier (see e.g. page 80), employment status was included in the PA and sleep Profiles that were constructed by gender. When already stratified by gender, further stratification by employment status would have resulted in a risk of sparseness in the models and also for this reason the employment status variable was chosen to be included in the LCA.

6.5   IMPLICATIONS AND FUTURE DIRECTIONS

In this thesis a person-oriented approach was chosen to study the interrelationship between PA and sleep at population level. The result suggest that PA and sleep are likely to cluster and unfavorable behaviors are likely occuring within the same cluster. This finding differs from previously reported associations between PA and sleep, which most often only reflect associations between variables, assuming interindividual heterogeneity to be random. Together with previous observations, this thesis supports the important correlation between PA and sleep also in initially CVD free adults.

Some evidence from previous literature suggest that sleep is a stronger predictor of consequent PA than PA of following sleep, even though PA can be an effective mean to enhance sleep quality. Therefore, more research is needed, particularly in larger and more varying adult samples about the longitudinal association between PA and sleep and about how a change in the behaviors is reflected in the other.

In health promotion work, attention should be paid on the clustering of short or poor sleep, high sedentary behavior and insufficient PA as these most likely associate with poor cardiovascular health. In this thesis the joint association of low PA and insufficient sleep with worse cardiometabolic risk factors was found to be evident particularly in women, whereas the

associations in men were more uncertain, but cannot either be ruled out. Men with poor sleep, high leisure time sitting and low PA did show a high 10-year CVD risk. Furthermore, men with low LTPA and short sleep were more likely than men with recommended levels of PA and mid-range sleep to die from CVD, where the synergistic effect of the two behaviors was more than their summation.

The role of more often repeated or chronic evening PA in relation for sleep needs to be studied and the role of chronotype should be taken into account. Our inherent circadian rhythm and our timing of sleep also play a role for PA and sedentary behaviors. Evening type persons, but also more evening-than-morning oriented persons with high morning tiredness need to be identified in health promotion work as unfavorable health behaviors seem to be related with both dimensions of the chronotype, with eventually the risk of low cardiovascular health increased in these persons.

The role of sedentary behaviors in the interplay between PA and sleep should not be forgotten and also this study gives reason to conclude on a significant interrelationship between sedentary behaviors, PA and sleep. However, even if increasing evidence suggest sedentary behaviors to be an independent risk factor for cardiovascular health, more studies are needed to confirm and explain the association. In future population studies objective or measured assessment of PA is likely conducted over a 24-hour period, which then can provide more detailed information to strengthen the knowledge about the interrelationship between PA, sedentary time and sleep. This kind of information includes for example different intensities of PA, timing of PA during 24-hours and the ratio between PA, sedentary behaviors and sleep. Furthermore, with objective assessment of sleep in larger samples there is a possibility to study the circadian variation of PA and its amplitudes in different populations. However, as observed in this study, self-estimated quality and sufficiency of sleep are important features of sleep that cannot be captured by accelerometry.

The person-oriented modelling still has more potential in epidemiological research, and in this thesis it served as a valuable tool for the analysis of the available broad data on PA and sleep. By means of the LCA it was possible to group the large sample to reflect sample-specific subpopulations and interpretable combinations of behaviors. In the operationalization of the chronotype, LCA modelling suited the purpose well, resulting in a characterized classification of different chronotypes. It needs to be remembered that the LCA includes many subjective choices that can affect the outcome, but as stated previously, person-oriented and variable-oriented methods can optimally fulfill each other.

7 CONCLUSIONS

This thesis studied the interrelationships between PA and sleep and their joint association with cardiometabolic risk factors and total CVD risk, in a large sample of initially CVD free participants. The operationalization of chronotype by a person-oriented method was performed to deepen the understanding of the associations between chronotype and health on population-level. In substudy IV the interaction between PA and sleep in relation to CVD mortality was also considered. Interrelationships of PA and sleep were observed and inter-individual variation or Profiles in men and women were identified based on the similarities in their PA and sleep behaviors. Almost half of men and women most likely belonged to the "*Physically active, normal range sleepers*" and *"Physically active, good sleepers",* respectively. These Profiles were characterized by employment, high LTPA, self-reported sufficient sleep and mid-range sleep duration. About 5% of men were estimated to be members in the *"Physically inactive, poor sleepers"* and 11% of women in the *"Pysically inactive, short sleepers"* Profile. These Profiles were identified by the likelihood of physical inactivity, high screen time sitting, self-reported insufficient sleep and short sleep duration. Operationalization of chronotype by a person-oriented method showed that in addition to evening preference morning tiredness did differentiate the chronotypes in the population based data. A relationship of "*evening type*" and "*tired, more evening type*" with low LTPA, and furthermore "*evening type*" and high amounts of sitting was observed. Women with membership in the *"Physically inactive, short sleepers"* had less favorable levels of blood pressure, triglycerides, glycated hemoglobin, CRP, BMI, waist circumference and HDL cholesterol, as compared to women with membership in the *"Physically active, good sleepers"* Profile. In men, clustering of PA and sleep behaviors was associated with smoking and alcohol consumption which together with sociodemographic factors attenuated the independent associations of membership in the PA and sleep Profiles with cardiometabolic risk factors. However, the estimated 10-year total CVD risk differed between the PA and sleep Profiles in both genders, with a high risk observed in the *"Physically inactive, poor sleepers"* and *"Physically inactive, short sleepers"* in men and women, respectively. It was also observed, that in a population of male former athletes and their healthy referents, low LTPA and short sleep predicted higher CVD mortality, as compared to high PA and mid-range sleep. Findings in this study thus suggest clustering of PA and sleep and important joint association with CVD risk, with some gender nuances. The results presented in this thesis, mostly generalizable to the adult general population, are relevant from a public health perspective considering the prevalences of physical inactivity and poor sleep in the population.

8 ACKNOWLEDGEMENTS

My deepest and most sincere gratitude I express to my two supervisors Adjunct Professor Katja Borodulin, THL, and Adjunct Professor Erkki Kronholm, THL. With you guiding my way through this process, the journey has been a most unforgettable, educative, safe and positive experience. I thank you Katja for offering me the opportunity to work with this topic, for believing in me and supporting me from the first day on. Your expertise in physical activity epidemiology and public health, your positive attitude, as well as your genuine and energetic person are admirable qualities that have made the collaboration with you most pleasant. To you Erkki, I express my gratitude for the committed guidance you have directed to me, especially in my times of insufficiency and despair. Your notable experience and knowledge in sleep epidemiology, your enthusiasm for research work and eagerness to continuously learn more, not to forget the touch of humor you carry along, have truly inspired me along the way.

I sincerely thank all my co-authors for contributing with their valuable comments and expertise in my work. Your input has been invaluable for the study. I particularly want to thank Professor Asko Tolvanen at the Univeristy of Jyväskylä, who sat down with me and provided me with comprehensive guidance to the Latent Class Analysis. I warmly recognize Marketta Taimi for her skillful technical assistance and for kindly revising the language of the final thesis with excellent care.

I want to thank the official reviewers Adjunct Professor Katja Pahkala at the University of Turku and Adjunct Professor Eva Roos at the Folkhälsan Research Center, Helsinki, for their careful consideration of this thesis. Your efforts and comments made this thesis improve as a whole. I thank Adjunct Professor Katriina Kukkonen-Harjula for accepting the role of opponent at my thesis defence.

To all my colleagues and co-workers in the Health Monitoring unit and THL I want to express my gratitude for all the great company and change of ideas you have provided me with during these years. I am happy to have had such great people around me. I thank Satu Männistö and Jaana Lindström for the informative and inspiring meetings they organized for us doctoral students. Special thanks I wish to dedicate to Arto Pietilä for always being ready with a helping hand in statistical problems, to Anne Juolevi for her company and empathies' as a roommate, and to Noora Kanerva for welcoming me not only as a colleague, but as a friend from my very first days at the office. I especially want to thank Noora for many fruitful conversations related to both the thesis process and to a working athlete's life.

I am grateful to my friends for their friendship and their interest in my work and the encouragement they have given me along the way. The times spent with you always lighten my mind in all matters. I particularly want to acknowledge the most brilliant "Northern Stars", my teammates, with whom I can spend the best possible time off from work and daily routine. Your friendship and support, and our achievements together have provided me with irreplaceable energy and joy that also has conducted to my work.

I want to thank my family for being there for me no matter what. I am deeply grateful to my mother and grandmother for their care and unconditional support in life. My deep and loving thanks I owe to Juha, especially for standing by me when I took on this project, with everything that it included, such as moving to a new city. Thank you for believing in me and reinforcing my confidence when it is shattered, and for making me smile and enjoy life.

To my father, I wish you could have been here for this day and all the days before. You used to encourage me to be brave, but not foolhardy. I am glad that I was brave and seezed this opportunity that was offered to me four years ago. And I think you would agree.

Time goes by, but memories stay, so also of this project.

Helsinki, October 2016
    Heini

REFERENCES

Aadahl M., Andreasen A.H., Hammer-Helmich L., Buhelt L., Jorgensen T., and Glumer C. Recent Temporal Trends in Sleep Duration, Domain-Specific Sedentary Behaviour and Physical Activity. A Survey among 25-79-Year-Old Danish Adults. Scand J Public Health 2013: 41: 706-711.

Adan A., Archer S.N., Paz Hidalgo M., Di Milia L., Natale V., and Randler C. Circadian Typology: A Comprehensive Review. Chronobiol Int 2012: 29: 1153-1175.

Aggio D., Smith L., and Hamer M. Effects of Reallocating Time in Different Activity Intensities on Health and Fitness: A Cross Sectional Study. Int J Behav Nutr Phys Act 2015: 12: 83.

Ahmed H.M., Blaha M.J., Nasir K., Rivera J.J., and Blumenthal R.S. Effects of Physical Activity on Cardiovascular Disease. Am J Cardiol 2012: 109: 288-295.

Ainsworth B., Cahalin L., Buman M., and Ross R. The Current State of Physical Activity Assessment Tools. Prog Cardiovasc Dis 2015: 57: 387-395.

Ainsworth B.E., Haskell W.L., Herrmann S.D., Meckes N., Bassett D.R.,Jr, Tudor-Locke C., Greer J.L., Vezina J., Whitt-Glover M.C., and Leon A.S. 2011 Compendium of Physical Activities: A Second Update of Codes and MET Values. Med Sci Sports Exerc 2011: 43: 1575-1581.

Altman N.G., Izci-Balserak B., Schopfer E., Jackson N., Rattanaumpawan P., Gehrman P.R., Patel N.P., and Grandner M.A. Sleep Duration Versus Sleep Insufficiency as Predictors of Cardiometabolic Health Outcomes. Sleep Med 2012: 13: 1261-1270.

Ancoli-Israel S., Cole R., Alessi C., Chambers M., Moorcroft W., and Pollak C.P. The Role of Actigraphy in the Study of Sleep and Circadian Rhythms. Sleep 2003: 26: 342-392.

Anothaisintawee T., Reutrakul S., Van Cauter E., and Thakkinstian A. Clinical Review: Sleep Disturbances Compared to Traditional Risk Factors for Diabetes Development: Systematic Review and Meta-Analysis. Sleep Medicine Reviews 2016: 30: 11-24.

Archer E. and Blair S.N. Physical Activity and the Prevention of Cardiovascular Disease: From Evolution to Epidemiology. Prog Cardiovasc Dis 2011: 53: 387-396.

Aritake-Okada S., Kaneita Y., Uchiyama M., Mishima K., and Ohida T. Non-Pharmacological Self-Management of Sleep among the Japanese General Population. Journal of Clinical Sleep Medicine 2009: 5: 464-469.

Atkinson G. and Davenne D. Relationships between Sleep, Physical Activity and Human Health. Physiol Behav 2007: 90: 229-235.

Australian Government, The Department of Health .Australia's Physical Activity and Sedentary Behaviour Guidelines. Australian Government. The Department of Health 2014 Available at: http://www.health.gov.au/internet/main/publishing.nsf/content/health-pubhlth-strateg-phys-act-guidelines Retrieved: April, 2016.

Autenrieth C.S., Baumert J., Baumeister S.E., Fischer B., Peters A., Doring A., and Thorand B. Association between Domains of Physical Activity and all-Cause, Cardiovascular and Cancer Mortality. Eur J Epidemiol 2011: 26: 91-99.

Authors/Task Force Members, Ryden L., Grant P.J., Anker S.D., Berne C., Cosentino F., Danchin N., Deaton C., Escaned J., Hammes H.P., Huikuri H., Marre M., Marx N., Mellbin L., Ostergren J., Patrono C., Seferovic P., Uva M.S., Taskinen M.R., Tendera M., Tuomilehto J., Valensi P., Zamorano J.L., ESC Committee for Practice Guidelines (CPG), Zamorano J.L., Achenbach S., Baumgartner H., Bax J.J., Bueno H., Dean V., Deaton C., Erol C., Fagard R., Ferrari R., Hasdai D., Hoes A.W., Kirchhof P., Knuuti J., Kolh P., Lancellotti P., Linhart A., Nihoyannopoulos P., Piepoli M.F., Ponikowski P., Sirnes P.A., Tamargo J.L., Tendera M., Torbicki A., Wijns W., Windecker S., Document Reviewers, De Backer G., Sirnes P.A., Ezquerra E.A., Avogaro A., Badimon L., Baranova E., Baumgartner H., Betteridge J., Ceriello A., Fagard R., Funck-Brentano C., Gulba D.C., Hasdai D., Hoes A.W., Kjekshus J.K., Knuuti J., Kolh P., Lev E., Mueller C., Neyses L., Nilsson P.M., Perk J., Ponikowski P., Reiner Z., Sattar N., Schachinger V., Scheen A., Schirmer H., Stromberg A., Sudzhaeva S., Tamargo J.L., Viigimaa M., Vlachopoulos C., and Xuereb R.G. ESC Guidelines on Diabetes, Pre-Diabetes, and Cardiovascular Diseases Developed in Collaboration with the EASD: The Task Force on Diabetes, Pre-Diabetes, and Cardiovascular Diseases of the European Society of Cardiology (ESC) and Developed in Collaboration with the European Association for the Study of Diabetes (EASD). Eur Heart J 2013: 34: 3035-3087.

Bachorik P.S. and Ross J.W. National Cholesterol Education Program Recommendations for Measurement of Low-Density Lipoprotein Cholesterol: Executive Summary. the National Cholesterol Education Program Working Group on Lipoprotein Measurement. Clin Chem 1995: 41: 1414-1420.

Badran M., Yassin B.A., Fox N., Laher I., and Ayas N. Epidemiology of Sleep Disturbances and Cardiovascular Consequences. Can J Cardiol 2015: 31: 873-879.

Bansil P., Kuklina E.V., Merritt R.K., and Yoon P.W. Associations between Sleep Disorders, Sleep Duration, Quality of Sleep, and Hypertension: Results from the

National Health and Nutrition Examination Survey, 2005 to 2008. J Clin Hypertens (Greenwich) 2011: 13: 739-743.

Barclay N.L. and Gregory A.M. Quantitative Genetic Research on Sleep: A Review of Normal Sleep, Sleep Disturbances and Associated Emotional, Behavioural, and Health-Related Difficulties. Sleep Med Rev 2013: 17: 29-40.

Barengo N.C., Hu G., Lakka T.A., Pekkarinen H., Nissinen A., and Tuomilehto J. Low Physical Activity as a Predictor for Total and Cardiovascular Disease Mortality in Middle-Aged Men and Women in Finland. Eur Heart J 2004: 25: 2204-2211.

Basner M., Fomberstein K.M., Razavi F.M., Banks S., William J.H., Rosa R.R., and Dinges D.F. American Time use Survey: Sleep Time and its Relationship to Waking Activities. Sleep 2007: 30: 1085-1095.

Bauman A.E., Reis R.S., Sallis J.F., Wells J.C., Loos R.J.F., and Martin B.W. Correlates of Physical Activity: Why are some People Physically Active and Others Not? The Lancet 2012: 380: 258-271.

Bellavia A., Åkerstedt T., Bottai M., Wolk A., and Orsini N. Sleep Duration and Survival Percentiles Across Categories of Physical Activity. Am J Epidemiol 2014: 179: 484-491.

Benloucif S., Orbeta L., Ortiz R., Janssen I., Finkel S.I., Bleiberg J., and Zee P.C. Morning Or Evening Activity Improves Neuropsychological Performance and Subjective Sleep Quality in Older Adults. Sleep 2004: 27: 1542-1551.

Bergman L.R. and Trost K. The Person-Oriented Versus the Variable-Oriented Approach: Are they Complementary, Opposites, Or Exploring Different Worlds? Merrill-Palmer Quarterly 2006: 52: 601-632.

Berrigan D., Dodd K., Troiano R.P., Krebs-Smith S.M., and Barbash R.B. Patterns of Health Behavior in U.S. Adults. Prev Med 2003: 36: 615-623.

Berry J.D., Willis B., Gupta S., Barlow C.E., Lakoski S.G., Khera A., Rohatgi A., de Lemos J.A., Haskell W., and Lloyd-Jones D.M. Lifetime Risks for Cardiovascular Disease Mortality by Cardiorespiratory Fitness Levels Measured at Ages 45, 55, and 65 Years in Men. the Cooper Center Longitudinal Study. J Am Coll Cardiol 2011: 57: 1604-1610.

Borbely A.A., Daan S., Wirz-Justice A., and Deboer T. The Two-Process Model of Sleep Regulation: A Reappraisal. J Sleep Res 2016: 25: 131-143.

Borodulin K., Harald K., Jousilahti P., Laatikainen T., Männistö S., and Vartiainen E. Time Trends in Physical Activity from 1982 to 2012 in Finland. Scand J Med Sci Sports 2016: 26: 93-100.

Borodulin K., Kärki A., Laatikainen T., Peltonen M., and Luoto R. Daily Sedentary Time and Risk of Cardiovascular Disease: The National FINRISK 2002 Study. J Phys Act Health 2014a: 12: 904-908.

Borodulin K., Vartiainen E., Peltonen M., Jousilahti P., Juolevi A., Laatikainen T., Männistö S., Salomaa V., Sundvall J., and Puska P. Forty-Year Trends in Cardiovascular Risk Factors in Finland. Eur J Public Health 2014b: 25: 539-546.

Bramble D.M. and Lieberman D.E. Endurance Running and the Evolution of Homo. Nature 2004: 432: 345-352.

Brassington G. and Hicks R. Aerobic Exercise and Self-Reported Sleep Quality in Elderly Individuals. J Aging Phys Act 1995: 3: 120-134.

Bromley L.E., Booth J.N.,3rd, Kilkus J.M., Imperial J.G., and Penev P.D. Sleep Restriction Decreases the Physical Activity of Adults at Risk for Type 2 Diabetes. Sleep 2012: 35: 977-984.

Broms U., Pennanen M., Patja K., Ollila H., Korhonen T., Kankaanpää A., Haukkala A., Tuulio-Henriksson A., Koskenvuo M., Kronholm E., Laatikainen T., Peltonen M., Partonen T., and Kaprio J. Diurnal Evening Type is Associated with Current Smoking, Nicotine Dependence and Nicotine Intake in the Population Based National FINRISK 2007 Study. J Addict Res Ther 2012: S2: 002.

Broms U., Pitkäniemi J., Bäckmand H., Heikkilä K., Koskenvuo M., Peltonen M., Sarna S., Vartiainen E., Kaprio J., and Partonen T. Long-Term Consistency of Diurnal-Type Preferences among Men. Chronobiol Int 2014: 31: 182-188.

Buman M.P., Phillips B.A., Youngstedt S.D., Kline C.E., and Hirshkowitz M. Does Nighttime Exercise really Disturb Sleep? Results from the 2013 National Sleep Foundation Sleep in America Poll. Sleep Med 2014a: 15: 755-761.

Buman M.P., Winkler E.A., Kurka J.M., Hekler E.B., Baldwin C.M., Owen N., Ainsworth B.E., Healy G.N., and Gardiner P.A. Reallocating Time to Sleep, Sedentary Behaviors, Or Active Behaviors: Associations with Cardiovascular Disease Risk Biomarkers, NHANES 2005-2006. Am J Epidemiol 2014b: 179: 323-334.

Burns D.M. Epidemiology of Smoking-Induced Cardiovascular Disease. Prog Cardiovasc Dis 2003: 46: 11-29.

Buxton O.M. and Marcelli E. Short and Long Sleep are Positively Associated with Obesity, Diabetes, Hypertension, and Cardiovascular Disease among Adults in the United States. Soc Sci Med 2010: 71: 1027-1036.

Buysse D.J., Grunstein R., Horne J., and Lavie P. Can an Improvement in Sleep Positively Impact on Health? Sleep Med Rev 2010: 14: 405-410.

References

Buysse D.J., Reynolds C.F.,3rd, Monk T.H., Berman S.R., and Kupfer D.J. The Pittsburgh Sleep Quality Index: A New Instrument for Psychiatric Practice and Research. Psychiatry Res 1989: 28: 193-213.

Bäckmand H., Kaprio J., Kujala U., and Sarna S. Personality and Mood of Former Elite Male Athletes--a Descriptive Study. Int J Sports Med 2001: 22: 215-221.

Cai H., Shu X.O., Xiang Y.B., Yang G., Li H., Ji B.T., Gao J., Gao Y.T., and Zheng W. Sleep Duration and Mortality: A Prospective Study of 113 138 Middle-Aged and Elderly Chinese Men and Women. Sleep 2015: 38: 529-536.

Cappuccio F.P., Cooper D., D'Elia L., Strazzullo P., and Miller M.A. Sleep Duration Predicts Cardiovascular Outcomes: A Systematic Review and Meta-Analysis of Prospective Studies. Eur Heart J 2011: 32: 1484-1492.

Cappuccio F.P., D'Elia L., Strazzullo P., and Miller M.A. Sleep Duration and all-Cause Mortality: A Systematic Review and Meta-Analysis of Prospective Studies. Sleep 2010: 33: 585-592.

Casas R.S., Pettee Gabriel K.K., Kriska A.M., Kuller L.H., and Conroy M.B. Association of Leisure Physical Activity and Sleep with Cardiovascular Risk Factors in Postmenopausal Women. Menopause 2012: 19: 413-419.

Caspersen C.J., Powell K.E., and Christenson G.M. Physical Activity, Exercise, and Physical Fitness: Definitions and Distinctions for Health-Related Research. Public Health Rep 1985: 100: 126-131.

Chastin S.F., Egerton T., Leask C., and Stamatakis E. Meta-Analysis of the Relationship between Breaks in Sedentary Behavior and Cardiometabolic Health. Obesity (Silver Spring) 2015a: 23: 1800-1810.

Chastin S.F.M., Palarea-Albaladejo J., Dontje M.L., and Skelton D.A. Combined Effects of Time Spent in Physical Activity, Sedentary Behaviors and Sleep on Obesity and Cardio-Metabolic Health Markers: A Novel Compositional Data Analysis Approach. PLoS One 2015b: 10: e0139984.

Chau J.Y., Grunseit A., Midthjell K., Holmen J., Holmen T.L., Bauman A.E., and van der Ploeg H.P. Cross-Sectional Associations of Total Sitting and Leisure Screen Time with Cardiometabolic Risk in Adults. Results from the HUNT Study, Norway. J Sci Med Sport 2014: 17: 78-84.

Chau J.Y., van H.P., Merom D., Chey T., and Bauman A.E. Cross-Sectional Associations between Occupational and Leisure-Time Sitting, Physical Activity and Obesity in Working Adults. Prev Med 2012: 54: 195-200.

Chennaoui M., Arnal P.J., Sauvet F., and Leger D. Sleep and Exercise: A Reciprocal Issue? Sleep Med Rev 2015: 20: 59-72.

Cintra F., Bittencourt L.R., Santos-Silva R., Andersen M., de Paola A., Poyares D., and Tufik S. The Association between the Framingham Risk Score and Sleep: A Sao Paulo Epidemiological Sleep Study. Sleep Med 2012: 13: 577-582.

Clark B.K., Sugiyama T., Healy G.N., Salmon J., Dunstan D.W., and Owen N. Validity and Reliability of Measures of Television Viewing Time and Other Non-Occupational Sedentary Behaviour of Adults: A Review. Obes Rev 2009: 10: 7-16.

Collins L.M. and Lanza S.T. .Latent Class and Latent Transition Analysis. with Applications in the Social, Behavioral, and Health Sciences. Wiley series in probability and statistics. Hoboken, New Jersey, USA. 2010.

Conroy M.B., Cook N.R., Manson J.E., Buring J.E., and Lee I. Past Physical Activity, Current Physical Activity, and Risk of Coronary Heart Disease. Medicine & Science in Sports & Exercise 2005: 37: 1251-1256.

Conry M.C., Morgan K., Curry P., McGee H., Harrington J., Ward M., and Shelley E. The Clustering of Health Behaviours in Ireland and their Relationship with Mental Health, Self-Rated Health and Quality of Life. BMC Public Health 2011: 11: 692.

D'Agostino R.B.S., Vasan R.S., Pencina M.J., Wolf P.A., Cobain M., Massaro J.M., and Kannel W.B. General Cardiovascular Risk Profile for use in Primary Care: The Framingham Heart Study. Circulation 2008: 117: 743-753.

de Bourdeaudhuij I. and van Oost P. A Cluster-Analytical Approach Toward Physical Activity and Other Health Related Behaviors. Med Sci Sports Exerc 1999: 31: 605-612.

DeFina L.F., Haskell W.L., Willis B.L., Barlow C.E., Finley C.E., Levine B.D., and Cooper K.H. Physical Activity Versus Cardiorespiratory Fitness: Two (Partly) Distinct Components of Cardiovascular Health? Prog Cardiovasc Dis 2015: 57: 324-329.

Dempsey P.C., Owen N., Biddle S.J., and Dunstan D.W. Managing Sedentary Behavior to Reduce the Risk of Diabetes and Cardiovascular Disease. Curr Diab Rep 2014: 14: 522.

Di Milia L., Adan A., Natale V., and Randler C. Reviewing the Psychometric Properties of Contemporary Circadian Typology Measures. Chronobiol Int 2013: 30: 1261-1271.

Diaz K.M., Howard V.J., Hutto B., Colabianchi N., Vena J.E., Blair S.N., and Hooker S.P. Patterns of Sedentary Behavior in US Middle-Age and Older Adults: The REGARDS Study. Med Sci Sports Exerc 2016: 48: 430-438.

Digdon N.L. and Rhodes S. Methods used to Cope with Sleepiness may Perpetuate Sleepiness in College Students with an Evening Type Circadian Preference. Biol Rhythm Res 2009: 40: 129-144.

Ding D., Rogers K., Macniven R., Kamalesh V., Kritharides L., Chalmers J., and Bauman A. Revisiting Lifestyle Risk Index Assessment in a Large Australian Sample: Should Sedentary Behavior and Sleep be Included as Additional Risk Factors? Prev Med 2014: 60: 102-106.

Dishman R.K., Sui X., Church T.S., Kline C.E., Youngstedt S.D., and Blair S.N. Decline in Cardiorespiratory Fitness and Odds of Incident Sleep Complaints. Med Sci Sports Exerc 2015: 47: 960-966.

Dobree L. How do we Keep in Time? Understanding Human Circadian Rhythms. Prof Nurse 1993: 8: 446-49.

Driver H. and Taylor S. Exercise and Sleep. Sleep Medicine Reviews 2000: 4: 387-402.

Dunstan D.W., Howard B., Healy G.N., and Owen N. Too Much Sitting - A Health Hazard. Diabetes Res Clin Pract 2012a: 97: 368-376.

Dunstan D.W., Kingwell B.A., Larsen R., Healy G.N., Cerin E., Hamilton M.T., Shaw J.E., Bertovic D.A., Zimmet P.Z., Salmon J., and Owen N. Breaking Up Prolonged Sitting Reduces Postprandial Glucose and Insulin Responses. Diabetes Care 2012b: 35: 976-983.

Dzau V.J., Antman E.M., Black H.R., Hayes D.L., Manson J.E., Plutzky J., Popma J.J., and Stevenson W. The Cardiovascular Disease Continuum Validated: Clinical Evidence of Improved Patient Outcomes: Part I: Pathophysiology and Clinical Trial Evidence (Risk Factors through Stable Coronary Artery Disease). Circulation 2006: 114: 2850-2870.

Eguchi E., Iso H., Tanabe N., Wada Y., Yatsuya H., Kikuchi S., Inaba Y., Tamakoshi A., and Japan Collaborative Cohort Study Group. Healthy Lifestyle Behaviours and Cardiovascular Mortality among Japanese Men and Women: The Japan Collaborative Cohort Study. Eur Heart J 2012: 33: 467-477.

Emerging Risk Factors Collaboration, Di Angelantonio E., Sarwar N., Perry P., Kaptoge S., Ray K.K., Thompson A., Wood A.M., Lewington S., Sattar N., Packard C.J., Collins R., Thompson S.G., and Danesh J. Major Lipids, Apolipoproteins, and Risk of Vascular Disease. Jama 2009: 302: 1993-2000.

Emerging Risk Factors Collaboration, Kaptoge S., Di Angelantonio E., Pennells L., Wood A.M., White I.R., Gao P., Walker M., Thompson A., Sarwar N., Caslake M., Butterworth A.S., Amouyel P., Assmann G., Bakker S.J., Barr E.L., Barrett-Connor E., Benjamin E.J., Bjorkelund C., Brenner H., Brunner E., Clarke R., Cooper J.A., Cremer P., Cushman M., Dagenais G.R., D'Agostino RB S., Dankner R., Davey-Smith G., Deeg D., Dekker J.M., Engstrom G., Folsom

A.R., Fowkes F.G., Gallacher J., Gaziano J.M., Giampaoli S., Gillum R.F., Hofman A., Howard B.V., Ingelsson E., Iso H., Jorgensen T., Kiechl S., Kitamura A., Kiyohara Y., Koenig W., Kromhout D., Kuller L.H., Lawlor D.A., Meade T.W., Nissinen A., Nordestgaard B.G., Onat A., Panagiotakos D.B., Psaty B.M., Rodriguez B., Rosengren A., Salomaa V., Kauhanen J., Salonen J.T., Shaffer J.A., Shea S., Ford I., Stehouwer C.D., Strandberg T.E., Tipping R.W., Tosetto A., Wassertheil-Smoller S., Wennberg P., Westendorp R.G., Whincup P.H., Wilhelmsen L., Woodward M., Lowe G.D., Wareham N.J., Khaw K.T., Sattar N., Packard C.J., Gudnason V., Ridker P.M., Pepys M.B., Thompson S.G., and Danesh J. C-Reactive Protein, Fibrinogen, and Cardiovascular Disease Prediction. N Engl J Med 2012: 367: 1310-1320.

Fabsitz R.R., Sholinsky P., and Goldberg J. Correlates of Sleep Problems among Men: The Vietnam Era Twin Registry. J Sleep Res 1997: 6: 50-56.

Fagt S., Andersen L.F., Anderssen S.A., Becker W., Borodulin K., Fogelholm M., Groth M.V., Gunnarsdottir I., Helakorpi S., Kolle E., Matthiessen J., Rosenlund-Sorensen M., Simonen R., Sveinsson T., Tammelin T., Thorgeirsdottir H., Valsta L., and Trolle E. Nordic Monitoring of Diet, Physical Activity and Overweight. Validation of Indicators. Nordic Council of Ministers 2011. TemaNord 2011:556.

Feng Q., Zhang Q.L., Du Y., Ye Y.L., and He Q.Q. Associations of Physical Activity, Screen Time with Depression, Anxiety and Sleep Quality among Chinese College Freshmen. PLoS One 2014: 9: e100914.

Ferrara M. and De Gennaro L. How Much Sleep do we Need? Sleep Med Rev 2001: 5: 155-179.

Ferrie J.E., Kumari M., Salo P., Singh-Manoux A., and Kivimaki M. Sleep Epidemiology--a Rapidly Growing Field. Int J Epidemiol 2011: 40: 1431-1437.

Flausino N.H., Da Silva Prado J.M., de Queiroz S.S., Tufik S., and de Mello M.T. Physical Exercise Performed before Bedtime Improves the Sleep Pattern of Healthy Young Good Sleepers. Psychophysiology 2012: 49: 186-192.

Fogelholm M., Kaprio J., and Sarna S. Healthy Lifestyles of Former Finnish World Class Athletes. Med Sci Sports Exerc 1994: 26: 224-229.

Fogelholm M., Kronholm E., Kukkonen-Harjula K., Partonen T., Partinen M., and Härmä M. Sleep-Related Disturbances and Physical Inactivity are Independently Associated with Obesity in Adults. Int J Obes (Lond) 2007: 31: 1713-1721.

Foley D., Ancoli-Israel S., Britz P., and Walsh J. Sleep Disturbances and Chronic Disease in Older Adults - Results of the 2003 National Sleep Foundation Sleep in America Survey. J Psychosom Res 2004: 56: 497-502.

Folsom A.R., Yatsuya H., Nettleton J.A., Lutsey P.L., Cushman M., and Rosamond W.D. Community Prevalence of Ideal Cardiovascular Health, by the American Heart Association Definition, and Relationship with Cardiovascular Disease Incidence. J Am Coll Cardiol 2011: 57: 1690-1696.

Ford E.S. and Caspersen C.J. Sedentary Behaviour and Cardiovascular Disease: A Review of Prospective Studies. Int J Epidemiol 2012: 41: 1338-1353.

Ford E.S., Zhao G., and Li C. Pre-Diabetes and the Risk for Cardiovascular Disease: A Systematic Review of the Evidence. J Am Coll Cardiol 2010: 55: 1310-1317.

Gallicchio L. and Kalesan B. Sleep Duration and Mortality: A Systematic Review and Meta-Analysis. J Sleep Res 2009: 18: 148-158.

Gangwisch J.E. Epidemiological Evidence for the Links between Sleep, Circadian Rhythms and Metabolism. Obes Rev 2009: 10 Suppl 2: 37-45.

Gardiner P.A., Healy G.N., Eakin E.G., Clark B.K., Dunstan D.W., Shaw J.E., Zimmet P.Z., and Owen N. Associations between Television Viewing Time and overall Sitting Time with the Metabolic Syndrome in Older Men and Women: The Australian Diabetes Obesity and Lifestyle Study. J Am Geriatr Soc 2011: 59: 788-796.

GBD 2013 Mortality and Causes of Death Collaborators. Global, Regional, and National Age–sex Specific all-Cause and Cause-Specific Mortality for 240 Causes of Death, 1990–2013: A Systematic Analysis for the Global Burden of Disease Study 2013. The Lancet 2015: 385: 117-171.

Gibbs B.B., Hergenroeder A.L., Katzmarzyk P.T., Lee I.M., and Jakicic J.M. Definition, Measurement, and Health Risks Associated with Sedentary Behavior. Med Sci Sports Exerc 2015: 47: 1295-1300.

Girschik J., Fritschi L., Heyworth J., and Waters F. Validation of Self-Reported Sleep Against Actigraphy. J Epidemiol 2012: 22: 462-468.

Glazer N.L., Lyass A., Esliger D.W., Blease S.J., Freedson P.S., Massaro J.M., Murabito J.M., and Vasan R.S. Sustained and Shorter Bouts of Physical Activity are Related to Cardiovascular Health. Med Sci Sports Exerc 2013: 45: 109-115.

Goff D.C.,Jr, Lloyd-Jones D.M., Bennett G., Coady S., D'Agostino R.B., Gibbons R., Greenland P., Lackland D.T., Levy D., O'Donnell C.J., Robinson J.G., Schwartz J.S., Shero S.T., Smith S.C.,Jr, Sorlie P., Stone N.J., Wilson P.W., Jordan H.S., Nevo L., Wnek J., Anderson J.L., Halperin J.L., Albert N.M., Bozkurt B., Brindis R.G., Curtis L.H., DeMets D., Hochman J.S., Kovacs R.J., Ohman E.M., Pressler S.J., Sellke F.W., Shen W.K., Smith S.C.,Jr, Tomaselli G.F., and American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of

Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014: 129: S49-73.

Goldberg I.J., Eckel R.H., and McPherson R. Triglycerides and Heart Disease: Still a Hypothesis? Arterioscler Thromb Vasc Biol 2011: 31: 1716-1725.

Goldstein D.E., Little R.R., Lorenz R.A., Malone J.I., Nathan D.M., Peterson C.M., and American Diabetes Association. Tests of Glycemia in Diabetes. Diabetes Care 2003: 26 Suppl 1: S106-8.

Grandner M.A. and Drummond S.P.A. Who are the Long Sleepers? Towards an Understanding of the Mortality Relationship. Sleep Med Rev 2007: 11: 341-360.

Grandner M.A., Patel N.P., Gehrman P.R., Perlis M.L., and Pack A.I. Problems Associated with Short Sleep: Bridging the Gap between Laboratory and Epidemiological Studies. Sleep Medicine Reviews 2010: 14: 239-247.

Grandner M.A., Sands-Lincoln M., Pak V.M., and Garland S.N. Sleep Duration, Cardiovascular Disease, and Proinflammatory Biomarkers. Nature & Science of Sleep 2013: 5: 93.

Green M.J., Espie C.A., Hunt K., and Benzeval M. The Longitudinal Course of Insomnia Symptoms: Inequalities by Sex and Occupational Class among Two Different Age Cohorts Followed for 20 Years in the West of Scotland. Sleep 2012: 35: 815-823.

Guallar-Castillon P., Bayan-Bravo A., Leon-Munoz L.M., Balboa-Castillo T., Lopez-Garcia E., Gutierrez-Fisac J.L., and Rodriguez-Artalejo F. The Association of Major Patterns of Physical Activity, Sedentary Behavior and Sleep with Health-Related Quality of Life: A Cohort Study. Prev Med 2014: 67: 248-254.

Haario P., Rahkonen O., Laaksonen M., Lahelma E., and Lallukka T. Bidirectional Associations between Insomnia Symptoms and Unhealthy Behaviours. J Sleep Res 2012: 22: 89-95.

Hague J.F., Gilbert S.S., Burgess H.J., Ferguson S.A., and Dawson D. A Sedentary Day: Effects on Subsequent Sleep and Body Temperatures in Trained Athletes. Physiol Behav 2003: 78: 261-267.

Hamer M. and Chida Y. Active Commuting and Cardiovascular Risk: A Meta-Analytic Review. Prev Med 2008: 46: 9-13.

Hamer M., Batty G.D., Stamatakis E., and Kivimäki M. Comparison of Risk Factors for Fatal Stroke and Ischemic Heart Disease: A Prospective Follow Up of the Health Survey for England. Atherosclerosis 2011: 219: 807-810.

Haraszti R.A., Purebl G., Salavecz G., Poole L., Dockray S., and Steptoe A. Morningness-Eveningness Interferes with Perceived Health, Physical Activity, Diet and Stress Levels in Working Women: A Cross-Sectional Study. Chronobiol Int 2014: 31: 829-837.

Harrington D.M., Barreira T.V., Staiano A.E., and Katzmarzyk P.T. The Descriptive Epidemiology of Sitting among US Adults, NHANES 2009/2010. J Sci Med Sport 2014: 17: 371-375.

Haskell W.L., Lee I.M., Pate R.R., Powell K.E., Blair S.N., Franklin B.A., Macera C.A., Heath G.W., Thompson P.D., Bauman A., American College of Sports Medicine, and American Heart Association. Physical Activity and Public Health: Updated Recommendation for Adults from the American College of Sports Medicine and the American Heart Association. Circulation 2007: 116: 1081-1093.

Healy G.N., Clark B.K., Elisabeth A.H. Winkler, Gardiner P.A., Brown W.J., and Matthews C.E. Measurement of Adults' Sedentary Time in Population-Based Studies. Am J Prev Med 2011: 41: 216-227.

Healy G.N. and Owen N. Editorial: Sedentary Behaviour and Biomarkers of Cardiometabolic Health Risk in Adolescents: An Emerging Scientific and Public Health Issue. Revista Española De Cardiología (English Edition) 2010: 63: 261-264.

Heikkala E., Remes J., Paananen M., Taimela S., Auvinen J., and Karppinen J. Accumulation of Lifestyle and Psychosocial Problems and Persistence of Adverse Lifestyle Over Two-Year Follow-Up among Finnish Adolescents. BMC Public Health 2014: 14: 1620-1640.

Heinonen I., Helajärvi H., Pahkala K., Heinonen O.J., Hirvensalo M., Palve K., Tammelin T., Yang X., Juonala M., Mikkilä V., Kähönen M., Lehtimäki T., Viikari J., and Raitakari O.T. Sedentary Behaviours and Obesity in Adults: The Cardiovascular Risk in Young Finns Study. BMJ Open 2013: 3: e002901.

Hoevenaar-Blom M.P., Spijkerman A.M., Kromhout D., and Verschuren W.M. Sufficient Sleep Duration Contributes to Lower Cardiovascular Disease Risk in Addition to Four Traditional Lifestyle Factors: The MORGEN Study. Eur J Prev Cardiol 2014: 21: 1367-1375.

Holfeld B. and Ruthig J.C. A Longitudinal Examination of Sleep Quality and Physical Activity in Older Adults. J Appl Gerontol 2014: 33: 791-807.

Holtermann A., Marott J.L., Gyntelberg F., Sogaard K., Suadicani P., Mortensen O.S., Prescott E., and Schnohr P. Occupational and Leisure Time Physical Activity: Risk of all-Cause Mortality and Myocardial Infarction in the Copenhagen City Heart Study. A Prospective Cohort Study. BMJ Open 2012: 2: e000556.

Horne J.A. and Östberg O. A Self-Assessment Questionnaire to Determine Morningness-Eveningness in Human Circadian Rhythms. Int J Chronobiol 1976: 4: 97-110.

Howard B.J., Balkau B., Thorp A.A., Magliano D.J., Shaw J.E., Owen N., and Dunstan D.W. Associations of overall Sitting Time and TV Viewing Time with Fibrinogen and C Reactive Protein: The AusDiab Study. Br J Sports Med 2015: 49: 255-258.

Hsueh M.C., Liao Y., and Chang S.H. Associations of Total and Domain-Specific Sedentary Time with Type 2 Diabetes in Taiwanese Older Adults. J Epidemiol 2016: 26:348-54.

Hu G., Jousilahti P., Borodulin K., Barengo N.C., Lakka T.A., Nissinen A., and Tuomilehto J. Occupational, Commuting and Leisure-Time Physical Activity in Relation to Coronary Heart Disease among Middle-Aged Finnish Men and Women. Atherosclerosis 2007: 194: 490-497.

Hublin C., Kaprio J., Partinen M., and Koskenvuo M. Insufficient Sleep--a Population-Based Study in Adults. Sleep 2001: 24: 392-400.

Hublin C., Partinen M., Koskenvuo K., Silventoinen K., Koskenvuo M., and Kaprio J. Shift-Work and Cardiovascular Disease: A Population-Based 22-Year Follow-Up Study. Eur J Epidemiol 2010: 25: 315-323.

Hublin C., Partinen M., Koskenvuo M., and Kaprio J. Sleep and Mortality: A Population-Based 22-Year Follow-Up Study. Sleep 2007: 30: 1245-1253.

Husu P., Suni J., Vähä-Ypyä H., Sievänen H., Tokola K., Valkeinen H., Mäki-Opas T., and Vasankari T. Suomalaisten aikuisten kiihtyvyysmittarilla mitattu fyysinen aktiivisuus ja liikkumattomuus [the Level of Physical Activity and Sedentary Behaviour in Finnish Adults. Abstract in English]. Suom Lääkäril 2014: 69: 1860-1866.

Hätönen T., Forsblom S., Kieseppä T., Lönnqvist J., and Partonen T. Circadian Phenotype in Patients with the Co-Morbid Alcohol use and Bipolar Disorders. Alcohol &Alcoholism 2008: 43: 564-568.

Jackson C.L., Redline S., and Emmons K.M. Sleep as a Potential Fundamental Contributor to Disparities in Cardiovascular Health. Annu Rev Public Health 2015: 36: 417-440.

Jacobson T.A., Miller M., and Schaefer E.J. Hypertriglyceridemia and Cardiovascular Risk Reduction. Clin Ther 2007: 29: 763-777.

Jousilahti P., Laatikainen T., Peltonen M., Borodulin K., Männistö S., Jula A., Salomaa V., Harald K., Puska P., and Vartiainen E. Primary Prevention and Risk Factor Reduction in Coronary Heart Disease Mortality among Working

Aged Men and Women in Eastern Finland Over 40 Years: Population Based Observational Study. BMJ 2016: 352.

Järvenpää T., Rinne J.O., Koskenvuo M., Räihä I., and Kaprio J. Binge Drinking in Midlife and Dementia Risk. Epidemiology 2005: 16: 766-771.

Kanerva N., Kaartinen N.E., Ovaskainen M.L., Konttinen H., Kontto J., and Mannisto S. A Diet Following Finnish Nutrition Recommendations does Not Contribute to the Current Epidemic of Obesity. Public Health Nutr 2013: 16: 786-794.

Kanerva N., Kronholm E., Partonen T., Ovaskainen M.L., Kaartinen N.E., Konttinen H., Broms U., and Mannisto S. Tendency Toward Eveningness is Associated with Unhealthy Dietary Habits. Chronobiol Int 2012: 29: 920-927.

Kaprio J. and Koskenvuo M. A Prospective Study of Psychological and Socioeconomic Characteristics, Health Behavior and Morbidity in Cigarette Smokers Prior to Quitting Compared to Persistent Smokers and Non-Smokers. J Clin Epidemiol 1988: 41: 139-150.

Katzmarzyk P.T., Church T.S., Craig C.L., and Bouchard C. Sitting Time and Mortality from all Causes, Cardiovascular Disease, and Cancer. Med Sci Sports Exerc 2009: 41: 998-1005.

Kauderer S. and Randler C. Differences in Time use among Chronotypes in Adolescents. Biol Rhythm Res 2013: 44: 601-608.

Kestilä P., Magnussen C.G., Viikari J.S.A., Kähönen M., Hutri-Kähönen N., Taittonen L., Jula A., Loo B., Pietikäinen M., Jokinen E., Lehtimäki T., Kivimäki M., Juonala M., and Raitakari O.T. Socioeconomic Status, Cardiovascular Risk Factors, and Subclinical Atherosclerosis in Young Adults: The Cardiovascular Risk in Young Finns Study. Arterioscler Thromb Vasc Biol 2012: 32: 815-821.

Kettunen J.A., Kujala U.M., Kaprio J., Bäckmand H., Peltonen M., Eriksson J.G., and Sarna S. All-Cause and Disease-Specific Mortality among Male, Former Elite Athletes: An Average 50-Year Follow-Up. Br J Sports Med 2015: 49: 893-897.

Kim K., Uchiyama M., Okawa M., Liu X., and Ogihara R. An Epidemiological Study of Insomnia among the Japanese General Population. Sleep 2000: 23: 41-47.

Klatsky A.L. Alcohol and Cardiovascular Diseases: Where do we Stand Today? J Intern Med 2015: 278: 238-250.

Knol M.J. and VanderWeele T.J. Recommendations for Presenting Analyses of Effect Modification and Interaction. Int J Epidemiol 2011: 41: 514-520.

Knutson K.L. Sleep Duration and Cardiometabolic Risk: A Review of the Epidemiologic Evidence. Best Pract Res Clin Endocrinol Metab 2010: 24: 731-743.

Knutson K.L., Rathouz P.J., Yan L.L., Liu K., and Lauderdale D.S. Intra-Individual Daily and Yearly Variability in Actigraphically Recorded Sleep Measures: The CARDIA Study. Sleep 2007: 30: 793-796.

Knutson K.L. and Turek F.W. The U-Shaped Association between Sleep and Health: The 2 Peaks do Not Mean the Same Thing. Sleep 2006: 29: 878-879.

Knutson K.L. and Van Cauter E. Associations between Sleep Loss and Increased Risk of Obesity and Diabetes. Ann N Y Acad Sci 2008: 1129: 287-304.

Kohl H.W. and Murray T.D. .Cardiorespiratory and Metabolic Health. Human Kinetics. 2012a. in: Harold W. Kohl and Tinker D. Murray. Foundations of physical activity and public health. pp: 73-93.Sheridan Books, USA.

Kohl H.W. and Murray T.D. .Measuring Physical Activity. Human Kinetics. 2012b. in: Harold W. Kohl and Tinker D. Murray. Foundations of physical activity and public health. pp: 55-69.Sheridan Books, USA.

Konttinen H., Kronholm E., Partonen T., Kanerva N., Männistö S., and Haukkala A. Morningness-Eveningness, Depressive Symptoms, and Emotional Eating: A Population-Based Study. Chronobiol Int 2014: 31: 554-563.

Koskenvuo M., Hublin C., Partinen M., Heikkilä K., and Kaprio J. Heritability of Diurnal Type: A Nationwide Study of 8753 Adult Twin Pairs. J Sleep Res 2007: 16: 156-162.

Koskenvuo M., Langinvainio H., Kaprio J., Rantasalo I., and Sarna S. Baseline Characteristics of Finnish Twin Registry: Section III: Occupational and Psychosocial Factors. Helsinki University Press 1979. M49.

Koski S., Lahti-Koski M., Vartiainen E., and Laatikainen T. Sydän- ja verisuonisairauksien ja diabeteksen asiantuntijaryhmän raportti 2015 [Report of the Expert Group for Cardiovascular Diseases and Diabetes 2015. Abstract in English.]. National Institute of Health and Welfare 2015. Directions 17/2014.

Kredlow M.A., Capozzoli M.C., Hearon B.A., Calkins A.W., and Otto M.W. The Effects of Physical Activity on Sleep: A Meta-Analytic Review. J Behav Med 2015: 38: 427-449.

Kronholm E., Laatikainen T., Peltonen M., Sippola R., and Partonen T. Self-Reported Sleep Duration, all-Cause Mortality, Cardiovascular Mortality and Morbidity in Finland. Sleep Med 2011: 12: 215-221.

Kronholm E., Partonen T., Harma M., Hublin C., Lallukka T., Peltonen M., and Laatikainen T. Prevalence of Insomnia-Related Symptoms Continues to Increase in the Finnish Working-Age Population. J Sleep Res 2016: 25: 454-57.

Kronholm E., Partonen T., Laatikainen T., Peltonen M., Härmä M., Hublin C., Kaprio J., Aro A.R., Partinen M., Fogelholm M., Valve R., Vahtera J., Oksanen T., Kivimäki M., Koskenvuo M., and Sutela H. Trends in Self-Reported Sleep Duration and Insomnia-Related Symptoms in Finland from 1972 to 2005: A Comparative Review and Re-Analysis of Finnish Population Samples. J Sleep Res 2008: 17: 54-62.

Kronholm E., Härmä M., Hublin C., Aro A.R., and Partonen T. Self-Reported Sleep Duration in Finnish General Population. J Sleep Res 2006: 15: 276-290.

Krystal A.D. and Edinger J.D. Measuring Sleep Quality. Sleep Med 2008: 9 Suppl 1: S10-17.

Kubitz K.A., Landers D.M., Petruzzello S.J., and Han M. The Effects of Acute and Chronic Exercise on Sleep. A Meta-Analytic Review. Sports Med 1996: 21: 277-291.

Kujala U.M., Sarna S., Kaprio J., Koskenvuo M., and Karjalainen J. Heart Attacks and Lower-Limb Function in Master Endurance Athletes. Med Sci Sports Exerc 1999: 31: 1041-1046.

Kukkonen-Harjula K. Liikunnan ja unen yhteyksien tutkimusmenetelmät. Liikunnan ja unen yhteyksien tutkiminen – Tutkimusasetelmat, -kysymykset ja -tuloksia. Suomalainen Lääkäriseura Duodecim 2015. nix02248.

Laaksonen M., Talala K., Martelin T., Rahkonen O., Roos E., Helakorpi S., Laatikainen T., and Prättälä R. Health Behaviours as Explanations for Educational Level Differences in Cardiovascular and all-Cause Mortality: A Follow-Up of 60 000 Men and Women Over 23 Years. Eur J Public Health 2008: 18: 38-43.

Lakerveld J., Mackenbach J.D., Horvath E., Rutters F., Compernolle S., Bardos H., De Bourdeaudhuij I., Charreire H., Rutter H., Oppert J.M., McKee M., and Brug J. The Relation between Sleep Duration and Sedentary Behaviours in European Adults. Obes Rev 2016: 17 Suppl 1: 62-67.

Lang C., Kalak N., Brand S., Holsboer-Trachsler E., Pühse U., and Gerber M. Clinical Review: The Relationship between Physical Activity and Sleep from Mid Adolescence to Early Adulthood. A Systematic Review of Methodological Approaches and Meta-Analysis. Sleep Medicine Reviews 2016: 28: 28-41.

Lanza S.T., Collins L.M., Lemmon D.R., and Schafer J.L. PROC LCA: A SAS Procedure for Latent Class Analysis. Struct Equ Modeling 2007: 14: 671-694.

Lastella M., Roach G.D., Halson S.L., and Sargent C. Sleep/Wake Behaviours of Elite Athletes from Individual and Team Sports. Eur J Sport Sci 2015: 15: 94-100.

Laugsand L.E., Vatten L.J., Platou C., and Janszky I. Insomnia and the Risk of Acute Myocardial Infarction: A Population Study. Circulation 2011: 124: 2073-2081.

Lavie C.J., Arena R., Swift D.L., Johannsen N.M., Sui X., Lee D.C., Earnest C.P., Church T.S., O'Keefe J.H., Milani R.V., and Blair S.N. Exercise and the Cardiovascular System: Clinical Science and Cardiovascular Outcomes. Circ Res 2015: 117: 207-219.

Lee I.M. and Paffenbarger R.S.,Jr. Associations of Light, Moderate, and Vigorous Intensity Physical Activity with Longevity. the Harvard Alumni Health Study. Am J Epidemiol 2000: 151: 293-299.

Lee I.M., Shiroma E.J., Lobelo F., Puska P., Blair S.N., Katzmarzyk P.T., and Lancet Physical Activity Series Working Group. Effect of Physical Inactivity on Major Non-Communicable Diseases Worldwide: An Analysis of Burden of Disease and Life Expectancy. Lancet 2012: 380: 219-229.

Lee I.M. and Skerrett P.J. Physical Activity and all-Cause Mortality: What is the Dose-Response Relation? Medicine & Science in Sports & Exercise 2001: 33: S459-S471.

Li J. and Siegrist J. Physical Activity and Risk of Cardiovascular Disease--a Meta-Analysis of Prospective Cohort Studies. Int J Environ Res Public Health 2012: 9: 391-407.

Libby P. Inflammation and Cardiovascular Disease Mechanisms. Am J Clin Nutr 2006: 83: 456S-460S.

Lira F.S., Pimentel G.D., Santos R.V., Oyama L.M., Damaso A.R., Oller do Nascimento C.M., Viana V.A., Boscolo R.A., Grassmann V., Santana M.G., Esteves A.M., Tufik S., and de Mello M.T. Exercise Training Improves Sleep Pattern and Metabolic Profile in Elderly People in a Time-Dependent Manner. Lipids Health Dis 2011: 10: 1-6.

Littman A.J., Vitiello M.V., Foster-Schubert K., Ulrich C.M., Tworoger S.S., Potter J.D., Weigle D.S., and McTiernan A. Sleep, Ghrelin, Leptin and Changes in Body Weight during a 1-Year Moderate-Intensity Physical Activity Intervention. Int J Obes 2007: 31: 466-475.

Liu L., Miura K., Fujiyoshi A., Kadota A., Miyagawa N., Nakamura Y., Ohkubo T., Okayama A., Okamura T., and Ueshima H. Impact of Metabolic Syndrome on the Risk of Cardiovascular Disease Mortality in the United States and in Japan. Am J Cardiol 2014: 113: 84-89.

References

Lloyd-Jones D.M. Cardiovascular Risk Prediction: Basic Concepts, Current Status, and Future Directions. Circulation 2010: 121: 1768-1777.

Lloyd-Jones D.M. Cardiovascular Health and Protection Against CVD: More than the Sum of the Parts? Circulation 2014: 130: 1671-1673.

Lloyd-Jones D.M., Hong Y., Labarthe D., Mozaffarian D., Appel L.J., Van Horn L., Greenlund K., Daniels S., Nichol G., Tomaselli G.F., Arnett D.K., Fonarow G.C., Ho P.M., Lauer M.S., Masoudi F.A., Robertson R.M., Roger V., Schwamm L.H., Sorlie P., Yancy C.W., Rosamond W.D., and American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and Setting National Goals for Cardiovascular Health Promotion and Disease Reduction: The American Heart Association's Strategic Impact Goal through 2020 and Beyond. Circulation 2010: 121: 586-613.

Loponen M., Hublin C., Kalimo R., Mänttäri M., and Tenkanen L. Joint Effect of Self-Reported Sleep Problems and Three Components of the Metabolic Syndrome on Risk of Coronary Heart Disease. J Psychosom Res 2010: 68: 149-158.

Loyen A., van der Ploeg H.P., Bauman A., Brug J., and Lakerveld J. European Sitting Championship: Prevalence and Correlates of Self-Reported Sitting Time in the 28 European Union Member States. PLoS One 2016: 11: e0149320.

Lubke G. and Muthen B. Investigating Population Heterogeneity with Factor Mixture Models. Psychol Methods 2005: 10: 21-39.

Luyster F.S., Strollo P.J.,Jr, Zee P.C., Walsh J.K., and Boards of Directors of the American Academy of Sleep Medicine and the Sleep Research Society. Sleep: A Health Imperative. Sleep 2012: 35: 727-734.

Magee C.A., Kritharides L., Attia J., Mcelduff P., and Banks E. Short and Long Sleep Duration are Associated with Prevalent Cardiovascular Disease in Australian Adults. J Sleep Res 2012: 21: 441-447.

Marino M., Li Y., Rueschman M.N., Winkelman J.W., Ellenbogen J.M., Solet J.M., Dulin H., Berkman L.F., and Buxton O.M. Measuring Sleep: Accuracy, Sensitivity, and Specificity of Wrist Actigraphy Compared to Polysomnography. Sleep 2013: 36: 1747-1755.

Matthews C.E., Chen K.Y., Freedson P.S., Buchowski M.S., Beech B.M., Pate R.R., and Troiano R.P. Amount of Time Spent in Sedentary Behaviors in the United States, 2003-2004. Am J Epidemiol 2008: 167: 875-881.

Matthews K.A., Strollo P.J.,Jr, Hall M., Mezick E.J., Kamarck T.W., Owens J.F., Buysse D.J., and Reis S.E. Associations of Framingham Risk Score Profile and Coronary Artery Calcification with Sleep Characteristics in Middle-Aged Men and Women: Pittsburgh SleepSCORE Study. Sleep 2011: 34: 711-716.

McAloney K., Graham H., Law C., and Platt L. A Scoping Review of Statistical Approaches to the Analysis of Multiple Health-Related Behaviours. Prev Med 2013: 56: 365-371.

McClain J.J., Lewin D.S., Laposky A.D., Kahle L., and Berrigan D. Associations between Physical Activity, Sedentary Time, Sleep Duration and Daytime Sleepiness in US Adults. Prev Med 2014: 66: 68-73.

Merikanto I., Kronholm E., Peltonen M., Laatikainen T., Lahti T., and Partonen T. Relation of Chronotype to Sleep Complaints in the General Finnish Population. Chronobiol Int 2012: 29: 311-317.

Merikanto I., Lahti T., Puolijoki H., Vanhala M., Peltonen M., Laatikainen T., Vartiainen E., Salomaa V., Kronholm E., and Partonen T. Associations of Chronotype and Sleep with Cardiovascular Diseases and Type 2 Diabetes. Chronobiol Int 2013: 30: 470-477.

Merikanto I., Englund A., Kronholm E., Laatikainen T., Peltonen M., Vartiainen E., and Partonen T. Evening Chronotypes have the Increased Odds for Bronchial Asthma and Nocturnal Asthma. Chronobiol Int 2014: 31: 95-101.

Mezick E.J., Hall M., and Matthews K.A. Are Sleep and Depression Independent Or Overlapping Risk Factors for Cardiometabolic Disease? Sleep Med Rev 2011: 15: 51-63.

Mindell J.S., Giampaoli S., Goesswald A., Kamtsiuris P., Mann C., Mannisto S., Morgan K., Shelton N.J., Verschuren W.M., Tolonen H., and HES Response Rate Group. Sample Selection, Recruitment and Participation Rates in Health Examination Surveys in Europe--Experience from Seven National Surveys. BMC Med Res Methodol 2015: 15: 78.

Morgan K. Daytime Activity and Risk Factors for Late-Life Insomnia. J Sleep Res 2003: 12: 231-238.

Morris C.J., Aeschbach D., and Scheer F.A. Circadian System, Sleep and Endocrinology. Mol Cell Endocrinol 2012: 349: 91-104.

Morris C.J., Purvis T.E., Hu K., and Scheer F.A.J.L. Circadian Misalignment Increases Cardiovascular Disease Risk Factors in Humans. Proceedings of the National Academy of Sciences 2016: 113: E1402-E1411.

Morris J.N., Heady J.A., Raffle P.A., Roberts C.G., and Parks J.W. Coronary Heart-Disease and Physical Activity of Work. Lancet 1953: 265: 1111-20.

Myers J., McAuley P., Lavie C.J., Despres J.P., Arena R., and Kokkinos P. Physical Activity and Cardiorespiratory Fitness as Major Markers of Cardiovascular Risk: Their Independent and Interwoven Importance to Health Status. Prog Cardiovasc Dis 2015: 57: 306-314.

References

Myllymäki T., Rusko H., Syväoja H., Juuti T., Kinnunen M.L., and Kyröläinen H. Effects of Exercise Intensity and Duration on Nocturnal Heart Rate Variability and Sleep Quality. Eur J Appl Physiol 2012: 112: 801-809.

Mäkinen T., Borodulin K., Laatikainen T., Fogelholm M., and Prättälä R. Twenty-Five Year Socioeconomic Trends in Leisure-Time and Commuting Physical Activity among Employed Finns. Scand J Med Sci Sports 2009: 19: 188-197.

Mäkinen T.E., Sippola R., Borodulin K., Rahkonen O., Kunst A., Klumbiene J., Regidor E., Ekholm O., Mackenbach J., and Prättälä R. Explaining Educational Differences in Leisure-Time Physical Activity in Europe: The Contribution of Work-Related Factors. Scand J Med Sci Sports 2012: 22: 439-447.

Nagin D. Group-Based Modeling of Development. 2005 Harvard University Press. Cambridge, Massachusetts, USA.

Nam B.H., Kannel W.B., and D'Agostino R.B. Search for an Optimal Atherogenic Lipid Risk Profile: From the Framingham Study. Am J Cardiol 2006: 97: 372-375.

Natale V. and Cicogna P. Morningness-Eveningness Dimension: Is it really a Continuum? Personality and Individual Differences 2002: 32: 809-816.

Nelson R.H. Hyperlipidemia as a Risk Factor for Cardiovascular Disease. Prim Care 2013: 40: 195-211.

Noble N., Paul C., Turon H., and Oldmeadow C. Review: Which Modifiable Health Risk Behaviours are Related? A Systematic Review of the Clustering of Smoking, Nutrition, Alcohol and Physical Activity ('SNAP') Health Risk Factors. Prev Med 2015: 81: 16-41.

Nuutinen T., Ray C., and Roos E. Do Computer use, TV Viewing, and the Presence of the Media in the Bedroom Predict School-Aged Children's Sleep Habits in a Longitudinal Study? BMC Public Health 2013: 13: 684.

Odegaard A.O., Woon-Puay Koh, Gross M.D., Jian-Min Yuan, and Pereira M.A. Combined Lifestyle Factors and Cardiovascular Disease Mortality in Chinese Men and Women. Circulation 2011: 124: 2847-2854.

Ohayon M.M. Epidemiology of Insomnia: What we Know and what we Still Need to Learn. Sleep Med Rev 2002: 6: 97-111.

Ohayon M.M., Guilleminault C., and Chokroverty S. Sleep Epidemiology 30 Years Later: Where are we? Sleep Med 2010: 11: 961-962.

Ohida T., Kamal A.M., Uchiyama M., Kim K., Takemura S., Sone T., and Ishii T. The Influence of Lifestyle and Health Status Factors on Sleep Loss among the Japanese General Population. Sleep 2001: 24: 333-338.

Oja P. Dose Response between Total Volume of Physical Activity and Health and Fitness. Medicine & Science in Sports & Exercise 2001: 33: S428-S437.

Osonoi Y., Mita T., Osonoi T., Saito M., Tamasawa A., Nakayama S., Someya Y., Ishida H., Kanazawa A., Gosho M., Fujitani Y., and Watada H. Morningness-Eveningness Questionnaire Score and Metabolic Parameters in Patients with Type 2 Diabetes Mellitus. Chronobiol Int 2014: 31: 1017-1023.

Owen N., Sugiyama T., Eakin E.E., Gardiner P.A., Tremblay M.S., and Sallis J.F. Adults' Sedentary Behavior Determinants and Interventions. Am J Prev Med 2011: 41: 189-196.

Paffenbarger R.S.,Jr and Lee I.M. A Natural History of Athleticism, Health and Longevity. J Sports Sci 1998: 16 Suppl: S31-45.

Pahkala K., Heinonen O.J., Simell O., Viikari J.S., Rönnemaa T., Niinikoski H., and Raitakari O.T. Association of Physical Activity with Vascular Endothelial Function and Intima-Media Thickness. Circulation 2011: 124: 1956-1963.

Paine S.J., Gander P.H., and Travier N. The Epidemiology of Morningness/Eveningness: Influence of Age, Gender, Ethnicity, and Socioeconomic Factors in Adults (30-49 Years). J Biol Rhythms 2006: 21: 68-76.

Passos G.S., Poyares D.L., Santana M.G., Tufik S., and Mello M.T. Is Exercise an Alternative Treatment for Chronic Insomnia? Clinics (Sao Paulo) 2012: 67: 653-660.

Pate R.R., O'Neill J.R., and Lobelo F. The Evolving Definition of "Sedentary". Exerc Sport Sci Rev 2008: 36: 173-178.

Patel S.R., Malhotra A., Gottlieb D.J., White D.P., and Hu F.B. Correlates of Long Sleep Duration. Sleep 2006: 29: 881-889.

Peltonen M., Laatikainen T., Borodulin K., Wikström K., Jousilahti P., Jula A., Männistö S., Salomaa V., Vartiainen E., and Puska P. Prevalence of Ideal Cardiovascular Health in an Adult Finnish Population: The National FINRISK 2007 Study. International Heart and Vascular Disease Journal 2014: 2: 3.

Pepin V., Boucetta S., Chan-Thim E., Parwanta Z., Gouin J., and Dang-Vu T. The Role of Sleep and Physical Activity on the Risk for Cardiovascular Disease. Current Cardiovascular Risk Reports 2014: 8: 1.

Poortinga W. The Prevalence and Clustering of Four Major Lifestyle Risk Factors in an English Adult Population. Prev Med 2007: 44: 124-128.

Powell K.E., Paluch A.E., and Blair S.N. Physical Activity for Health: What Kind? how Much? how Intense? on Top of what? Annu Rev Public Health 2011: 32: 349-365.

References

Rajaratnam S.M. and Arendt J. Health in a 24-H Society. Lancet 2001: 358: 999-1005.

Randler C. and Vollmer C. Epidemiological Evidence for the Bimodal Chronotype using the Composite Scale of Morningness. Chronobiol Int 2012: 29: 1-4.

Redline S. and Foody J. Sleep Disturbances: Time to Join the Top 10 Potentially Modifiable Cardiovascular Risk Factors? Circulation 2011: 124: 2049-2051.

Rhodes R.E., Mark R.S., and Temmel C.P. Review and Special Article: Adult Sedentary Behavior. A Systematic Review. Am J Prev Med 2012: 42: e3-e28.

Ridker P.M. C-Reactive Protein: Eighty Years from Discovery to Emergence as a Major Risk Marker for Cardiovascular Disease. Clin Chem 2009: 55: 209-215.

Ridker P.M. and Silvertown J.D. Inflammation, C-Reactive Protein, and Atherothrombosis. J Periodontol 2008: 79: 1544-1551.

Roberts C.K., Hevener A.L., and Barnard R.J. Metabolic Syndrome and Insulin Resistance: Underlying Causes and Modification by Exercise Training. Compr Physiol 2013: 3: 1-58.

Roenneberg T., Allebrandt K.V., Merrow M., and Vetter C. Social Jetlag and Obesity. Curr Biol 2012: 22: 939-943.

Roenneberg T., Kuehnle T., Juda M., Kantermann T., Allebrandt K., Gordijn M., and Merrow M. Epidemiology of the Human Circadian Clock. Sleep Med Rev 2007: 11: 429-438.

Romanov K., Rose R.J., Kaprio J., Koskenvuo M., Langinvainio H., and Sarna S. Self-Reported Alcohol use: A Longitudinal Study of 12,994 Adults. Alcohol Alcohol Suppl 1987: 1: 619-623.

Rutters F., Lemmens S.G., Adam T.C., Bremmer M.A., Elders P.J., Nijpels G., and Dekker J.M. Is Social Jetlag Associated with an Adverse Endocrine, Behavioral, and Cardiovascular Risk Profile? J Biol Rhythms 2014: 29: 377-383.

Sabanayagam C. and Shankar A. Sleep Duration and Cardiovascular Disease: Results from the National Health Interview Survey. Sleep 2010: 33: 1037-1042.

Same R.V., Feldman D.I., Shah N., Martin S.S., Al Rifai M., Blaha M.J., Graham G., and Ahmed H.M. Relationship between Sedentary Behavior and Cardiovascular Risk. Curr Cardiol Rep 2016: 18: 6.

Samitz G., Egger M., and Zwahlen M. Domains of Physical Activity and all-Cause Mortality: Systematic Review and Dose-Response Meta-Analysis of Cohort Studies. Int J Epidemiol 2011: 40: 1382-1400.

Sarna S., Sahi T., Koskenvuo M., and Kaprio J. Increased Life Expectancy of World Class Male Athletes. Med Sci Sports Exerc 1993: 25: 237-244.

Sattelmair J., Pertman J., Ding E.L., Kohl H.W.,3rd, Haskell W., and Lee I.M. Dose Response between Physical Activity and Risk of Coronary Heart Disease: A Meta-Analysis. Circulation 2011: 124: 789-795.

Schaal S., Peter M., and Randler C. Morningness-Eveningness and Physical Activity in Adolescents. International Journal of Sport and Exercise Psychology 2010: 8: 147-159.

Scheer F.A.J.L., Hilton M.F., Mantzoros C.S., and Shea S.A. Adverse Metabolic and Cardiovascular Consequences of Circadian Misalignment. Proceedings of the National Academy of Sciences 2009: 17: 4453-4458.

Schmid S.M., Hallschmid M., Jauch-Chara K., Wilms B., Benedict C., Lehnert H., Born J., and Schultes B. Short-Term Sleep Loss Decreases Physical Activity Under Free-Living Conditions but does Not Increase Food Intake Under Time-Deprived Laboratory Conditions in Healthy Men. Am J Clin Nutr 2009: 90: 1476-1482.

Schottker B., Rathmann W., Herder C., Thorand B., Wilsgaard T., Njolstad I., Siganos G., Mathiesen E.B., Saum K.U., Peasey A., Feskens E., Boffetta P., Trichopoulou A., Kuulasmaa K., Kee F., Brenner H., and CHANCES group. HbA1c Levels in Non-Diabetic Older Adults - no J-Shaped Associations with Primary Cardiovascular Events, Cardiovascular and all-Cause Mortality After Adjustment for Confounders in a Meta-Analysis of Individual Participant Data from Six Cohort Studies. BMC Med 2016: 14: 26.

Schwartz S., McDowell Anderson W., Cole S.R., Cornoni-Huntley J., Hays J.C., and Blazer D. Insomnia and Heart Disease: A Review of Epidemiologic Studies. J Psychosom Res 1999: 47: 313-333.

Sedentary Behaviour Research N. Letter to the Editor: Standardized use of the Terms "Sedentary" and "Sedentary Behaviours". Appl Physiol Nutr Metab 2012: 37: 540-542.

Shankar A., Charumathi S., and Kalidindi S. Sleep Duration and Self-Rated Health: The National Health Interview Survey 2008. Sleep 2011: 34: 1173-1177.

Shephard R.J. Limits to the Measurement of Habitual Physical Activity by Questionnaires. Br J Sports Med 2003: 37: 197-206.

Silva D.A., Peres K.G., Boing A.F., Gonzalez-Chica D.A., and Peres M.A. Clustering of Risk Behaviors for Chronic Noncommunicable Diseases: A Population-Based Study in Southern Brazil. Prev Med 2013: 56: 20-24.

References

Simmonds M.C. and Wald N.J. Risk Estimation Versus Screening Performance: A Comparison of Six Risk Algorithms for Cardiovascular Disease. J Med Screen 2012: 19: 201-205.

Simons L.A., Simons J., Friedlander Y., and McCallum J. A Comparison of Risk Factors for Coronary Heart Disease and Ischaemic Stroke: The Dubbo Study of Australian Elderly. Heart Lung Circ 2009: 18: 330-333.

Sisson S.B., Camhi S.M., Church T.S., Martin C.K., Tudor-Locke C., Bouchard C., Earnest C.P., Smith S.R., Newton R.L.,Jr, Rankinen T., and Katzmarzyk P.T. Leisure Time Sedentary Behavior, Occupational/Domestic Physical Activity, and Metabolic Syndrome in U.S. Men and Women. Metab Syndr Relat Disord 2009: 7: 529-536.

Sivertsen B., Krokstad S., Overland S., and Mykletun A. The Epidemiology of Insomnia: Associations with Physical and Mental Health. the HUNT-2 Study. J Psychosom Res 2009: 67: 109-116.

Soltani M., Haytabakhsh M.R., Najman J.M., Williams G.M., O'Callaghan M.J., Bor W., Dingle K., and Clavarino A. Sleepless Nights: The Effect of Socioeconomic Status, Physical Activity, and Lifestyle Factors on Sleep Quality in a Large Cohort of Australian Women. Arch Womens Ment Health 2012: 15: 237-247.

Spiegel K., Tasali E., Leproult R., and Van Cauter E. Effects of Poor and Short Sleep on Glucose Metabolism and Obesity Risk. Nat Rev Endocrinol 2009: 5: 253-261.

Staiano A.E., Harrington D.M., Barreira T.V., and Katzmarzyk P.T. Sitting Time and Cardiometabolic Risk in US Adults: Associations by Sex, Race, Socioeconomic Status and Activity Level. Br J Sports Med 2014: 48: 213-219.

Stamatakis E., Chau J.Y., Pedisic Z., Bauman A., Macniven R., Coombs N., and Hamer M. Are Sitting Occupations Associated with Increased all-Cause, Cancer, and Cardiovascular Disease Mortality Risk? A Pooled Analysis of Seven British Population Cohorts. PLoS One 2013: 8: e73753.

Stamatakis E., Hamer M., Tilling K., and Lawlor D.A. Sedentary Time in Relation to Cardio-Metabolic Risk Factors: Differential Associations for Self-Report Vs Accelerometry in Working Age Adults. Int J Epidemiol 2012: 41: 1328-1337.

Stamatakis E., Hillsdon M., and Primatesta P. Domestic Physical Activity in Relationship to Multiple CVD Risk Factors. Am J Prev Med 2007: 32: 320-327.

Stamatakis E., Rogers K., Ding D., Berrigan D., Chau J., Hamer M., and Bauman A. All-Cause Mortality Effects of Replacing Sedentary Time with Physical Activity and Sleeping using an Isotemporal Substitution Model: A Prospective Study of 201,129 Mid-Aged and Older Adults. Int J Behav Nutr Phys Act 2015: 12: 121.

Stamatakis K.A. and Punjabi N.M. Long Sleep Duration: A Risk to Health or a Marker of Risk? Sleep Med Rev 2007: 11: 337-339.

Steinberg D. Thematic Review Series: The Pathogenesis of Atherosclerosis. An Interpretive History of the Cholesterol Controversy: Part II: The Early Evidence Linking Hypercholesterolemia to Coronary Disease in Humans. J Lipid Res 2005: 46: 179-190.

Stenholm S., Kronholm E., Bandinelli S., Guralnik J.M., and Ferrucci L. Self-Reported Sleep Duration and Time in Bed as Predictors of Physical Function Decline: Results from the InCHIANTI Study. Sleep: 2011: 34: 1583-1593.

Stranges S., Dorn J.M., Shipley M.J., Kandala N.B., Trevisan M., Miller M.A., Donahue R.P., Hovey K.M., Ferrie J.E., Marmot M.G., and Cappuccio F.P. Correlates of Short and Long Sleep Duration: A Cross-Cultural Comparison between the United Kingdom and the United States: The Whitehall II Study and the Western New York Health Study. Am J Epidemiol 2008: 168: 1353-1364.

Strath S.J., Kaminsky L.A., Ainsworth B.E., Ekelund U., Freedson P.S., Gary R.A., Richardson C.R., Smith D.T., Swartz A.M., and American Heart Association Physical Activity Committee of the Council on Lifestyle and Cardiometabolic Health and Cardiovascular, Exercise, Cardiac Rehabilitation and Prevention Committee of the Council on Clinical Cardiology, and Council. Guide to the Assessment of Physical Activity: Clinical and Research Applications: A Scientific Statement from the American Heart Association. Circulation 2013: 128: 2259-2279.

Strine T.W. and Chapman D.P. Associations of Frequent Sleep Insufficiency with Health-Related Quality of Life and Health Behaviors. Sleep Med 2005: 6: 23-27.

Suomen virallinen tilasto. Kuolemansyyt. Tilastokeskus 2014. Available at:http://www.stat.fi/til/ksyyt/2014/ksyyt_2014_2015-12-30_tie_001_fi.html Retrieved: March, 2016.

The Canadian Society for Exercise Physiology. Canadian Physical Activity, and Sedentary Behaviour Guidelines. Canadian Society for Exercise Physiology 2012.

The U.S. Department of Health and Human Services. 2008 Physical Activity Guidelines for Americans. Office of Disease Prevention and Health Promotion 2008. U0036.

Tolonen H., Kuulasmaa K., Laatikainen T., Wolf H., and EHRM. European Health Risk Monitoring Project. Recommendation for Indicators, International Collaboration, Protocol and Manual of Operations for Chronic Disease Risk Factor Surveys. National Public Health Institute 2002.

References

Tolonen H., Helakorpi S., Talala K., Helasoja V., Martelin T., and Prättälä R. 25-Year Trends and Socio-Demographic Differences in Response Rates: Finnish Adult Health Behaviour Survey. Eur J Epidemiol 2006: 21: 409-415.

Tremblay M.S., Colley R.C., Saunders T.J., Healy G.N., and Owen N. Physiological and Health Implications of a Sedentary Lifestyle. Applied Physiology, Nutrition & Metabolism 2010: 35: 725-740.

Tu X., Cai H., Gao Y.T., Wu X., Ji B.T., Yang G., Li H., Zheng W., and Shu X.O. Sleep Duration and its Correlates in Middle-Aged and Elderly Chinese Women: The Shanghai Women's Health Study. Sleep Med 2012: 13: 1138-1145.

Tudor-Locke C., Leonardi C., Johnson W.D., and Katzmarzyk P.T. Time Spent in Physical Activity and Sedentary Behaviors on the Working Day: The American Time use Survey. J Occup Environ Med 2011: 53: 1382-1387.

University Park: The Methodology Center, Penn State . PROC LCA & PROC LTA. 2013: 1.3.0.: http://methodology.psu.edu.

Urban R., Magyarodi T., and Rigo A. Morningness-Eveningness, Chronotypes and Health-Impairing Behaviors in Adolescents. Chronobiol Int 2011: 28: 238-247.

Vartiainen E., Laatikainen T., Salomaa V., Jousilahti P., Peltonen M., and Puska P. Sydäninfarkti- ja aivohalvausriskin arviointi FINRISKI -tutkimuksessa [Assessment of Risk of Acute Myocardial Infarction and Stroke in the National FINRISK Study]. Suom Lääkäril 2007: 62: 4507-4513.

von Eye A., Bogat G.A., and Rhodes J.E. Variable-Oriented and Person-Oriented Perspectives of Analysis: The Example of Alcohol Consumption in Adolescence. J Adolesc 2006: 29: 981-1004.

Vuori I., Urponen H., Hasan J., and Partinen M. Epidemiology of Exercise Effects on Sleep. Acta Physiol Scand Suppl 1988: 574: 3-7.

Waller K., Kaprio J., and Kujala U.M. Associations between Long-Term Physical Activity, Waist Circumference and Weight Gain: A 30-Year Longitudinal Twin Study. Int J Obes (Lond) 2008: 32: 353-361.

Wilmot E.G., Edwardson C.L., Achana F.A., Davies M.J., Gorely T., Gray L.J., Khunti K., Yates T., and Biddle S.J. Sedentary Time in Adults and the Association with Diabetes, Cardiovascular Disease and Death: Systematic Review and Meta-Analysis. Diabetologia 2012: 55: 2895-2905.

Wittmann M., Dinich J., Merrow M., and Roenneberg T. Social Jetlag: Misalignment of Biological and Social Time. Chronobiol Int 2006: 23: 497-509.

Wittmann M., Paulus M., and Roenneberg T. Decreased Psychological Well-being in Late 'Chronotypes' is Mediated by Smoking and Alcohol Consumption. Subst use Misuse 2010: 45: 15-30.

Wong P.M., Hasler B.P., Kamarck T.W., Muldoon M.F., and Manuck S.B. Social Jetlag, Chronotype, and Cardiometabolic Risk. J Clin Endocrinol Metab 2015: 100: 4612-4620.

Working group appointed by the Finnish Medical Society Duodecim and the Executive Board of Current Care. Physical Activity (Online). Current Care Guidelines. Abstract in English. Finnish Medical Society Duodecim 2016. Available at:www.kaypahoito.fi Retrieved: February, 2016.

Working group appointed by the Finnish Medical Society Duodecim and the Finnish Association for the Study of Obesity. Obesity (Adult) (Online). Current Care Guidelines. Abstract in English. Finnish Medical Society Duodecim 2013. Available at:www.kaypahoito.fi Retrieved: February, 2016.

Working group appointed by the Finnish Medical Society Duodecim and the Finnish Hypertension Society. Hypertension (Online). Current Care Guidelines. Abstract in English. Finnish Medical Society Duodecim 2014. Available at:www.kaypahoito.fi Retrieved: February, 2016.

Working group appointed by the Finnish Medical Society Duodecim, the Finnish Society of Internal Medicine and the Medical Advisory Board of the Finnish Diabetes Society. Diabetes (Online). Current Care Guidelines. Abstract in English. Finnish Medical Society Duodecim 2016. Available at:www.kaypahoito.fi Retrieved: February, 2016.

Working group for health promoting physical activity/Ministry of Social Affairs and Health. ISTU VÄHEMMÄN - VOI PAREMMIN! Kansalliset suositukset istumisen vähentämiseen. [REDUCE Sedentary Time – GET HEALTHIER! National Recommendations to Reduce Sedentary Time. Summary in English]. Ministry of Social Affairs and Health and UKK-Institute for Research and Health Promotion 2015.

Working group set up by the Finnish Medical Society Duodecim and Finnish Society of Internal Medicine. Dyslipidaemias (Online). Current Care Guidelines. Abstract in English. Finnish Medical Society Duodecim 2013. Available at:www.kaypahoito.fi Retrieved: February, 2016.

World Health Organization. The World Health Organization MONICA Project (Monitoring Trends and Determinants in Cardiovascular Disease): A Major International Collaboration. WHO MONICA Project Principal Investigators. J Clin Epidemiol 1988: 41: 105-114.

World Health Organization. Obesity: Preventing and Managing the Global Epidemic: Report of a WHO Consultation. 2000. 894 Available at:http://www.who.int/nutrition/publications/obesity/WHO_TRS_894/en/ Retrieved: May, 2016.

World Health Organization. Prevention of Cardiovascular Disease (CVDs). Pocket Guidelines for Assessment and Management of CVD Risk. World Health

Organization 2007. Available at:
http://www.who.int/cardiovascular_diseases/guidelines/Pocket_GL_information
/en/ Retrieved: February, 2016.

World Health Organization. Global Health Risks. World Health Organization 2009.
Available at:
http://www.who.int/healthinfo/global_burden_disease/global_health_risks/en/
Retrieved: October, 2012.

World Health Organization. Global Recommendations on Physical Activity for
Health. World Health Organization 2010. Available at:
http://www.who.int/dietphysicalactivity/publications/9789241599979/en/
Retrieved: May, 2015.

World Health Organization. Global Status Report on Noncommunicable Diseases.
World Health Organization 2014. Available at:
http://www.who.int/nmh/publications/ncd-status-report-2014/en/ Retrieved:
March, 2016.

World Health Organization .Cardiovascular Diseases (CVDs). Fact Sheet Nr317.
World Health Organization 2015 Available at:
http://www.who.int/mediacentre/factsheets/fs317/en/ Retrieved: January, 2016.

Wright K.P.,Jr, Bogan R.K., and Wyatt J.K. Shift Work and the Assessment and
Management of Shift Work Disorder (SWD). Sleep Med Rev 2013a: 17: 41-54.

Wright K.P.,Jr, McHill A.W., Birks B.R., Griffin B.R., Rusterholz T., and Chinoy
E.D. Entrainment of the Human Circadian Clock to the Natural Light-Dark
Cycle. Curr Biol 2013b: 23: 1554-1558.

Wu X., Tao S., Zhang Y., Zhang S., and Tao F. Low Physical Activity and High
Screen Time can Increase the Risks of Mental Health Problems and Poor Sleep
Quality among Chinese College Students. PLoS One 2015: 10: e0119607.

Xiao Q., Keadle S.K., Hollenbeck A.R., and Matthews C.E. Sleep Duration and
Total and Cause-Specific Mortality in a Large US Cohort: Interrelationships
with Physical Activity, Sedentary Behavior, and Body Mass Index. Am J
Epidemiol 2014: 180: 997-1006.

Yamanaka Y., Honma K., Hashimoto S., Takasu N., Miyazaki T., and Honma S.
Effects of Physical Exercise on Human Circadian Rhythms. Sleep and
Biological Rhythms 2006: 4: 199-206.

Yang P.Y., Ho K.H., Chen H.C., and Chien M.Y. Exercise Training Improves Sleep
Quality in Middle-Aged and Older Adults with Sleep Problems: A Systematic
Review. J Physiother 2012: 58: 157-163.

Yetish G., Kaplan H., Gurven M., Wood B., Pontzer H., Manger P.R., Wilson C., McGregor R., and Siegel J.M. Natural Sleep and its Seasonal Variations in Three Pre-Industrial Societies. Curr Biol 2015: 25: 2862-2868.

Yoon H.S., Yang J.J., Song M., Lee H.W., Han S., Lee S.A., Choi J.Y., Lee J.K., and Kang D. Correlates of Self-Reported Sleep Duration in Middle-Aged and Elderly Koreans: From the Health Examinees Study. PLoS One 2015: 10: e0123510.

Youngstedt S.D., O'Connor P.J., and Dishman R.K. The Effects of Acute Exercise on Sleep: A Quantitative Synthesis. Sleep 1997: 20: 203-214.

Youngstedt S.D., Goff E.E., Reynolds A.M., Kripke D.F., Irwin M.R., Bootzin R.R., Khan N., and Jean-Louis G. Clinical Review: Has Adult Sleep Duration Declined Over the Last 50+ Years? Sleep Medicine Reviews 2016: 28: 65-81.

Zinkhan M., Berger K., Hense S., Nagel M., Obst A., Koch B., Penzel T., Fietze I., Ahrens W., Young P., Happe S., Kantelhardt J.W., Kluttig A., Schmidt-Pokrzywniak A., Pillmann F., and Stang A. Agreement of Different Methods for Assessing Sleep Characteristics: A Comparison of Two Actigraphs, Wrist and Hip Placement, and Self-Report with Polysomnography. Sleep Med 2014: 15: 1107-1114.

Åkerstedt T., Knutsson A., Westerholm P., Theorell T., Alfredsson L., and Kecklund G. Sleep Disturbances, Work Stress and Work Hours - A Cross-Sectional Study. J Psychosom Res 2002: 53: 741-748.