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Metabolic Health and Cognitive Function

The Roles of Lifestyle and Shift Work

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Abstract

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The risk of cognitive impairment and metabolic disturbances increases during aging. Healthy lifestyle habits, such as a regular intake of fatty fish and adherence to the Mediterranean diet (MeDi), have been shown to slow age-related cognitive decline and decrease the risk of metabolic disturbances. Conversely, poor lifestyle habits including habitual short sleep duration as well as irregular work schedules (e.g. night shift work) have been correlated with lower cognitive performance and increased risk of having metabolic syndrome (MetS). However evidence is not conclusive regarding the above mentioned associations. The aim of this thesis was to investigate associations of diet, sleep, and shift work with metabolic health or cognitive performance in two Swedish cohorts.

In Paper I and II we examined whether the dietary intake of omega-3 fatty acids and adherence to MeDi were related to measures of brain health in elderly subjects. To this aim, we used scores from the 7-minute cognitive screening test (7MS) and brain volume determined by magnetic resonance imaging. In Paper I, self-reported dietary intake of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) at age 70 was positively associated with cognitive performance and global gray matter volume at age 75. In Paper II, the fully-adjusted main analysis revealed that the MeDi score was not linked to measures of brain health. However, low intake of the MeDi component meat and meat products was associated with better performance on the 7MS and larger total brain volume.

Paper III and IV included subjects aged 45-75 years. In Paper III we demonstrated that current and recent former shift workers (including shifts outside traditional working hours during the past 5 years at the time of the survey) performed worse on the trail making test (TMT) than non-shift workers. The TMT is a test evaluating executive cognitive function, and the performance on this test decreases with age. In Paper IV, sleep duration, sleep disturbances, and sleep-disordered breathing were all linked to an increased prevalence of MetS. Some of the observed associations were age-specific. For example, whereas both short and long sleep durations were linked to a higher prevalence of MetS in younger individuals (<65 years), only long sleep duration did so in the older participants. Collectively, the findings of this thesis suggest that maintaining healthy dietary habits, having high-quality sleep, and following a regular work schedule may be recommended strategies to mitigate age-related morbidities.

Keywords: cognitive function, Mediterranean diet, omega-3 fatty acids, MRI, shift work history, sleep, metabolic syndrome

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To my family

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I   Titova, O.E., Sjogren, P., Brooks, S.J., Kullberg, J., Ax, E., Kilander, L., Riserus, U., Cederholm, T., Larsson, E.M., Johansson, L., Ahlstrom, H., Lind, L., Schioth, H.B., Benedict, C. (2013) Dietary intake of eicosapentaenoic and docosahexaenoic acids is linked to gray matter volume and cognitive function in elderly. *Age*, 35(4):1495-505

II   Titova, O.E., Ax, E., Brooks, S.J., Sjogren, P., Cederholm, T., Kilander, L., Kullberg, J., Larsson, E.M., Johansson, L., Ahlstrom, H., Lind, L., Schioth, H.B., Benedict, C. (2013) Mediterranean diet habits in older individuals: Associations with cognitive functioning and brain volumes. *Exp Gerontol*, 48(12):1443-8

III   Titova, O.E., Lindberg, E., Elmstahl, S., Lind, L., Schioth, H.B., Benedict, C. (2016) Association between shift work history and performance on the trail making test in middle-aged and elderly humans: the EpiHealth study. *Neurobiol Aging*, 45:23-9

IV   Titova, O.E., Lindberg, E., Elmståhl, S., Lind, L., Schiöth, H.B., Benedict, C. (2018) Associations between the prevalence of metabolic syndrome and sleep parameters vary by age. *Front Endocrinol (Lausanne)*, 9:234

Additional publications

Tan X, Titova OE, Lindberg E, Elmstahl S, Lind L, Schioth HB, Benedict C (2018) Association between self-reported sleep duration and body composition in middle-aged and older adults. *J Clin Sleep Med.*, accepted.

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Boström, A.E., Ciuculete, D.M., Attwood, M., Krattinger, R., Nikontovic, L., Titova, O.E., Kullak-Ublick, G.A., Mwinyi, J., Schiöth, H.B. (2017) A MIR4646 associated methylation locus is hypomethylated in adolescent depression. *J Affect Disord*, 220:117-28

Wiemerslage, L., Nilsson, E.K., Solstrand Dahlberg, L., Ence-Eriksson, F., Castillo, S., Larsen, A.L., Bylund, S.B., Hogenkamp, P.S., Olivo, G., Bandstein, M., Titova OE, Larsson, E.M., Benedict, C., Brooks, S. J., Schioth, H. B. (2016) An obesity-associated risk allele within the FTO gene affects human brain activity for areas important for emotion, impulse control and reward in response to food images. *Eur J Neurosci*, 43(9):1173-80

Olivo, G., Wiemerslage, L., Nilsson, E.K., Solstrand Dahlberg, L., Larsen, A.L., Olaya Bucaro, M., Gustafsson, V.P., Titova, O.E., Bandstein, M., Larsson, E. M., Benedict, C., Brooks, S. J., Schioth, H. B. (2016) Resting-State Brain and the FTO Obesity Risk Allele: Default Mode, Sensorimotor, and Salience Network Connectivity Underlying Different Somatosensory Integration and Reward Processing between Genotypes. *Front Hum Neurosci*, 10:52

Titova, O.E., Hogenkamp, P.S., Jacobsson, J.A., Feldman, I., Schiöth, H.B., Benedict, C. (2015) Associations of self-reported sleep disturbance and duration with academic failure in community-dwelling Swedish adolescents: sleep and academic performance at school. *Sleep Med*, 16(1):87-93

Titova, O.E., Hjorth, O.C., Schioth, H.B., Brooks, S.J. (2013). Anorexia nervosa is linked to reduced brain structure in reward and somatosensory regions: a meta-analysis of VBM studies. *BMC Psychiatry*, 13:110

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Contents

Abbreviations

7MS test	Seven minute screening test
AD	Alzheimer's Disease
APOE	Apolipoprotein E
BMI	Body mass index
BTO	Benton temporal orientation
CD	Clock drawing
CNS	Central nervous system
CSF	Cerebral spinal fluid
CVD	Cardiovascular disease
DAGs	Directed acyclic graphs
DHA	Docosahexaenoic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5th edition
ECR	Enhanced cued recall
EPA	Eicosapentaenoic acid
FA	Fatty acids
fMRI	Functional magnetic resonance imaging
FWE	Family Wise Error
GM	Gray matter
HDL	High-density lipoprotein
HOMA-IR	Homeostatic model assessment- insulin resistance
IDF	The International Diabetes Federation
LDL	Low-density lipoprotein cholesterol
MCI	Mild cognitive impairment
MeDi	Mediterranean diet
MetS	Metabolic syndrome
MMSE	Mini-mental state examination
MNI	Montreal Neurological Institute
MRI	Magnetic resonance imaging
OSA	Obstructive sleep apnea
PA	Physical activity
PET	Positron-Emission Tomography
PR	Prevalence ratios

PUFA	Polyunsaturated fatty acids
ROI	Region of interest
SD	Standard deviation
SDB	Sleep-disordered breathing
SEM	Standard error of mean
SPM	Statistical parametric mapping
SPSS	"Statistical Package for the Social Sciences"
TBV	Total brain volume
TIV	Total intracranial volume
TMT	The trail making test
VBM	Voxel Based Morphometry
VF	Verbal fluency
WM	White matter

Introduction

Dynamics of population aging

The proportion of the elderly population is steadily growing worldwide. In 2010, it was estimated that 524 million people were aged 65 years and older, which corresponds to approximately 8% of the world's population. By 2050, the elderly population aged 65 years and older is expected to reach 1.5 billion, corresponding to 16% of the world's population (World Health Organization, 2011). The population aging phenomenon can be explained by increasing life expectancy and declining birth rates. People are living longer which can be related to better health care and economic resources. However, the risk of developing severe diseases increases as we age. Cognitive impairment is one of the major health problems among elderly. The incidence of neurological disorders such as Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD) increases in connection with the growth of the elderly population (Plassman *et al.*, 2011). Age-related decline in cognitive functions causes increased concern because of the potential negative effects on the physical functioning and quality of life of older adults.

Another public health concern of modern society is the high prevalence of cardiovascular and metabolic dysregulations, such as central obesity, hypertension, hyperglycemia and dyslipidemia, which in turn can contribute to the development of neurodegenerative disorders (Motamedi *et al.*, 2017). A cluster of risk factors for cardiovascular disease and type 2 diabetes mellitus are known as metabolic syndrome (MetS) (Kaur, 2014). In recent years the prevalence of MetS has increased worldwide. For example, according to the International Diabetes Federation (IDF) approximately 25% of the world's adult population may have MetS (O'Neill and O'Driscoll, 2015). Furthermore, the risk to develop MetS also increases as we age (Kaur, 2014).

The rapid growth of the aging population affects many aspects of public life, such as increased health care needs and economic resources to maintain good quality of life in older generation. It is therefore extremely important to develop preventive and therapeutic strategies which may help to maintain optimal cognitive function and metabolic health, as well as to prevent or delay the onset of disease. Multiple factors have been proposed either to restrain or accelerate the development of age-related cognitive deficits and/or metabolic dysregulations, such as lifestyle, genetic factors, intellectual attainment, and occupational stress. In the last decades, modifiable life-

style factors, such as diet, physical activity, and sleep habits have received increased research attention in relation to their beneficial effects on cognitive function and metabolic health.

Age-related changes in cognition and brain structure

According to the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5), six cognitive domains were suggested for the purpose of classifying neurocognitive disorders that include: complex attention, executive function, language, learning and memory, perceptual-motor function, and social cognition (*Figure 1*). Each domain consists of subdomains (Sachdev *et al.*, 2014).
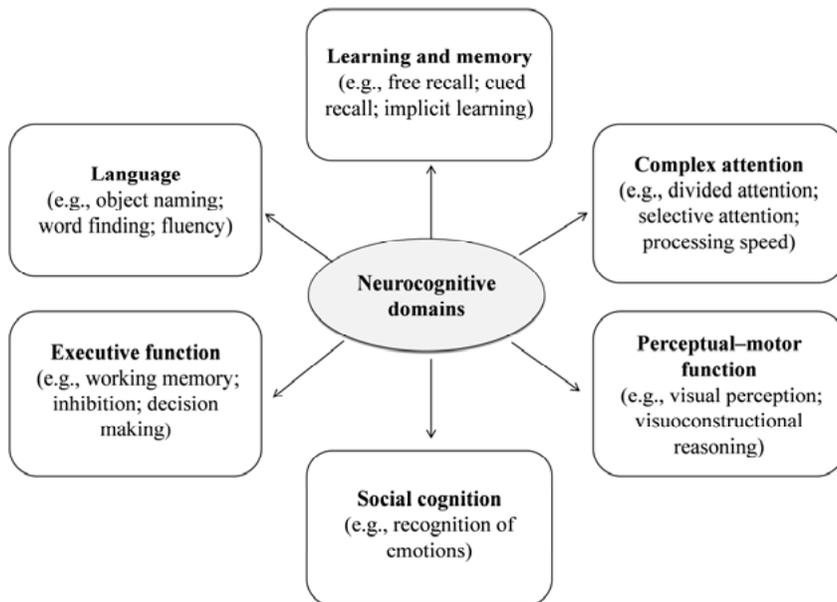

Figure 1. Domains of cognitive function based on the DSM-5. Adapted from Sachdev et al. (2014).

It is well recognized that normal aging is associated with structural changes in different brain regions and decline in several cognitive domains. Various studies showed that cognitively healthy older individuals perform worse than younger adults on several cognitive tasks, especially tests on working memory, episodic memory, attention, and executive functioning (Riddle, 2007). However, some cognitive abilities such as vocabulary can remain intact and may improve with age (Harada *et al.*, 2013; Lockhart and DeCarli, 2014). Age-related cognitive decline has been attributed to structural and

functional changes in the brain as well as an increase in apoptosis, inflammation and oxidative stress (Masana *et al.*, 2017).

Modern neuroimaging technics allow researchers to shed light on structural and functional changes in the brain related to healthy aging or pathological conditions. Gray matter (GM) is mainly composed of neuronal cell bodies, dendrites, unmyelinated axons, and synapses which form the neural circuits that process information (Laughlin and Sejnowski, 2003). White matter (WM) consists mostly of axon tracts and is essential for transmission of electrical signals to different brain regions (Purves D, 2012). Several longitudinal and cross-sectional MRI studies reported age-related decrease in total GM, and WM volumes (Ge *et al.*, 2002; Fjell *et al.*, 2013; Farokhian *et al.*, 2017; Schippling *et al.*, 2017); enlargement of the brain ventricles (Apostolova *et al.*, 2012), as well as thinning of the cerebral cortex (Salat *et al.*, 2004). Neuroimaging studies have also shown age-related regional GM volume decrease in several brain areas, such as prefrontal regions, temporal lobe, hippocampus, and cingulate cortex (Good *et al.*, 2001; Jernigan *et al.*, 2001; Resnick *et al.*, 2003; Raz *et al.*, 2005; Fjell*, et al.*, 2013; Farokhian*, et al.*, 2017). In addition, age-related regional WM changes have been reported (Xiong and Mok, 2011; Farokhian*, et al.*, 2017; Lindemer *et al.*, 2017). These changes in brain structure can be partly explained by neuronal degeneration and synaptic density reduction in certain brain areas related to normal aging (Anderton, 2002; Lockhart and DeCarli, 2014). Age-related changes in GM and WM may coincide with the cognitive decline observed in the elderly. There are several studies which aimed to investigate age-related structural changes in the brain in relation to concurrent and future cognitive performance (Carmichael *et al.*, 2012; Lockhart and DeCarli, 2014; Arvanitakis *et al.*, 2016). For example, an MRI study on 307 elderly individuals found that larger baseline whole brain volumes and smaller baseline white matter hyperintensities volume predicted slower subsequent rate of decline in several cognitive domains (Carmichael*, et al.*, 2012).

Cerebral amyloid-β aggregation, an early recognizable pathological change in AD, begins decades before the clinical onset of dementia. A recent meta-analysis revealed that the prevalence of amyloid pathology as determined by Positron-Emission Tomography (PET) or cerebrospinal fluid (CSF) biomarkers, increased from age 50 to 90 years from approximately 10% to 44% among individuals with normal cognition (Jansen *et al.*, 2015).

Methods to examine brain aging

A wide range of tools to assess cognitive function and brain health have been developed, such as cognitive screening tools, brain imaging techniques, genetic testing, and biomarker testing. For example, the mini-mental state examination (MMSE) is a brief 30-point test which is widely used to screen and monitor the progression of cognitive impairment in clinical practice

(Folstein *et al.*, 1975). The MMSE includes tests of orientation, attention, memory, language and visual-spatial skills. The MMSE correlates well with other neuropsychological tests for dementia screening and has good reliability and construct validity (Velayudhan *et al.*, 2014). Most often the score of 24 is used as a cut-off value to indicate cognitive impairment. However, performance on this test can be affected by education, language, cultural background, and age (Velayudhan*, et al.*, 2014). For example, persons with a lower level of education can obtain lower scores and be wrongly classified as having dementia while those with higher levels of education can be missed (Woodford and George, 2007). That is why the modified cut-off scores which take into account age and educational level can be appropriate (O'Bryant *et al.*, 2008; Velayudhan*, et al.*, 2014). A cut-off score of 27 (26 or below) has been suggested for people with a higher educational level (O'Bryant*, et al.*, 2008).

The seven minute screen (7MS) test is another neurocognitive screening tool designed to identify mild cognitive impairment and the early stages of Alzheimer's disease. It consists of four cognitive tests (Solomon *et al.*, 1998): Benton temporal orientation (BTO, the orientation for time, (Benton, 1983)); clock drawing (CD, visuospatial and visuoconstruction, (Freedman, 1994)); enhanced cued recall (ECR, memory test, (Grober *et al.*, 1988)) and categorical verbal fluency (VF, a semantic memory test). The 7MS test is a brief test and is not biased by education or age (Velayudhan*, et al.*, 2014). It demonstrates good psychometric properties and diagnostic accuracy (Meulen *et al.*, 2004).

Genetic testing, neuroimaging, and biomarker testing are seldom applied for clinical assessment of cognitive impairment (Langa and Levine, 2014). These methods are primarily utilized for research purpose. For instance, structural magnetic resonance imaging (MRI) is one of the most extensively used methods to study brain aging (Lockhart and DeCarli, 2014). MRI is a non-invasive imaging radiology technique which uses strong magnetic fields and radio waves to generate three dimensional detailed anatomical images. MRI generates images which reveal structural details in the brain (Purves D, 2012). An application of MRI, named Diffusion-Weighted Imaging (DWI), generates image contrast based on differences in the magnitude of diffusion of water molecules within the brain (Huisman, 2010). Diffusion tensor imaging (DTI), a specific type of modeling of the DWI datasets, evaluates the three-dimensional shape of the diffusion, also known as diffusion tensor (Soares *et al.*, 2013). It allows the researchers to examine the microstructure of brain tissue, for example, the structure of axons fiber tracts in the brain (Huisman, 2010). Another variant of MRI, named functional magnetic resonance imaging (fMRI), provides insights into the neural activity during resting state or performance on a selected cognitive task. The task-related fMRI detects changes in blood flow and therefore identifies areas of the brain which are particularly active during a given task. This technique relies on the

fact that when the brain region is activated, it receives more blood due to increased metabolic demands in comparison with relatively inactive regions (Purves D, 2012). Thus, in the task-related fMRI, the use of oxygen by the most active regions of the brain during a specific task is detected. Such changes in the concentration of oxygen and blood flow lead to the blood-oxygen-level dependent (BOLD) changes in the magnetic resonance signal (Purves D, 2012). The resting-state fMRI measures fluctuations in the BOLD signal in task-free conditions. This approach can be used for example to explore differences in resting state functional brain connectivity associated with cognitive decline (Lin *et al.*, 2018). Another functional brain imaging technique, the Positron-Emission Tomography (PET), can be used to investigate cerebral blood flow, oxygen use, and glucose metabolism in the human brain as well as the presence of certain disease biomarkers (e.g., beta amyloid and tau) (Purves D, 2012; Heurling *et al.*, 2017). In PET scanning, positron-emitting isotopes are incorporated into different reagents (e.g., glucose) and infused into the bloodstream. Emitted gamma rays are then detected and images of tissue isotope density are generated demonstrating the location of active regions in the brain (Purves D, 2012). For instance, Fluorodeoxyglucose Positron-Emission Tomography (FDG-PET) has been used in research of mild cognitive impairment and its progression to AD (Herholz *et al.*, 2007). Additionally, evidence suggests that levels of neurobiological markers in the cerebrospinal fluid (e.g., beta amyloid and tau protein) may help to identify subjects with MCI who are at high risk to progress to AD (Langa and Levine, 2014). In recent years, the identification of genetic biomarkers for cognitive aging and AD has become an important area of research (Lin *et al.*, 2017). A number of studies have focused on investigation of genetic risk factors for AD. For example, the ε4 allele of apolipoprotein E (APOE) is considered to be the strongest genetic risk factor for AD (Liu *et al.*, 2013).

Lifestyle and cognitive decline

Dietary factors

Omega-3 fatty acids: structure and function

Eicosapentaenoic acid (EPA, 20:5, n-3) and docosahexaenoic acid (DHA, 22:6, n-3), also known as omega-3 fatty acids (FA), are long-chain polyunsaturated fatty acids (PUFA) that are mainly found in oily fish and food of marine origin. Omega-3 FA, including EPA and DHA, are structural lipid components of cell membranes and are involved in different brain functions, such as maintaining an optimal cell membrane fluidity, neurotransmission and signal transduction (Hooijmans and Kiliaan, 2008). Moreover, the neuroprotective properties of omega-3 FA, such as antioxidative activity and

regulation of anti-inflammatory processes, have been described (Bos *et al.*, 2016). DHA is a key component of neural membranes and is the most abundant omega-3 FA in the brain and retina. In contrast, the amount of EPA in the brain is significantly lower (McNamara and Carlson, 2006; Tanaka *et al.*, 2012). In humans, these FA can be produced by desaturation and enzymatic elongation of their precursor α-linolenic acid (ALA, 18:3, n-3). However, this conversion is very inefficient (Burdge, 2004) and can be affected by factors such as age, sex and chronic diseases (Saunders *et al.*, 2013). Therefore the consumption of food rich in omega-3 FA and dietary supplementation are the primary sources of DHA and EPA. Dietary recommendations for EPA and DHA for healthy adults vary widely between different countries. Most often the intake of at least 250-500 mg/day is recommended (Kris-Etherton *et al.*, 2009; Calder *et al.*, 2010; Saunders*, et al.*, 2013).

Omega-3 fatty acids and cognitive health, epidemiological evidence

Several studies in middle-aged and elderly people have demonstrated that both high fish consumption and dietary intake of EPA and DHA may postpone cognitive decline in cognitively healthy middle-aged and elderly individuals (Kalmijn *et al.*, 2004; Morris *et al.*, 2005; van Gelder *et al.*, 2007). In addition, several longitudinal studies have shown that higher blood levels of n-3 PUFAs were associated with lower risk of cognitive decline (Samieri *et al.*, 2008; Whalley *et al.*, 2008). A recent cross-sectional autopsy study demonstrated that moderate seafood consumption assessed by a food frequency questionnaire in the years before death, was associated with less Alzheimer's disease specific neuropathology among APOE ε4 carriers. More specifically, 286 brain autopsies of participants free of dementia at baseline were performed. The mean age at death was 89.9 years. Seafood consumption was associated with less neuritic plaques and neurofibrillary tangles (Morris *et al.*, 2016).

There is evidence that supplementation with omega-3 FA may help to prevent cognitive decline in the elderly or reduce the rate of cognitive decline (Rangel-Huerta and Gil, 2018). For example, a prospective interventional study in 50-75 years old healthy individuals demonstrated that 26 weeks supplementation with omega-3 FA in form of fish oil (2.2 g/day omega-3 PUFA) was associated with improvement in executive function after intervention compared with placebo (Witte *et al.*, 2014). A recent meta-analysis of six randomized controlled trials involving 2013 participants and 1003 cases, revealed that omega-3 FA supplementation was associated with lower risk of cognitive decline based on MMSE score in elderly (Zhang *et al.*, 2016).

In addition, neuroprotective effects of omega-3 FA on human brain structure have been observed. Several studies have shown that higher dietary intake and higher plasma level of omega-3 FA are linked to larger total or regional GM volumes in healthy elderly subjects (Conklin *et al.*, 2007; Tan

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et al., 2012; Pottala *et al.*, 2014). The Alzheimer's Disease Neuroimaging Initiative (ADNI) retrospective cohort study examined the relationship between the use of fish oil supplements and cognition, as well as brain structure in participants with normal cognition, MCI and AD at age between 55 to 90 years. Several follow-up assessments were conducted. Supplementation with fish oil was associated with less cerebral cortex GM and hippocampal atrophy and better cognitive performance on MMSE and the Alzheimer's Disease Assessment Scale (ADAS) among cognitively healthy individuals. In addition, use of fish oil supplements was linked to less atrophy in brain regions of interest in AD and MCI groups (Daiello *et al.*, 2015). The beneficial effect of supplementation with EPA and DHA on white matter microstructural integrity and regional GM volume has also been reported (Witte*, et al.*, 2014). These findings support the view that a high intake of EPA and DHA during late adulthood could be beneficial for cognitive functions and brain structure among elderly. However, evidence is not conclusive as there are findings demonstrating that the dietary intake of omega-3 FA or supplementation do not affect the risk to develop dementia among healthy elderly (Engelhart *et al.*, 2002; Devore *et al.*, 2009) or the rate of cognitive decline in AD patients (Quinn *et al.*, 2010).

Mediterranean diet (MeDi) and brain health

The Mediterranean diet (MeDi) refers to the traditional eating habits of people living in Mediterranean regions, such as Crete and South Italy. The traditional MeDi is characterized by high consumption of plant products (vegetables, nuts, legumes, fruits, seeds, cereals and olive oil), a moderately high intake of fish, a low to moderate consumption of dairy products, a low intake of meat and poultry, and wine consumed in low to moderate amounts generally with meals (Willett *et al.*, 1995; Trichopoulou *et al.*, 2003). The MeDi received particular attention during the last decades as adherence to a Mediterranean-like diet has been associated with decreased mortality, and reduced risks of cardiovascular disease and cancer (Trichopoulou*, et al.*, 2003; Davis *et al.*, 2015). Moreover, adherence to the MeDi has been shown to slow the progression of age-related cognitive decline and hypothesized as a dietary strategy for successful cognitive aging (Barak and Aizenberg, 2010). Numerous cross-sectional and prospective epidemiological studies revealed that adherence to the MeDi has been associated with reduced risk for cognitive decline or dementia both in Mediterranean and non-Mediterranean populations (Feart *et al.*, 2009; Scarmeas *et al.*, 2009; Tangney *et al.*, 2011; Tsivgoulis *et al.*, 2013; Wengreen *et al.*, 2013; Anastasiou *et al.*, 2017). For example, in the Chicago Health and Aging Project (CHAP) involving 3,790 participants aged $\geq$ 65 years, the relationship between the adherence to the MeDi and global measure of cognitive function was assessed repeatedly during a mean of 7.6 years. Higher MeDi scores were linked to slower rates of cognitive decline (Tangney*, et al.*, 2011). A recent randomized clinical

study in 334 cognitively healthy older participants with high cardiovascular risk demonstrated cognitive improvement in participants assigned to the MeDi that were supplemented with either extra virgin olive oil or nuts, and cognitive decline in those assigned to a control diet at a median follow-up of 4.1 years (Valls-Pedret *et al.*, 2015). Several meta-analyses confirmed the association between adherence to the MeDi and reduced risk for cognitive impairment and AD as well as reduced risk for progressing from MCI to AD (Psaltopoulou *et al.*, 2013; Singh *et al.*, 2014). It is not clear yet if the beneficial effect on the cognitive health could be explained with the overall MeDi pattern or specific food components of the MeDi. Data regarding the relationships between individual components of MeDi and cognitive function as well as brain atrophy are scarce. The findings from several studies suggested a potential beneficial role of the fish component of MeDi (Gu *et al.*, 2015), vegetables and fruits (Lee *et al.*, 2010; Roberts *et al.*, 2010), and a detrimental effect of meat and meat products on brain health (Gu*, et al.*, 2015).

The mechanisms which could explain the protective effect of MeDi on cognitive health are not fully understood. One of the reasons why MeDi is thought to promote cognitive health among elderly could be the fact that certain food components of MedDi, such as moderately high fish consumption, high intake of vegetables and fruits, and a moderate intake of alcohol, exert protective effects on the human brain (Scarmeas *et al.*, 2006; Scarmeas*, et al.*, 2009). For example, vegetables and fruits contain vitamin C, B-complex vitamins and flavonoids which have broad neuroprotective effects, ranging from anti-inflammatory and anti-oxidant properties, to synaptic plasticity-enhancing effects and neurotransmitter formation (Harrison and May, 2009; Spencer, 2009; Kennedy, 2016). It has also been suggested that the beneficial effect of the MeDi on cognitive ability could be mediated via positive effects on cardiovascular risk factors, such as hypertension and dyslipidemia (Wade *et al.*, 2017). For example, hypertension and atherosclerosis cause blood vessel wall pathology, which in turn may lead to hypoperfusion, alterations in the blood brain barrier function, and ischemia in the brain. All these factors are related to cognitive impairment and may lead to pathological process in the brain (Hooijmans and Kiliaan, 2008).

Moreover, the protective effect of the MeDi or its components on the brain structure is well documented. Several MRI studies performed in elderly individuals without clinical signs of dementia revealed that higher adherence to the MeDi is associated with less brain atrophy (Gu*, et al.*, 2015), greater thickness in AD-vulnerable regions of interest (ROI) (e.g., orbital frontal cortex, entorhinal cortex, posterior cingulate cortex of the left hemisphere) (Mosconi *et al.*, 2014), and reduced cerebrovascular disease burden (white matter hyperintensities, a marker of small vessel damage in the brain) (Gardener *et al.*, 2012).

However, results regarding the association between the adherence to the MeDi and brain function in older populations are not conclusive. For in-

stance, in a prospective cohort study of 1410 older adults, a higher adherence to the MeDi was not associated with reduced risk for incident dementia (Feart, *et al.*, 2009). In another large longitudinal investigation of generally healthy individuals, a higher adherence to the MeDi did not show protective effect against cognitive impairment (Cherbuin and Anstey, 2012).

Shift work

A considerably large proportion of today's workforce performs shift work (e.g., medical doctors, nurses, firemen, and police officers). Shift work is usually defined as work performed outside the traditional daytime working hours, or a schedule different from the standard working week (Nea *et al.*, 2015). There are different shift patterns, such as evening or night shifts, early morning shifts, and a rotating shift schedule (Nea, *et al.*, 2015). Accumulating evidence indicates that performing shift work might have adverse effects on human health. Studies have, for instance, shown that shift workers run an increased risk of developing type 2 diabetes, obesity, cancer, and cardiovascular diseases (Esquirol *et al.*, 2011; Itani *et al.*, 2011; Wang *et al.*, 2015; Vimalananda *et al.*, 2015). This might be driven by poor lifestyle habits, including smoking, lack of physical activity, insufficient sleep, adherence to unhealthy diets, regular excessive alcohol intake, and stress which are frequently reported among shift workers (Morikawa *et al.*, 2013; Nea, *et al.*, 2015; Ramin *et al.*, 2015). Shift work, and particularly night shift, is often characterized by working, eating and sleeping at the wrong biological time which may modulate physiological processes that follow circadian rhythms, such as the sleep-wake cycle, body temperature, blood pressure, and hormone production (Kuhn, 2001). Thus, the disruption of circadian rhythms, inadequate sleep, and poor lifestyle habits associated with shift work may have an adverse effect on physical and mental health.

In recent years, several studies suggested that shift work may influence cognitive functions in humans (Meijman *et al.*, 1993; Ansiau *et al.*, 2008). For example, a French prospective study on aging, health, and work (named VISAT) revealed that night work (i.e., at least part of the work activity had taken place before 6 a.m. or after 10 p.m.) was associated with poorer performances on verbal memory and selective attention tests the next day (Ansiau, *et al.*, 2008). Another study based on the VISAT cohort demonstrated that shift work (including rotating and night shifts) was linked to lower global cognitive test scores in those with a shift work history of more than 10 years. Furthermore, this study indicated that the recovery of cognitive functioning after having left shift work took at least 5 years (Marquie *et al.*, 2015). Experimental studies support these findings. Short periods of experimentally simulated night shift work have also been shown to impair cognitive performance, mood and sleep parameters in humans (Reid and Dawson, 2001; Hart *et al.*, 2006). Compromised cognitive performance due

to atypical working conditions may increase the risk of transport and industrial accidents, and human errors (Folkard *et al.*, 2005).

The evidence is not conclusive, as there are studies which did not show the link between shift work and cognitive performance. For instance, utilizing data from the United States Nurses' Health Study, no association was found between shift work history and composite measures of general cognition and verbal memory in later life (Devore *et al.*, 2013).

Lifestyle and metabolic health

Metabolic syndrome

Metabolic syndrome (MetS), known also as syndrome X, is defined as a cluster of several risk factors for cardiovascular disease (CVD), type 2 diabetes mellitus and all-cause mortality (Kaur, 2014). Currently, there are several clinical criteria for defining MetS. The most widely accepted definitions are those proposed by the International Diabetes Federation (IDF), the World Health Organization (WHO) and the National Cholesterol Education Program-Third Adult Treatment Panel (NCEP:ATPIII) (Saklayen, 2018). The most commonly used components of MetS are hypertension, hyperglycemia, reduced blood concentrations of high density lipoprotein (HDL) cholesterol, increased triglycerides, and abdominal obesity (Alberti *et al.*, 2009). The presence of three or more components is often used for the definition of MetS (Alberti*, et al.*, 2009). The prevalence of MetS in the general population is estimated to be more than 25% and increases in advanced ages (Ford *et al.*, 2002). The existence of several definitions makes it more difficult to estimate the real prevalence of MetS. Moreover, estimates may vary due to differences in age, gender, and ethnicity of the studied populations. In addition, several other factors besides those traditionally used to define MetS were suggested such as proinflammatory and prothrombotic states (Grundy *et al.*, 2004).

Components of metabolic syndrome

Overweight and obesity are defined as excessive accumulation of body fat. Obesity is associated with increased risks for hypertension, type 2 diabetes, dyslipidemia, sleep apnea, CVD, and some forms of cancer (Aronne and Segal, 2002; O'Neill and O'Driscoll, 2015). Body mass index (BMI) and waist circumference (WC) are the most commonly used variables to estimate excessive body weight. BMI is calculated by dividing the body weight (in kilograms) by the height (in meters) squared. A BMI ≥ 25 kg/m^2 is considered overweight while a BMI value ≥ 30 kg/m^2 is considered obese (Oliveros *et al.*, 2014). BMI correlates well with body fatness, but it does not provide insight into the body fat distribution or composition (Aronne and Segal,

2002). It has been suggested that abdominal obesity measured by WC is a better predictor of obesity-related health risks than BMI (Janssen *et al.*, 2004). There are different thresholds for WC to define abdominal obesity which are usually ethnicity and gender specific (O'Neill and O'Driscoll, 2015). For example, WC ≥102 cm for men and WC ≥88 cm for women have been suggested as a cut points for elevated WC in European populations (Alberti*, et al.*, 2009). Abdominal obesity is considered to be a predominant risk factor for MetS development (Paley and Johnson, 2018).

An elevated fasting blood glucose or high concentration of insulin is another core component of MetS. The cut-off points for fasting blood glucose in the most often used definitions of MetS are 100 mg/dL (5.6 mmol/L) or 110 mg/dL (6.1 mmol/L) (O'Neill and O'Driscoll, 2015; Saklayen, 2018). Insulin resistance (IR) is characterized by an impaired response of tissues, such as the skeletal muscle, the liver, and adipose tissue, to insulin. Since insulin is involved in systemic glucose disposal, IR can result in hyperglycemia and compensatory hyperinsulinemia (Freeman and Pennings, 2018). Dyslipidemia and visceral adiposity are also frequently seen in those suffering from IR (Grundy*, et al.*, 2004; Freeman and Pennings, 2018). The predominant long-term consequence of IR is type 2 diabetes (Freeman and Pennings, 2018).

Lipid abnormalities, such as decreased concentration of HDL cholesterol as well as raised triglycerides, have been shown to contribute to inflammation and atherosclerosis (Welty, 2013) as well as to be independently associated with cardiovascular disease (Kolovou *et al.*, 2005). Blood concentration of triglycerides ≥150 mg/dL (≥ 1.7 mmol/L) is usually used as a threshold for elevated triglycerides levels (O'Neill and O'Driscoll, 2015). In most MetS definitions, low HDL cholesterol is defined as <40 mg/dL [<1.0 mmol/L] for men and <50 mg/dL [<1.3 mmol/L] for women (O'Neill and O'Driscoll, 2015).

Elevated blood pressure has been shown to be strongly associated with obesity and commonly occurs in insulin-resistant individuals (Grundy*, et al.*, 2004). In several MetS definitions, elevated blood pressure is defined as systolic blood pressure ≥ 130 and /or diastolic ≥85 mm Hg (O'Neill and O'Driscoll, 2015). A systematic analysis of population-based studies from 90 countries revealed that in 2010, more than 31% of the world's adult individuals suffered from hypertension (Mills *et al.*, 2016). The same study reported that approximately 60% of older people aged 60-69 years and 73% of individuals aged 70 or older had hypertension (Mills*, et al.*, 2016).

Risk factors for development of metabolic syndrome
A number of different parameters have been proposed as risk factors for metabolic dysregulation. Low physical activity and unhealthy dietary choices are the major risk factors for developing MetS (O'Neill and O'Driscoll, 2015). Additionally, genetics, aging, male gender, smoking, socioeconomic

status, stress, and hormonal changes may contribute to the development of MetS (Park *et al.*, 2003; Kaur, 2014). Accumulating evidence suggests that chronic poor sleep patterns may also increase the risk of having MetS, or some of its components (Hall *et al.*, 2008; Koren *et al.*, 2016; Song *et al.*, 2016).

Sleep and metabolic syndrome

Sleep plays an essential role in the health and well-being across the lifespan. Epidemiological evidence suggests that the prevalence of sleep-related problems, such as poor sleep quality, snoring, sleep apnea as well as sleep outside the recommended sleep duration hours, are getting more prevalent. Thus, the prevalence of chronic insomnia or insomnia symptoms in the general population is estimated to vary from ~10 to 40% (Depner *et al.*, 2014). Approximately 33 % of adults sleep less than 6 hours per night (Tan *et al.*, 2018). Between 20 to 40% of the general population exhibit signs of sleep disordered breathing (SDB) (Kitakata *et al.*, 2018). This is alarming, as it is well documented that sleep is important in maintaining metabolic homeostasis (Sharma and Kavuru, 2010).

Sleep physiology

Human sleep consists of four sleep stages (*Figure 2*) which is based on measurements of electroencephalogram (EEG), electromyogram, and electro-oculogram (Gulia and Kumar, 2018). The first three stages are called non-rapid eye movement (NREM) sleep. Stage 1 sleep (also called N1 or NREM 1) is a transitional phase between wake and sleep, which is characterized by a slowing of the heart rate and muscle tension reduction. Stage 2 sleep (also called N2 or NREM2) is mainly defined by EEG phenomena such as sleep spindles and K-complexes (Breedlove, 2017). Stage 2 is typically followed by slow-wave sleep (SWS, or N3 or NREM3); predominantly defined by the presence of large amplitude, very slow waves, and deep sleep with the body being the least metabolically active (Sharma and Kavuru, 2010). Rapid-eye movement (REM) sleep (also called R) is mainly characterized by loss of muscle tone, vivid dreams, rapid, low-voltage EEG, and intermittent rapid eye movements (Sharma and Kavuru, 2010). Normal sleep consists of 4-6 sleep cycles, each has duration of about 90-120 min, during which episodes of REM sleep and SWS alternate. In the first half of the night SWS is more prevalent, while REM is more predominant in the second half (Sharma and Kavuru, 2010). There are differences in energy metabolism between sleep stages. Energy metabolism starts to increase prior to awakening (Kayaba *et al.*, 2017).

Sleep architecture can be influenced by genetic and environmental factors, such as gender, age, ethnicity, socioeconomic status, stress and medication use (Miner and Kryger, 2017). For example, age-related changes in

sleep architecture are well documented. Thus, older people spend more time in the lighter stages of sleep (N1 and N2) than in deep SWS (Ohayon *et al.*, 2004). Moreover, aging is associated with reduced nocturnal sleep duration with corresponding decrease in the percentage of time in SWS and REM sleep, increased frequency of daytime naps, and decreased ability to maintain sleep (Miner and Kryger, 2017; Li *et al.*, 2018). Sleep needs vary across the lifespan. The National Sleep Foundation recommends 7-9 hours of sleep for young adults and adults and 7-8 hours of sleep for older individuals (≥ 65 years) (Hirshkowitz *et al.*, 2015).
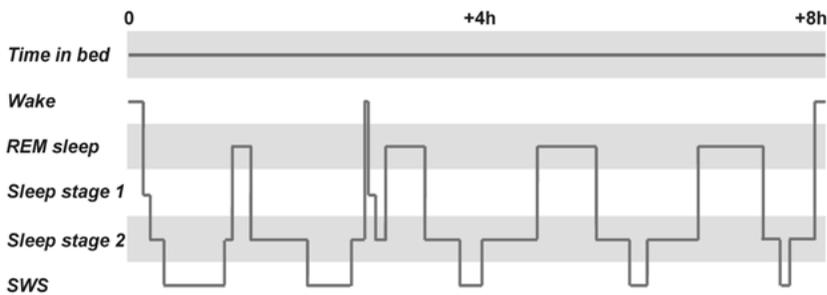

Figure 2. Hypnogram illustrating the time spent in the various sleep stages (kindly provided by Christian Benedict, unpublished figure).

Epidemiological evidence

Accumulating evidence suggests that both short and long sleep durations, sleep disturbances, and SDB are linked to an increased risk of having MetS, or some of its components such as hyperglycemia and obesity (Mallon *et al.*, 2005; Jennings *et al.*, 2007; Theorell-Haglow *et al.*, 2011; Morselli *et al.*, 2012). For instance, a Swedish 12-year follow-up study involving more than 1200 men and women aged 45–65 years, revealed that short sleep duration (< 5 hours) and difficulty initiating or maintaining sleep were associated with a higher incidence of diabetes in men (Mallon*, et al.*, 2005). Another study utilizing data from 1,214 participants from the *Adult Health and Behavior Project registry* (aged 30 to 54 years), demonstrated that the odds for having MetS increased by more than 45% in both short and long sleepers, compared with those sleeping 7 to 8 hours per night (Hall*, et al.*, 2008). A meta-analysis involving 76,027 participants confirmed these findings further demonstrating that short (defined as ≤6 h/day) and long sleep durations (defined as >8 h/day) were associated with increased risk of MetS as compared with normal sleep duration (Ju and Choi, 2013). This suggests the existence of a U-shaped association between sleep duration and risk of MetS. Another

meta-analysis revealed that subjects with obstructive sleep apnea (OSA; hallmarked by recurrent episodes of either partial or full cessation of breathing while asleep) were at 1.72 fold higher risk for MetS, than those without OSA (Qian *et al.*, 2016).

Associations between poor sleep patterns and parameters of MetS may vary by age. For example, a large population-based study demonstrated that short sleep durations (≤5 and 6h) were positively associated with prediabetes, but not diabetes, in young (< 40 years) and older (≥40 years) subjects. In contrast, long sleep duration (≥ 8h) was inversely associated with prediabetes in younger subjects, but was positively linked to diabetes in older participants (Nakajima *et al.*, 2017). Another study involving 5,393 participants revealed that young and middle-aged adults (19–64 years) who slept <6 h a day, were more likely to have hypertension compared to those who slept 7 h a day. This association was not found among those aged ≥65 years (Kim and Jo, 2010).

Sleep deprivation, poor sleep quality, SDB, and circadian misalignment may cause metabolic dysregulation (*Figure 3*) through mechanisms involving sympathetic overstimulation, hormonal imbalance, and subclinical inflammation (Sharma and Kavuru, 2010). For instance, SDB comprises alterations in respiratory rate, rhythm, and depth present during sleep (Baekey *et al.*, 2009). Obstruction of the upper airway during sleep has been associated with hypoxia, pulmonary hypertension, and light sleep (Lam *et al.*, 2012) (Young *et al.*, 2005), all of which may cause metabolic perturbations (Barcelo *et al.*, 2000; Dyugovskaya *et al.*, 2002; Lam*, et al.*, 2012; Koren*, et al.*, 2016).
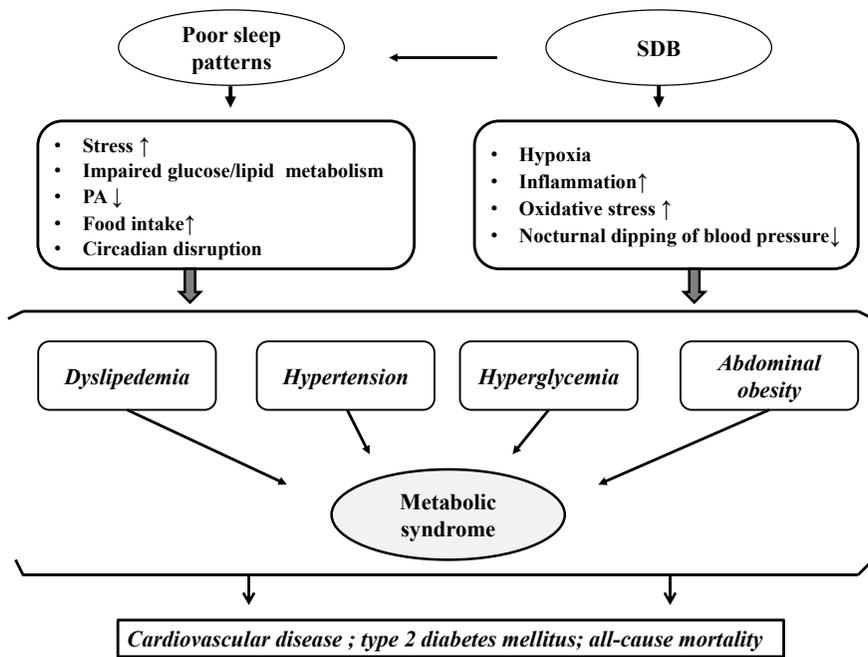
Poor sleep patterns

SDB

- **Stress ↑**
- **Impaired glucose/lipid metabolism**
- **PA ↓**
- **Food intake↑**
- **Circadian disruption**

- **Hypoxia**
- **Inflammation↑**
- **Oxidative stress ↑**
- **Nocturnal dipping of blood pressure↓**

Dyslipedemia   *Hypertension*   *Hyperglycemia*   *Abdominal obesity*

Metabolic syndrome

Cardiovascular disease ; type 2 diabetes mellitus; all-cause mortality

Figure 3. Candidate mechanisms underlying associations between sleep-related problems and MetS.

Aims

The aim of this thesis was to investigate associations between several life-style factors, shift work, metabolic health, and cognitive function in middle-aged and older individuals. The specific aims for each paper were:

Paper I
In *Paper I* we aimed to explore whether there are associations between dietary intake of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and cognitive test scores as well as brain volumes in elderly.

Paper II
The aim of *paper II* was to investigate the relationships between adherence to the Mediterranean-like diet, cognitive performance and brain volumes in older individuals.

Paper III
In *paper III* we sought to explore whether self-reported shift work history is linked to performance on the trail making test (TMT) in middle-aged and elderly individuals.

Paper IV
In *paper IV* we aimed to examine whether associations of sleep duration outside the recommended range (7–8 h per day), sleep disturbances (such as problems with falling and staying asleep), and sleep-disordered breathing (SDB) symptoms (such as snoring and sleep apneas) with MetS vary by age (45–64 vs. ≥65 years).

Materials and Methods

PIVUS cohort

Subjects from the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) cohort were included in Paper I and II. The PIVUS cohort initially included 1,016 (50 % females) individuals aged 70 living in the community of Uppsala, Sweden (Lind *et al.*, 2005). The subjects were chosen from the register of community living and were invited in a randomized order. The subjects received an invitation by letter to participate in the study within 2 months of their 70th birthday. The study was approved by the Ethics Committee of Uppsala (EPN) and the participants gave informed consent (Lind*, et al.*, 2005). During participant recruitment, a 7-day food diary was obtained. 827 subjects from the initial cohort agreed to participate in a follow-up investigation 5 years later (81.4 % response rate), i.e., when they were 75 years old. Of the individuals who were reinvestigated at the age of 75 years, a subsample of 409 elderly agreed to participate in a magnetic resonance imaging (MRI) scan of their brains (49.5 % of the cohort that was reinvestigated at the age of 75 years). Inclusion criteria for both studies (Paper I and Paper II) were cognitively normal clinical status (identified by an MMSE score greater than 26) (Folstein*, et al.*, 1975), absence of strokes or neurologic diseases (e.g., tumors) at ages 70 and 75, valid measures from the MRI brain scan, and an availability of the food diary record at the age of 70 years. Additionally, individuals with BMI > 3SD and those who had type 1/type 2 diabetes were excluded. Exclusions were administered to minimize the confounding effects of variables related to our main questions. For example, such disorders as diabetes, stroke, and cognitive impairment can induce changes in diet and lifestyle. In Paper I, 252 subjects met inclusion criteria. In addition, a subpopulation (n=198) was created in which individuals with unreliable dietary records were excluded. In Paper II, 194 individuals were included.

Dietary assessment in PIVUS cohort

Information on dietary habits was obtained at the age of 70 years. Briefly, the participants were given oral instructions by a dietitian on how to perform the 7-days dietary registration. The amounts consumed were specified as portion sizes or reported in household measurements (Sjogren *et al.*, 2010;

Titova *et al.*, 2013b). Non-adequate reporters of energy intake were identified using the Goldberg cutoff (Black, 2000), taking into consideration the level of physical activity and basal metabolic rate. In this procedure, an acceptable range of energy intake is identified for each individual in relation to estimated energy expenditure - i.e., producing a 95% confidence interval (CI) for energy intake that is required for weight maintenance (Sjogren*, et al.*, 2010). Energy expenditure was calculated by adding basal metabolic rate (according to the age adjusted Schofields formula) and exercise-dependent metabolic rate (derived from questionnaires). Subjects with a reported energy intake outside the 95% CI were considered as non-adequate reporters (Titova *et al.*, 2013a). Dietary habits were not reinvestigated during follow-up.

Assessments of dietary intake of EPA and DHA
The daily intake of EPA and DHA was calculated by using a database from the Swedish National Food Agency containing about 1500 food items, drinks, and recipes.

Assessments of adherence to MeDi in PIVUS cohort
The adherence to MeDi was defined as a scale ranging from 0 (not adherent at all to MeDi) to 8 points (very adherent to MeDi) based on the 7-days dietary registration. The MeDi score is a population-based quality score. The median dietary intake in the population served as the cut off for each food component typical for a Mediterranean diet. Men and women were scored separately (Sjogren*, et al.*, 2010; Titova*, et al.*, 2013a). An intake of a food component on the favorable side of the median was coded 1; otherwise it was coded 0. For instance, those whose fish consumption during a week was above the population median were assigned a value of 1, whereas those whose fish intake was below the median obtained a value of 0. In terms of alcohol intake, a value of 1 was assigned for a moderate alcohol consumption, which was defined as an intake of 10–50 g/day for males and 5-25 g/day for females, respectively with no biochemical signs of alcohol abuse (i.e., aspartate aminotransferase: alanine aminotransferase ratio < 2). The MeDi score was applied with slight modifications. Compared with the original score (Trichopoulou*, et al.*, 2003), polyunsaturated fatty acids (PUFAs) replaced monounsaturated fatty acids when estimating dietary fat quality since the consumption of olive oil in the present cohort was very low; and in a traditional Swedish diet saturated and monounsaturated fats have similar food origins. In addition, nuts and seeds were excluded because of their very low intake, and dietary leguminous plants were pooled with vegetables in the present score. The reported intake of potatoes was added to cereals, because potato consumption contributes considerably to carbohydrate intake in a Swedish population of older adults. All intakes were energy adjusted with the residual adjusted method prior to scoring (Willett *et al.*, 1997).

Baseline investigation (at the age of 70 years)

Blood samples and anthropometric measurements were taken after an overnight fast. Lipid variables and fasting blood glucose were measured by standard laboratory techniques. Plasma glucose and serum insulin concentration values were used to calculate the homeostasis model assessment-insulin resistance (HOMA-IR; [(fasting plasma glucose × fasting serum insulin)/22.5]) (Wallace and Matthews, 2002). The proportion of DHA and EPA in serum phospholipids was measured by gas chromatography as previously described (Warensjo *et al.*, 2009). Body mass index (BMI) was calculated as weight divided by squared height (kg/m^2). Blood pressure was measured by a calibrated mercury sphygmomanometer in the non-cannulated arm to the nearest mmHg after at least 30 min of rest.

A standardized questionnaire was used to assess PA and educational status. The participants were asked how many times per week they performed light (e.g., walking, gardening) respectively hard exercise (e.g., running, swimming) for at least 30 min. Self-reported leisure time PA was divided into four PA categories: very low, low, medium, and high. The educational level was defined as primary school, secondary school, and university level.

Cognitive measures

At the age of 75 years, the mini-mental state examination (MMSE) and the 7 minute screen (7MS) test was administered to the participants by trained research nurses. MMSE is a brief 30-point test which widely used to screen for cognitive impairment in clinical practice (Folstein*, et al.*, 1975). In MMSE, scores greater than 26 are considered as normal cognitive function (Kukull *et al.*, 1994). The raw scores of the four subtests of the 7MS were summed with the logistic regression formula described previously (Solomon*, et al.*, 1998):

$$Ln\ [P/(1-P)] = 35.59 - 1.303*ECR - 1.378*VF + 3.298*BTO - 0.838*CD$$

where P is the probability of having dementia. The natural logarithm (ln) of P/(1−P) is equal to the total 7MS score. The more negative the total raw score on the 7MS test, the lower the probability of having dementia (Solomon*, et al.*, 1998). For purposes of presentation in the current analysis, scores were inverted such that the higher the score the better the performance on the 7MS test.

MRI acquisition and processing

At the age of 75 years, regional measures of brain volume were obtained with magnetic resonance imaging (MRI). A high resolution 3D T1-weighted volumetric "Turbo Field Echo" (TFE) scan was acquired using a Philips 1.5 Tesla scanner (Gyroscan NT, Philips Medical Systems, Best, The Nether-

lands). The three dimensional gradient echo sequence was acquired with the scan parameters TR 8.6 ms, TE 4.0 ms, flip angle = 8°. Sagittal slices with a field of view of 240 mm, a slice thickness of 1.2 mm, and an in-slice resolution of 0.94 mm2 were reconstructed.

Images were processed using Voxel Based Morphometry (VBM), a technique using Statistical Parametric Mapping (SPM) to determine local concentrations of gray matter (GM) volumes on a voxel-by-voxel basis (Ashburner and Friston, 2000). GM was calculated by segmenting it from WM and CSF using the unified segmentation approach (Ashburner and Friston, 2005). Following this segmentation procedure, probability maps of GM were "modulated" to account for the effect of spatial normalisation, by multiplying the probability value of each voxel by its relative volume in native space before and after warping. Gray matter images based on probability maps at each voxel were normalized into Montreal Neurological Institute (MNI) standard space with a voxel size of 2 mm x 2 mm x 2 mm.

Modulated images were smoothed with an 8 mm Full Width Half Maximum (FWHM) Gaussian kernel, in line with other VBM studies (Walther *et al.*, 2010).This smoothing kernel was applied prior to statistical analysis, to reduce signal noise and to correct for image variability. VBM analyses were conducted using SPM8 (Functional Imaging Laboratory, University College London) (Ashburner and Friston, 2000).

EpiHealth cohort

Subjects from the EpiHealth cohort were included in Paper III and IV. The primary objective of EpiHealth cohort study is to provide a resource to investigate how interactions between several genotypes and lifestyle factors contribute to the development of common disorders in humans, such as cardiovascular diseases, cancer, depression and dementia (Lind *et al.*, 2013). To this aim, participants in the age between 45 and 75 years voluntarily filled out an internet-based questionnaire, and visited one of two Swedish test centers (located in Malmö or Uppsala, Sweden) to perform a collection of blood samples, and registration of physiological parameters. Invitation letters were sent to a random sample of participants who were resident in the municipalities and within the selected age limits using the Swedish Population Registry (Lind, *et al.*, 2013; Titova *et al.*, 2016). Participants' recruitment started in 2011.

In Paper III, 7143 subjects were considered eligible for the analysis after exclusions because of missing data. In Paper IV, data from 19,691 subjects (96% of the initial sample size) were available to investigate the association between sleep duration and MetS. From them, 19,142 participants had complete data on sleep disturbance and 16,467 on SDB symptoms. Study III and Study IV were approved by the EpiHealth Data Access Committee and by

the Ethics Committee of Uppsala University. Study participants provided written informed consents to participate.

Shift work history and occupational status

The variable *shift work history* was obtained using an internet-based questionnaire. Participants were asked to indicate whether they have performed shift work within the last 5 years or not. Participants could select one out of four possible responses: "yes, currently", "yes, in the past", "no", or "don't know/don't want to answer". The answer "don't know/don't want to answer" was treated as missing value (n = 33). Additionally, in a separate question, participants indicated if they have ever worked at night or not. The possible responses were: "no", "less than 1 year", "1 to 2 years", "3 to 5 years", "6 to 10 years", "11 to 20 years", or "more than 20 years". The following groups on shift work history were created for the study: nonshift workers (answered both questions with no); past shift workers (answered that they did not work shift during the past 5 years, but that they had worked night shifts more than 5 years ago); recent former shift workers (stated that they performed shift work during the past 5 years but not at the time of data collection); and current shift workers (performed shift work at time of data collection).

Main occupation and workplace during the last 5 years were obtained as free text response. Swedish Standard Classification of Occupations (2012), which is based on The International Standard Classification of Occupation-08, were utilized to assign participants into three groups as follows: white collar workers (managers; professionals; technicians and associate professionals; clerical support workers; and service and sales workers), blue collar workers (skilled agricultural, forestry and fishery workers; craft and related trades workers; plant and machine operators, and assemblers; and elementary occupations), and others. Participants were assigned to the occupational category "others" in case if there was insufficient information to identify the work category. Additionally, participants of the armed forces occupations class were assigned to the group "others" in the present analysis, as it only included 19 individuals.

The trail making test (TMT)

A computerized version of the TMT was administered when participants visited 1 of 2 test centers. This cognitive test consists of 2 parts, TMT-A and TMT-B. The TMT-A determines cognitive processing speed, whereas the TMT-B measures executive functions (Bowie and Harvey, 2006). In TMT-A, participants were requested to draw lines to connect circles labeled with numbers 1-25 in an ascending order. In TMT-B, participants perform the test in the same manner but must alternate between a set of numbers (1-13) and a

set of letters (A-L) in an ascending order (i.e., 1-A-2- B, etc.). The instruction was to complete these subtests as quickly as possible. The outcome measurement is the total time needed to connect correctly all symbols during each subtest, which included the time to correct erroneously chosen paths. Total errors on both subtests were recorded. In addition, the ratio between TMT-B and TMT-A was calculated (named TMT ratio in the following), as it has been proposed to be a more accurate measure of executive functions (Hester *et al.*, 2005).

Subjects' characteristics and lifestyle factors

Age and gender were recorded in the test center. Participants' educational status, physical activity (PA) during leisure time, alcohol consumption, and smoking habits were assessed by means of the internet-based questionnaire. Educational status was defined as follows: primary and elementary school (up to 9 years of formal schooling) vs. upper secondary school (up to 12 years of formal schooling) vs. university vs. other (e.g., further training).

In Paper III, leisure time PA was assessed on a scale ranging from 1 to 5 (1 = "mostly sedentary", 3 = "walking for 30 minutes per day", and 5 = "vigorous activity 60 minutes per day"). Based on responses, participants were categorized into three PA level groups: low (score range = 1-2), intermediate (score range = 3-4), and high (score range = 5). In Paper IV, PA during leisure time was measured on an eight-point scale and then categorized to three levels. A low level of PA was defined as spending most leisure time mostly sedentary or having light PA about 2–4 h per week (e.g., walking, and light housework). A medium level of PA was defined as moderate PA at least 1–2 times a week (e.g., jogging, swimming) or light PA for more than 4 h per week. A high PA level was defined as more strenuous PA at least three times a week, such as playing tennis, swimming, and running, etc. Alcohol consumption frequency during the last 12 months was categorized as "never/seldom", "2-3 times a month", "1 time/week", "2-3 times a week", "4 times a week or more often" in Paper I. In Paper II, alcohol consumption frequency was defined as "never," "≤1 time/week," "2–3 times/week," and "≥4 times/week". Smoking habits were defined as non-smokers or current smokers.

Perceived stress

To assess participants' perceived stress during the last month, the Perceived Stress Scale (PSS-10, scores range from 0 to 40) was utilized (Cohen *et al.*, 1983). The Cronbach's alpha of the 10 stress items used by this psychometric tool was 0.812.

Anthropometry and biochemical measurements

Participants visited a test center for collection of physical measurements and blood samples. Height and weight were recorded. Body mass index (BMI) was calculated as weight divided by squared height (kg/m^2). Waist circumference was measured at the umbilical level. Blood pressure was recorded twice in the sitting position by trained personnel with automatic device (Omron, Kyoto, Japan). Fasting glucose, LDL- and HDL-cholesterol, and serum triglycerides were determined at the hospital laboratory using an Architect Ci8200 analyzer (Abbott Laboratories, Abbott Park, IL, USA) (Lind, *et al.*, 2013).

Sleep variables

Sleep duration was reported in intervals of one hour from ≤4 h/day to ≥10 h/day. Sleep duration variable was categorized into three groups: short sleep duration (≤6 h/day), normal sleep duration (7-8 h/day), and long sleep duration (≥9 8 h/day). In Paper III, self-reported sleep disturbances were assessed by 6 symptoms: difficulties to stay awake during the day; difficulties getting back to sleep after nighttime awakenings; difficulties falling asleep; early awakenings; disturbed sleep; and feel not rested after sleep. The Cronbach's alpha was 0.77. Participants ratings (never/seldom, 1 to 3 times a month, 1 to 3 times a week, 4 or more times a week) were used to construct a cumulative sleep disturbance score (range 0-18, with 18 indicating the highest sleep difficulties).

In paper IV, the following sleep disturbance symptoms were used: difficulties in falling asleep, early awakenings, difficulties getting back to sleep after nighttime awakenings, and disturbed sleep. Symptoms of SDB included witnessed sleep apnea and heavy snoring (witnessed or according to participate him/herself). Participants who reported that they suffered from at least one of the above-mentioned sleep disturbance symptoms which occurred "4 or more times a week" were defined to have a sleep disturbance. Participants who indicated to experience either witnessed sleep apnea or heavy snoring for "4 or more times a week" (or both) was defined to have SDB symptoms.

Metabolic Syndrome

As described in Paper IV, the metabolic syndrome was defined as the presence of at least three of the following five conditions: elevated waist circumference (≥102 cm for men; ≥88 cm for women); hypertriglyceridemia, defined as a serum triglyceride concentration ≥150 mg/dL [≥1.7 mmol/L]; low HDL cholesterol (<40 mg/dL [<1.0 mmol/L] for men and <50 mg/dL [<1.3 mmol/L] for women); elevated blood pressure (systolic ≥130 and/or ≥85 diastolic mmHg) or antihypertensive drug treatment (Alberti, *et al.*, 2009);

and elevated fasting glucose (≥110 mg/dL [≥6.1 mmol/L]) or drug treatment for diabetes (Alberti and Zimmet, 1998).

Statistical analyses

In Papers I and II, multiple linear regression was utilized to determine the relationship between dietary intake variables and cognitive performance as well as brain volumes. GM, WM, and total brain volumes (TBV, the sum of WM and GM; named brain tissue in Paper I) were expressed as relative to the total intracranial volume (TIV, defined as the sum of GM, WM and CSF). In addition to global brain measures (i.e., GM, WM, and TBV), a voxel-based morphometry (VBM) regression analyses were conducted controlling for gender and TIV. All clusters and peak voxels of gray matter T statistic brain maps were thresholded at a P value <0.05 using Family Wise Error (FWE). Statistical analyses were performed using SPSS version 19 (SPSS Inc, Chicago, IL). VBM analyses were carried out using SPM8.

Paper I
The participants were divided into four groups according to their daily intake of EPA and DHA: very low (0.026–0.226 g; <25th percentile), low (0.228–0.387 g; 25th–50th percentile), medium (0.40–0.666 g; 50th–75th percentile), and high intake (0.667–1.910 g; >75th percentile). Three linear regression models were used: Model A: adjusting for gender, and exact age; Model B: Model A + energy intake, education, and self-reported PA; and Model C: Model B + serum concentration of low-density cholesterol, BMI, systolic blood pressure and HOMA-IR. These three models were applied in the main study population as well as in the subpopulation of adequate reporters of energy intake. Spearman's rank test was used to explore the association between the DHA and EPA content in serum phospholipids and dietary intake of these fatty acids. Additional regression analyses was conducted to evaluate the associations between the dietary intake of EPA and DHA and cognitive functions and brain structure in a subgroup of individuals with MMSE scores < 27 (n = 27).

Paper II
Two linear regression models were constructed to examine the associations between the MeDi score, cognitive functioning and brain volumes: Model A: adjusting for gender; Model B: Model A + energy intake, education, self-reported PA, serum concentration of low-density cholesterol, BMI, systolic blood pressure, and HOMA-IR. A separate analysis was conducted in order to examine associations between single MeDi components and cognitive functioning and brain volumes. All eight MeDi components were entered simultaneously as continuous variables into the constructed regression models. Alcohol intake was entered as squared term to capture possible non-

linear relationships with dependent variables. Skewed dietary variables were log-transformed to approach normality.

Paper III

A generalized linear models approach was used to examine associations between shift work history and TMT outcomes. For all generalized linear models, the gamma distribution and log link function were chosen to account for non-normal distributions of TMT outcomes. Two models were created: a basic model adjusted for gender and age; and a fully adjusted model which includes gender, age, educational status, PA level, alcohol consumption, smoking status, sleep duration, perceived stress, cumulative sleep disturbance score, BMI and occupational status. All statistical analyses were performed using SPSS, version 22.0 (SPSS Inc, Chicago, IL, USA).

Paper IV

Binomial regression with log link function was performed to examine associations between the prevalence of MetS and sleep parameters. All log-binomial regression models were adjusted for participants' age (expressed in years), gender, educational attainment, leisure PA level, current smoking status, and alcohol consumption frequency. Main results were presented as prevalence ratios (PR). Possible multiplicative interaction effects of sleep parameters with age (in years) and gender on MetS risk were investigated in fully adjusted models (i.e., sleep parameter × age and sleep parameter × gender). Potential confounders were selected based on existing information on risk factors for impaired sleep and MetS using the method of directed acyclic graphs (DAGs) (Textor *et al.*, 2011). Several sensitivity analyses were conducted.

Results and Discussion

Paper I

Using data from a community-based cohort of elderly Swedish men and women, we have shown that self-reported dietary intake of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) at age 70 years was positively associated with cognitive performance on the 7MS test (i.e., the total score obtained on four cognitive subtests) and global GM volume five years later. These results are in line with previous studies. For instance, both high fish consumption and dietary intake of EPA and DHA have been linked to lower risk of cognitive decline in the elderly (Kalmijn*, et al.*, 2004; van Gelder*, et al.*, 2007; Albanese *et al.*, 2009). A recent retrospective cohort study demonstrated that the use of fish oil supplements was associated with less atrophy in cerebral cortex GM and hippocampus as well as better cognitive performance in Mini-Mental State Examination and the Alzheimer's disease Assessment Scale among cognitively healthy individuals (Daiello*, et al.*, 2015). In our study, no association was observed between the dietary intake of EPA and DHA and global WM volume, TBV and regional GM volume.

Self-reported dietary records have several weaknesses, such as reporting bias (Johnson, 2002). An additional criteria, the Goldberg equation (Black, 2000), was applied to identify non-adequate reporters. Importantly, similar but slightly less significant results were obtained in a subgroup analysis when excluding those who apparently did not report their dietary intake properly. In addition, correlation analyses revealed that the estimated daily dietary intake of EPA and DHA was positively linked to the proportion of these FA in circulating phospholipids, suggesting that the 7-days food record was a valid measure to approximate the habitual intake of EPA and DHA in the current study. However, no associations between plasma proportions of these FA and cognitive tests or GM volume were observed.

There are also findings demonstrating that the dietary intake of omega-3 FA does not affect the rate of cognitive decline and the risk to develop dementia and its subtypes in older individuals (Engelhart*, et al.*, 2002; Devore*, et al.*, 2009). This inconsistency in results can be related to methodological differences, selection bias, and differences in the study cohorts in terms of culture, lifestyle and education. This makes the generalization of the results more difficult. Additionally, short duration of the intervention in clinical

trials could explain the lack of association between the omega-3 FA supplementation and cognitive function in older populations.

Due to the cross-sectional nature of our study, it is difficult to make an assumption regarding a cause and effect relationship. There are several potential neurobiological mechanisms which can explain the beneficial effects of omega-3 FAs on the human brain. It has been suggested that omega-3 FAs may modulate the structure and function of biological membranes, such as elasticity, membrane organization, activity of ion channels and ion transporters (Bruno *et al.*, 2007; Bos*, et al.*, 2016) which may facilitate neurotransmission and neuronal function (Bos*, et al.*, 2016). Additionally, omega-3 FAs have anti-inflammatory and vasodilatory properties which may protect general vascular health (Holub and Holub, 2004), and as a secondary effect, maintain blood perfusion of the brain.

Paper II

The main analysis revealed that the MeDi score was not associated with the performance on the 7MS and brain volumes while controlling for potential confounders. From the eight dietary components included in the MeDi score, a low consumption of meat and meat products was linked to a better performance on the 7MS test and larger TBV (the sum of WM and GM) five years later. A recent epidemiological study in older population supported our findings and demonstrated that higher consumption of red meat was associated with worse executive and global cognitive functions (Bajerska *et al.*, 2014). Another cross-sectional study performed in an elderly population without dementia revealed that lower meat intake as a component of MeDi score has been associated with larger GM and total brain volumes (Gu*, et al.*, 2015). The mechanisms by which a low intake of meat and meat products support cognitive functioning and brain volumes in the elderly cannot be derived from our data due to the cross-sectional nature of our study. However, there are findings from other studies that suggest potential mechanisms. For example, meat and meat products are sources of saturated FA. Previous studies in rats have shown that diets rich in saturated fat have an adverse effect on central nervous system pathways involved in brain plasticity and neuroprotection, as well as cognitive functioning (Granholm *et al.*, 2008; Sartorius *et al.*, 2012). Furthermore, large prospective cohort studies have found a link between saturated fat intake and cognitive decline (Morris *et al.*, 2004) and vascular dementia (Kalmijn *et al.*, 1997).

The inverse association between the adherence to the MeDi and cognitive decline, as well as incidence of MCI and AD in older populations was reported by several studies (Feart*, et al.*, 2009; Scarmeas*, et al.*, 2009; Tangney*, et al.*, 2011; Tsivgoulis*, et al.*, 2013; Anastasiou*, et al.*, 2017) and confirmed by meta-analyses (Psaltopoulou*, et al.*, 2013; Singh*, et al.*, 2014). There are however negative findings which are in line with our results (Cherbuin and Anstey, 2012; Samieri *et al.*, 2013). For example, in the

Women's Health Study which included 6174 participants, aged 65+, the MeDi score was not associated with global cognitive measurements and verbal memory five years later (Samieri, *et al.*, 2013). One possible reason for these contrasting findings might be that the MeDi scores that have been used in several studies to explore correlations between MeDi and health outcomes in elderly cohorts are population-specific, which may limit the generalizability of the results. Differences in dietary habits and overall population characteristics, such as education, socioeconomic status, and lifestyle, may also play a role. Thus, confounding factors might partly explain the inconsistency between studies. Moreover, differences in the cognitive assessment methods may contribute to the inconsistency in results across studies. Based on our study's findings, another explanation for these contradictory results could be that, under certain circumstances, integrating all dietary components into MeDi scores explains less variance in cognitive functioning and brain volumes than its single dietary components.

Paper III

A number of epidemiological and experimental studies have demonstrated that shift work may have a negative impact on human's health (Scheer *et al.*, 2009; Esquirol, *et al.*, 2011; Itani, *et al.*, 2011; Morris *et al.*, 2015; Nea, *et al.*, 2015; Wang, *et al.*, 2015; Vimalananda, *et al.*, 2015). However, information regarding short- and long-term effects of shift work on parameters of brain health is still fragmentary. By utilizing data from 7,143 participants of the Swedish EpiHealth cohort study, we investigated if shift work history linked to the performance on the TMT, the neuropsychological test which evaluates executive cognitive function (Ashendorf *et al.*, 2008).

The main analysis, adjusted for potential confounders, revealed that current and recent former shift workers (worked shifts during the past 5 years) performed worse on the TMT outcomes than nonshift workers. In contrast, performance on the TMT did not differ between past shift workers (off from shift work for more than 5 years) and nonshift workers. The latter could suggest that it may take at least a 5 years break from shift work to perform equally well as nonshift workers on the TMT.

Our findings are in line with other studies demonstrating the adverse association between shift work and cognitive performance (Rouch *et al.*, 2005; Ansiau, *et al.*, 2008; Machi *et al.*, 2012; Marquie, *et al.*, 2015). For instance, a study involving 3,237 workers at age 32-62 years revealed that current male shift-workers had lower cognitive performance on several neuropsychological scores than workers never exposed to shift work. The same study indicated that memory performance tended to decrease with the increase in the duration of shift work exposure (Rouch, *et al.*, 2005). In addition, shift work has been linked to lower global cognitive test scores in employed and retired individuals (Marquie, *et al.*, 2015). There are however, contrasting findings (Machi, *et al.*, 2012; Devore, *et al.*, 2013). For example, a study

involving 13 emergency physicians did not find changes in the performance on TMT before and after day and overnight shifts (Machi, *et al.*, 2012). In a separate observational study, no difference in late-life cognitive performance was found between individuals with a history of working shifts compared to those who had typical day work schedules during midlife (Bokenberger *et al.*, 2017). Possible reasons for these discrepancies may be related to differences in the design (e.g., short or long-term effect of shift work on cognitive performance); age of participants; and the effect of potential confounders (e.g., health status and medication) which were not taken into account. In addition, the variability in the shift work schedules makes it difficult to investigate the consequences of shift work on cognitive health.

There are several potential pathways that may explain the link between shift work history and cognitive performance. For instance, shift work, especially night shift, is associated with disruption of the circadian rhythms resulting in internal de-synchronization and subsequent psychological and physiological disturbances (Lupien *et al.*, 2009; Srivastava, 2010; Marquie, *et al.*, 2015). Human and animal studies have shown that stress has multiple adverse effects on the frontal of the brain such as diminished blood perfusion (Chung *et al.*, 2006), reduced gray matter volume (Li *et al.*, 2014), and decreased synaptic plasticity (Zheng *et al.*, 2011). Frontal lobe functions play an important role for the performance on the TMT (Stuss and Levine, 2002). As we have hypothesized in Paper III, stress may account for the relationship between shift work and reaction time on this test (Titova, *et al.*, 2016). Thus, our study revealed that current shift workers indicated slightly higher perceived stress than non-shift workers. Neuroinflammation as a consequence of sleep disturbances (Irwin *et al.*, 2016) and impairment of melatonin production due to shift work could also play a role (Burch *et al.*, 2005). In addition, changes in lifestyle related to shift work may influence the association between shift work and cognitive performance.

Paper IV
Of the total 19,691 middle-aged and older participants with complete data on sleep duration, 25.1% met criteria for MetS. Our study revealed high prevalence of sleep-related complaints in this cohort: 23% had sleep disturbance symptoms and 18% had symptoms of SDB which occurred ≥4 times per week. Moreover, 32% reported sleep ≤6 h per day and 4% of participants indicated that they slept ≥9 h.

Several experimental and epidemiological studies demonstrated that short or/and long sleep durations are linked to MetS or its components in adults (Choi *et al.*, 2008; Hall, *et al.*, 2008; Arora *et al.*, 2011; Benedict *et al.*, 2011; Song, *et al.*, 2016). Our study confirmed these findings and showed additionally that the association between sleep duration and MetS may vary by age. Thus, in middle-aged individuals (45–65 years), both short (defined as ≤6 h sleep per day) and long (≥9 h sleep per day) sleep duration were

linked to increased prevalence of MetS, compared with normal sleep duration (7–8 h sleep per day). In contrast, in older participants (aged ≥65 years), long but not short sleep duration was associated with a higher likelihood of having MetS. Overall, no interactions between gender and sleep parameters were found.

There are, however, conflicting findings concerning the association between sleep duration and MetS (Wu *et al.*, 2012; Chaput *et al.*, 2013; Chang *et al.*, 2015; Kim *et al.*, 2015). For instance, a longitudinal study from the Canadian Quebec Family Study involving 293 participants, aged 18 to 65 years, revealed that long sleep duration (defined as ≥ 9 hours) was not associated with a higher risk of developing MetS (Chaput*, et al.*, 2013). Possible explanations for these discrepant results between studies (including ours) could relate to differences in the design (cross-sectional vs longitudinal), sample size, selection of confounders, and participants' age.

Another finding of our study was that reports of sleep disturbances (e.g., difficulties in initiating or maintaining sleep) increased the prevalence of MetS. This relationship did not differ between age groups. The association between measures of sleep disturbance and MetS has been described by others (Jennings*, et al.*, 2007; Lin *et al.*, 2016). For instance, data from a nationwide epidemiological survey conducted on middle-aged residents (mean age <60 years; n = 4,197) showed that problems with falling and staying asleep were associated with an increased prevalence of MetS (Lin*, et al.*, 2016). There are, however, also negative results described in the literature. In a study of 796 Taiwanese male police officers (mean age = 37.4 years old), no association between sleep quality and MetS or its components was observed (Chang*, et al.*, 2015).

Additionally, our study revealed that participants who reported at least one symptom of sleep-disordered breathing (SDB; e.g. frequent snoring) ≥4 times per week were more likely to have MetS. This association became stronger the higher the number of SDB symptoms. These findings are in line with previous case-control studies demonstrating the link between SDB and increased prevalence of MetS and its core components (Coughlin *et al.*, 2004; Tseng *et al.*, 2017). Furthermore, our study revealed that middle-aged individuals with SDB symptoms had a higher prevalence of MetS, than older subjects with SDB. One possible explanation for the this finding could be that older individuals spend more time in the lighter stages of sleep and have reduced time in rapid eye movement (REM) sleep (Miner and Kryger, 2017). Thus, they may have a lower risk to suffer from apneas during REM than middle-aged subjects. Sleep apneas during REM sleep have been suggested to be particularly detrimental to metabolic health (Mokhlesi and Ayas, 2016; Reutrakul and Mokhlesi, 2017).

Although our observational study cannot establish causality, there are several potential pathways that may explain the association between sleep duration, sleep disturbance, SDB symptoms and risk of MetS. For example,

several laboratory studies have shown that acute sleep deprivation may cause an alteration in glucose metabolism (Spiegel *et al.*, 1999; Donga *et al.*, 2010) and hormones involved in appetite regulation, such as decreased leptin levels and increased ghrelin levels (Taheri *et al.*, 2004) as well as impair the ability to control food impulses (Cedernaes *et al.*, 2014). In the setting of chronically insufficient sleep, such behavioral and metabolic effects may predispose individuals to gain weight (Cedernaes *et al.*, 2015). Moreover, experimental studies have shown that acute sleep deprivation increases concentrations of C-reactive protein, an inflammation marker for cardiovascular morbidity (Meier-Ewert *et al.*, 2004). The association between long sleep duration and MetS may be bidirectional. Long sleep duration could be a consequence rather than a cause of MetS, possibly, representing an attempt of the body and the brain to cope with metabolic perturbations. On the other hand, long sleep could be speculated to lead to less physical activity and circadian disruption (as a result of reduced daytime light exposure), both of which may favor the development of MetS (Tan*, et al.*, 2018).

The effect of poor sleep quality on MetS is not clear. However, a case-control study by Vgontzas et al. demonstrated that insomnia was linked to increased concentrations of cortisol in adults (Vgontzas *et al.*, 2001). Increased cortisol has previously been reported to contribute to the pathogenesis of hypertension, visceral obesity and hyperglycemia (Whitworth *et al.*, 2005). SDB comprises a wide range of abnormalities, including partial airway collapse, manifested as loud snoring, and the more severe form, obstructive sleep apnea (OSA). OSA is characterized by recurrent temporary episodes of partial (hypopnea) or complete upper airway obstruction (apnea) resulting in hypoxemia, increased respiratory effort, and sleep fragmentation (Young*, et al.*, 2005). The underlying mechanisms of how SDB leads to metabolic dysregulations are not fully understood. Systemic inflammation, hypoxia and oxidative stress are proposed as key contributors in pathogenesis of metabolic disorders (Dyugovskaya*, et al.*, 2002; Lam*, et al.*, 2012; Koren*, et al.*, 2016). Several clinical and experimental studies have demonstrated an increased oxidative stress in OSA patients (Barcelo*, et al.*, 2000; Dyugovskaya*, et al.*, 2002). Increased oxidative stress may contribute to hyperglycemia, hypertension, hyperlipidemia, and obesity (Lavie, 2009). Additionally, decreased sleep duration due to sleep fragmentation, common in individuals with SDB, may lead to alterations in insulin secretion and insulin sensitivity, as well as increased cortisol levels (Young*, et al.*, 2005). Furthermore, both animal and human studies have demonstrated that intermittent hypoxia may lead to deregulation of glucose homeostasis (Polak *et al.*, 2013; Newhouse *et al.*, 2017).

Conclusions and Perspectives

Collectively, our findings suggest that lifestyle and occupational status may have an impact on metabolic or cognitive health in middle-aged and older individuals.

In Paper I we have shown the dietary intake of EPA and DHA was positively associated with global gray matter volume and cognitive performance. In Paper II, the fully-adjusted main analysis revealed that the adherence to MeDi was not associated with measures of brain health. A lower intake of meat and meat products was linked to larger total brain volume and better cognitive performance in cognitively healthy aged population. These findings suggest that healthy dietary habits may have beneficial effect on cognitive function in elderly. However, further research is warranted, e.g., large cohort studies and randomized prospective trials, including repeated measures of cognitive function and brain structure in both cognitively healthy elderly and individuals with cognitive impairment.

In paper III, by utilizing data from a large community-based cohort of middle-aged and elderly individuals, we have demonstrated that shift work history is linked to poorer performance on the TMT, a widely used neuropsychological test. It is evident that shift work is becoming more common in modern societies. Compromised cognitive performance may not only affect working productivity but also increase the likelihood of transport and industrial accidents, and other human errors (Folkard*, et al.*, 2005). Further studies are needed to examine the association of shift work and cognition, for example using other neuropsychological and occupation-specific tests. The relationship between history of shift work and cognitive performance is complex. Investigations which take into account measures of circadian disruption and misalignment and type of shift work are needed. The research focused on effects of shift work on human health is very important as it may help to develop strategies to cope with health consequences of atypical working conditions (e.g., reduced cognitive ability, sleep-related problems, circadian disruption, and stress).

In paper IV, we have shown that sleep duration outside 7-8 hours per day, sleep disturbances, and SDB were all linked to increased prevalence of MetS. The strongest association was observed between SDB and MetS. Our results demonstrated that the higher the number of SDB/sleep disturbance symptoms the higher the prevalence of MetS. Studies investigating the modulating effect of age on the relationship between sleep and MetS in adult

populations are rare. Our study provides an important piece of evidence that the association between sleep parameters and metabolic health may change during adulthood. It must be kept in mind that our study was cross-sectional and sleep variables were self-reported. Therefore, studies investigating sleep patterns over longer periods, *e.g.*, by means of wearable sleep trackers would further improve the understanding of the role of disrupted sleep in the development of metabolic syndrome. Taking into account the high prevalence of sleep-related problems and metabolic perturbations, educational programs aiming to optimize sleep could, therefore, represent promising interventions to improve metabolic health in middle-aged and older subjects.

As suggested by this thesis, maintaining healthy dietary habits and a normal sleep/wake-cycle may have beneficial effect on metabolic and brain health in later life.

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